RADIOLOGY AND ONCOLOGY

Special section

4th International Congress of Slovenian Association for Gastroenterology and Hepatology

Guest Editors: **Bojan Tepeš** and **Stojan Potrč**

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NOVO

Cilja na 2 procesa nastanka CINV* v 1 odmerku
Zagotavlja učinkovito 5-dnevno preprečevanje CINV [1-5]

En odmerek
Dvojno delovanje
5-dnevno preprečevanje[1-5]

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netupitant/palonosetron

* CINV: Chemotherapy-induced nausea and vomiting
[Slabost in bruhanje povzročena s kemoterapijo]

1. Aapro M et al. Ann Oncol. 2014 Jul;25(7):1328-33.
2. Hesketh et al. Ann Oncol. 2014 Jul;25(7):1340-46.
3. Gralla RJ et al, Ann Oncol. 2014 Jul;25(7):1333-39.
4. Rojas C et al. Eur J Pharmacol. 2014 Jan 5;722:26-37.
5. Akynzeo SmPC, junij 2016

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

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TERAPEVTSKE INDIKACIJE Pri odraslih za preprečevanje akutne in zakasnjene navzee in bruhanja, povezanih z zelo emetogeno kemoterapijo na osnovi cisplatina za zdravljenje raka ter z zmerno emetogeno kemoterapijo za zdravljenje raka. **ODMERJANJE IN NAČIN UPORABE** Eno 300 mg/0,5 mg kapsulo je treba dati približno eno uro pred začetkom vsakega cikla kemoterapije. Trdo kapsulo je treba pogoltniti celo. Kapsulo je mogoče vzeti s hrano ali brez nje. Priporočeni peroralni odmerek deksametazona je treba ob sočasni uporabi z Akynzeom zmanjšati za približno 50 %. Prilagoditev odmerka pri starejših bolnikih ni potrebna. Pri uporabi tega zdravila pri bolnikih, starejših od 75 let, je potrebna previdnost zaradi dolgega razpolovnega časa zdravilnih učinkovin in omejenih izkušenj s to populacijo. Varnost in učinkovitost Akynzea pri pediatrični populaciji nista bili dokazani. Prilagoditev odmerka pri bolnikih z blago do hudo okvaro ledvic predvidoma ni potrebna. Potrebno se je izogibati uporabi Akynzea pri bolnikih s končnim stadijem bolezni ledvic, ki potrebujejo hemodializo. Pri bolnikih z blago ali zmerno okvaro jeter (stopnje 5-8 po lestvici Child-Pugh) prilagoditev odmerka ni potrebna. Pri bolnikih s hudo okvaro jeter (stopnja ≥9 po lestvici Child-Pugh) je treba Akynzeo uporabljati previdno. **KONTRAINDIKACIJE** Preobčutljivost na zdravilni učinkovini ali katero koli pomožno snov, nosečnost. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI** Ker lahko palonosetron podaljša čas prehoda skozi debelo črevo, je treba bolnike z anamnezo zaprtja ali znaki subakutne zapore črevesa po dajanju zdravila spremljati. Pri uporabi antagonistov 5-HT3 samih ali v kombinaciji z drugimi serotonergičnimi zdravili (vključno s selektivnimi zaviralci ponovnega privzema serotonina (SSRI) in zaviralci ponovnega privzema serotonina in noradrenalina (SNRI)) so poročali o serotoninskem sindromu. Priporočamo ustrezno opazovanje bolnikov glede simptomov, podobnih kot pri serotoninskem sindromu. Ker Akynzeo vsebuje antagonist receptorjev 5-HT3, je potrebna previdnost pri sočasni uporabi z zdravili, ki podaljšujejo interval QT, ali pri bolnikih, ki so razvili podaljšan interval QT, oziroma je verjetno, da ga bodo. Tega zdravila ne smemo uporabljati za preprečevanje navzee in bruhanja v dneh po kemoterapiji, razen v povezavi z dajanjem naslednjega cikla kemoterapije. Ne smemo ga uporabljati za zdravljenje navzee in bruhanja po kemoterapiji. Pri bolnikih s hudo okvaro jeter je potrebna previdnost, saj je za te bolnike na voljo malo podatkov. To zdravilo je treba uporabljati previdno pri bolnikih, ki sočasno peroralno prejemajo zdravilne učinkovine, ki se primarno presnavljajo prek CYP3A4 in imajo ozko terapevtsko območje. Netupitant je zmeren zaviralec CYP3A4 in lahko poveča izpostavljenost kemoterapevtskim zdravilom, ki so substrati za CYP3A4, npr. docetakselu. Zaradi tega je treba bolnike spremljati glede povečane toksičnosti kemoterapevtskih zdravil, ki so substrati za CYP3A4, vključno z irinotekanom. Poleg tega lahko netupitant vpliva tudi na učinkovitost kemoterapevtskih zdravil, pri katerih je potrebna aktivacija prek presnove s CYP3A4. Akynzeo vsebuje sorbitol in saharozo. Bolniki z redko dedno intoleranco za fruktozo, malabsorpcijo glukoze/galaktoze ali pomanjkanjem saharoza-izomaltaze ne smejo jemati tega zdravila. Poleg tega lahko vsebuje tudi sledi lecitina, pridobljenega iz soje. Zaradi tega je treba bolnike z znano preobčutljivostjo na arašide ali sojo skrbno spremljati glede znakov alergijske reakcije. Ženske v rodni dobi ne smejo biti noseče ali zanositi med zdravljenjem z Akynzeom. Pred začetkom zdravljenja je treba opraviti test nosečnosti pri vseh ženskah, ki še niso imele menopavze. Ženske v rodni dobi morajo uporabljati učinkovito kontracepcijo med zdravljenjem in še do en mesec po njem. Akynzeo je kontraindiciran med nosečnostjo. Med zdravljenjem z Akynzeom in še 1 mesec po zadnjem odmerku je treba prenehati z dojenjem. **INTERAKCIJE** Ob sočasni uporabi Akynzea z drugim zaviralcem CYP3A4 lahko pride do zvišanja plazemskih koncentracij netupitanta. Pri sočasni uporabi Akynzea in zdravil, ki spodbujajo delovanje CYP3A4, lahko pride do znižanja plazemskih koncentracij netupitanta, kar lahko privede do zmanjšane učinkovitosti. Akynzeo lahko zviša plazemske koncentracije sočasno uporabljenih zdravil, ki se presnavljajo prek CYP3A4. Ob sočasnem dajanju deksametazona z Akynzeom je treba peroralni odmerek deksametazona zmanjšati za približno 50 %. Ob sočasnem dajanju z Akynzeom se je izpostavljenost docetakselu in etopozidu povečala za 37 % oziroma 21 %. Pri ciklofosfamidu po sočasnem dajanju netupitanta niso opazili konsistentnih učinkov. Pri eritromicinu, midazolamu ali drugih benzodiazepinih, ki se presnavljajo prek CYP3A4 (alprazolam, triazolam), je treba ob sočasnem dajanju Akynzea upoštevati možne učinke njihovih zvišanih plazemskih koncentracij. Pri sočasnem dajanju Akynzea z močnimi zaviralci CYP3A4 (npr. ketokonazol) je potrebna previdnost, sočasnemu dajanju z močnimi spodbujevalci CYP3A4 (npr. rifampicin) pa se je treba izogibati. Priporočamo previdnost pri uporabi netupitanta v kombinaciji s peroralnim substratom encima UGT2B7 (npr. zidovudin, valprojska kislina, morfin), ker *in vitro* podatki kažejo, da netupitant zavira UGT2B7. Priporočamo previdnost pri kombiniranju netupitanta z digoksinom ali drugimi substrati P-gp, kot sta dabigatran ali kolhicin, ker podatki *in vitro* kažejo, da je netupitant zaviralec P-gp. **NEŽELENI UČINKI** *Pogosti (≥1/100 do <1/10):* glavobol, zaprtje, utrujenost. *Občasni (≥1/1.000 do <1/100):* nevtropenija, levkocitoza, zmanjšan apetit, nespečnost, omotica, vrtoglavica, atrioventrikularni blok prve stopnje, kardiomiopatija, motnja prevajanja, hipertenzija, kolcanje, bolečina v trebuhu, driska, dispepsija, napenjanje, navzea, alopecija, urtikarija, astenija, zvišane jetrne transaminaze, zvišana alkalna fosfataza v krvi, zvišan kreatinin v krvi, podaljšanje QT na elektrokardiogramu. *Redki (≥1/10.000 do <1/1.000):* cistitis, levkopenija, limfocitoza, hipokaliemija, akutna psihoza, sprememba razpoloženja, motnja spanja, hipestezija, konjuktivitis, zamegljen vid, aritmija, atrioventrikularni blok druge stopnje, kračni blok, popuščanje mitralne zaklopke, miokardna ishemija, ventrikularne ekstrasistole, hipotenzija, disfagija, obložen jezik, bolečina v hrbtu, občutek vročine, nekardialna bolečina v prsnem košu, nenormalen okus zdravila, zvišan bilirubin v krvi, zvišana kreatin fosfokinaza MB v krvi, depresija segmenta ST na elektrokardiogramu, nenormalen segment ST-T na elektrokardiogramu, zvišan troponin. **Vrsta ovojnine in vsebina:** Škatla z eno kapsulo v pretisnem omotu iz aluminija. **Režim izdaje:** Rp **Imetnik dovoljenja za promet:** Helsinn Birex Pharmaceuticals Ltd, Damastown, Mulhuddart, Dublin 15, Irska
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contents

Selected papers from:
The 4th International Congress of Slovenian Association for Gastroenterology and Hepatology

research article

Helicobacter pylori treatment results in Slovenia in the period 2013–2015 as a part of European Registry on Helicobacter pylori Management

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Background. *Helicobacter pylori* (*H. pylori*) is the most common chronic bacterial infection in the world affecting over 50% of the world's population. *H. pylori* is a grade I carcinogen, responsible for the development of 89 % of non-cardia gastric cancers. In the present study we analyzed the data for *H. pylori* eradication treatments in Slovenia.

Patients and methods. Slovenia is a part of the European Registry on Helicobacter pylori Management from the beginning. In seven medical institutions data for *H. pylori* eradication treatments was collected for 1774 patients from April 16th 2013 to May 15th 2016. For further modified intention to treat (mITT) analysis 1519 patients were eligible and for per protocol (PP) analysis 1346 patients.

Results. Patients' dropout was 11.4%. Eradication rate for 7 day triple therapy with proton pump inhibitor (PPI) + Clarithromycin (C) + Amoxicillin (A) was 88.7% PP and 72.0% mITT; for PPI + C + Metronidazole (M) 85.2% PP and 84.4% mITT. Second line 14 day therapy PPI + A + Levofloxacin had 92.3% eradication rate PP and 87.1% mITT. Ten to fourteen day Bismuth quadruple therapy was the therapy in difficult to treat patients. At the end all patients that adhered to prescribed regimens were cured of their *H. pylori* infection.

Conclusions. High dropout rate deserves further analysis. Slovenia is still a country with < 15% *H. pylori* resistance to clarithromycin, triple therapy with PPI plus two antibiotics reaches PP eradication rate > 85%, but mITT eradication rates are suboptimal.

Key words: *Helicobacter pylori;* eradication treatment; European Registry on *Helicobacter pylori* management; Slovenian results

Introduction

Helicobacter pylori (*H. pylori*) is the cause of the most common chronic bacterial infection in the world, affecting over 50% of the world's population.[1] Approximately 20% of infected patients will develop peptic ulcer disease, mucosa associated lymphoid tissue lymphoma or gastric cancer at some point in their lives.[2] The WHO's International Agency for Research on Cancer classified *H. pylori*

as a definite (group 1) carcinogen.[3,4] *H. pylori* is the leading infectious cause of cancer worldwide and it was estimated that some 660 000 new cancer cases globally were directly attributable to *H. pylori* infection in 2008, which accounts for 33% of all infection-associated cancers, including 46% in developed regions and 29% in the developing regions.[5]

Several national guidelines have recommended eradication in all *H. pylori*-infected individuals to prevent the spread of infection and reduce the future burden of *H. pylori*-induced diseases, particularly gastric cancer.[6,7] In the Kyoto consensus on *H. pylori* gastritis the recommendation is to treat all *H. pylori* infected patients independent of whether clinical manifestations are present.[8]

The basis of modern *H. pylori* therapy is a proton pump inhibitor (PPI) plus two / three antibiotics for 7–14 days.[2] The desired eradication rate is > 90%, the acceptable eradication rate for first line therapy is > 80%.[9]

The treatment success depends on *H. pylori*'s susceptibility to antibiotics and patient's compliance. *H. pylori* resistance rate to antibiotics as well as treatment results should be carefully recorded and those results should guide the therapy in a certain country or region.[2] The European Registry on *H. pylori* management (Hp-EuReg) has been introduced in 2013 with the idea to collect treatment results, side effects, patients' compliance and antimicrobial susceptibility in different European countries. Thirty one countries and 280 recruiting investigators are included in the Hp-EuReg. So far, more than 15.000 patients have been included, and 12.270 patients have finished follow-up.[10]

We would like to present the Slovenian data collected in Hp-EuReg from April 16th 2013 to May 15th 2016.

Patients and methods

European Registry on *H. pylori* Management

The present manuscript is an interim analysis using the Slovenian data of the "European Registry on *H. pylori* Management" (Hp-EuReg), an international multicenter prospective non-interventionist registry that will last over ten years, promoted by the *European Helicobacter and Microbiota Study Group (www.helicobacter.org)*. The Scientific Committee of the project is comprised by Javier P. Gisbert (Principal Investigator), Francis Megraud, Colm O'Morain and Adrian G. McNicholl (Scientific Coordinator).

Ethics

Hp-EuReg protocol was approved by the Ethics Committee of the La Princesa Hospital (Madrid, Spain) that acted as reference IRB, and was prospectively registered at ClinicalTrials.gov under code NCT02328131.

National coordinators

A list of 30 European Countries has been selected. In each country a National Coordinator was elected based on its clinical and research activity. Slovenian National Coordinator is Bojan Tepes. The National Coordinators constitutes the monitoring and drafting committee of the registry in a certain country.

Recruiter investigators

The Recruiting Investigators are gastroenterologists attending an adult population with a gastroenterology outpatient clinic that assists *H. pylori* infected patients. Eradication confirmation tests have to be performed routinely. Patients are managed and registered following routine clinical practice. Slovenian recruiting investigators are authors BT, MK, MV, PL, MS and NBJ.

Electronic Case Report Form (e-CRF)

Study data were collected and managed using REDCap electronic data capture tools hosted at Asociación Española de Gastroenterología (AEG; www.aegastro.es).[11] AEG is a non-profit Scientific and Medical Society focused on Gastroenterology, and it provided this service free of charge, with the sole aim of promoting independent investigator driven research. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

Variables and outcomes

The e-CRF includes 290 variables including demographics, history and comorbidity, data on infection and diagnosis, previous eradication attempts, current treatment, compliance, adverse events and

efficacy. All patient data was anonymized. Main outcome is confirmed eradication at least 4 weeks after treatment.

Per protocol (PP) analysis include all patients who finished follow-up and took at least 90% of the treatment drugs, as defined in the approved protocol. As the registry is ongoing, a pure Intention to treat (ITT) analysis cannot be provided. A modified ITT (mITT) was designed trying to reach the closest result to those obtained in clinical practice. This mITT includes for analyses all patients whose outcome has been registered by their doctors (eradication success, failure or lost to follow up), plus those that although their result has not been registered were treated more than a year prior to analysis. Patients classified as failure, lost or without registered outcome will be considered treatment failure in the mITT analysis.

Statistical analyses

Continuous variables are presented as the arithmetic mean and SDs. Qualitative variables are presented as proportions and 95% confidence intervals (CIs). The statistical analyses of the results were carried out using the $\chi 2$-test. The 95% CIs were calculated by normal approximation. One- and two-sided tests were used for the analyses and the P-value cut off for significance was set to less than 0.05. The analyses were carried out using IBM SPSS Statistics 22.0.0.

Results

Data was collected in seven medical institutions in Slovenia from April 16 th 2013 to May 15 th 2016 for 1774 patients (Table 1).

Two hundred and fifty-five (14.4%) patients were excluded from the analysis because they either had incomplete/invalid data (e.g.: missing age, gender, compliance data etc.) or because they were treated within the last year of this analysis and the outcome of their treatment was not yet registered.

All the remaining 1519 patients were eligible for further analysis in the modified intention to treat (mITT) group; 918 (60.4%) were female patients and 601 (39.6%) were male patients (Table 2; p = 0.00).

Out of those, 1346 patients had their outcome registered and were eligible for analysis in the per protocol (PP) group.

There were 173 patients (11.4%) who did not have their outcome recorded and were treated more than a year prior to this analysis. We consider that group a drop out patients group. We do not know if these patients took their therapy or whether they had the UBT done in the primary medical care and because of that did not return to their gastroenterologist, which can be a realistic option.

TABLE 1. Medical institutions participating in the Slovenian part of EU-HpReg

Institution	Number		Excluded from analysis (% of hosp. data)[1]		Dropout (%)[2]	
AM DC Rogaska	805	(45.4%)	146	(18.1%)	16	(2.4%)
SB Slovenj Gradec	464	(26.2%)	8	(1.7%)	81	(17.8%)
DC Bled	287	(16.2%)	0	(0%)	60	(20.9%)
SB Murska Sobota	73	(4.1%)	10	(13.7%)	0	(0%)
SB Trbovlje	68	(3.8%)	34	(50%)	1	(2.9%)
UKC Ljubljana	66	(3.7%)	50	(75.8%)	14	(87.5%)
MC Heliks	11	(0.6%)	7	(63.6%)	1	(25%)
Total	**1774**	**(100.0%)**	**255**	**(14.4%)**	**173**	**(11.4%)**

[1] Excluded from analysis because of incomplete/invalid data or because the visit was within last year and there is no follow up data yet; [2] Patients whose visit was more than a year ago and who had no follow up (dropout = modified intention to treat [mITT] – per protocol [PP])

TABLE 2. Demographic data for modified intention to treat (mITT) patient group

Gender	N (percent)	Minimum Age	Maximum Age	Mean Age	Std. Deviation
Female	918 (60.4%)	18	91	52.3	15.14
Male	601 (39.6%)	18	88	53.3	14.76
Total	1519	18	91	52.7	15.0

Only in 56 patients who took part in a RCT, primary *H. pylori* resistance to antibiotics was recorded (Table 3). The highest resistance rate was for metronidazole (M; 28.6%), resistance rate to clarithromycin (C) was 14.3% and to amoxicillin (A) was 3.6%. All the other antimicrobial susceptibility tests have been performed in treatment failure patients. The percentage of resistance to different antibiotics rose with the number of treatment attempts.

Ten different 7–14 days triple combinations were used in 1305 patients as a first line treatment. The majority of patients (1.154) were treated accordingly to our therapeutic guidelines (Table 4) with 7 day triple therapies: PPI clarithromycin / amoxicillin / metronidazole. The eradication rate for PPI + Clarithromycin + Amoxicillin was 72.0% for the mITT group *vs*. 88.1% for the PP group. The eradication rate in 7 day PPI + Clarithromycin + Metronidazole was 84.4% for the mITT group *vs*. 85.2% for the PP group. No significant differences were found regarding the type of PPI used.

Six different triple 7-14 days treatments were used in 176 patients whose *H. pylori* was not eradicated with the first line treatment (Table 5). The

TABLE 3. Helicobacter pylori antibiotic resistance

Antibiotic	First treatment (95% C.I.)		Second treatment (95% C.I.)		Third treatment (95% C.I.)		Fourth treatment	Fifth treatment
No resistance	62.5%	(50.0%–75.4%)	6.1%	(0%–15.6%)	14.3%	(0%–36.4%)	0%	0
Nitroimidazole	28.6%	(16.7%–40.8%)	45.5%	(28.1%–63.0%)	57.1%	(30.0%–83.3%)	100%	100%
Clarithromycin	14.3%	(5.7%–24.2%)	87.9%	(75.7%–97.3%)	85.7%	(63.6%–100%)	100%	100%
Amoxicillin	3.6%	(0%–9.3%)	0%		0%		0%	0
Quinolone	0%		6.1%	(0%–15.6%)	7.1%	(0%–23.5%)	50%	0
Tetracycline	0%		3%	(0%–100%)	7.1%	(0%–23.5%)	0%	0
Total	**N = 56**		**N = 33**		**N = 14**		**N = 2**	**N =1**

C. I. = confidence interval

majority of them used 14 days PPI 40 mg bid, Amoxicillin (A) 1000 mg bid, and Levofloxacin (L) 500 mg oid with 92.3% eradication rate PP and 87.1% eradication rate mITT. This treatment is according to our guidelines the recommended one for second line. Dropout rate for the second treatment attempt was 6.3%.

Bismuth is not available in Slovenia and those that need third or fourth line treatment regimen should buy it in Germany or in any other country in Europe where it is available. At the moment this treatment is not reimbursed (Tables 6,7). Dropout rate after third line therapy was 18.2%. Seven patients were treated with fourth line treatment regimen (Table 7), one was treated with fifth, and one with sixth line treatment. No drop out has been recorded in the group with four or more treatment attempts.

At the end all patients that start their treatment and comply with the treatment regimens were cured of their *H. pylori* infection.

Discussion

High dropout rate - 11.4% - in the Slovenian Hp-EuReg data is the first important message. This percentage is lower than in the EU Hp-EuReg (13%).[10] Some logistic reasons can influence this high dropout rate. All 66 patients (3.73% of all patients) from University Medical Centre did not come back to their gastroenterologist. They were most probably controlled by their general practitioner, but we are not aware of their UBT results. And many more dropout patients from other medical centers could be treated in the same way. Real patients' compliance was never an issue, also in our previous reports / studies.[12,13]

H. pylori resistance to clarithromycin is still low in Slovenia. It was 10.5% in a recently published study and 25.9% for metronidazole.[12] In our Hp-EuReg data primary resistance to clarithromycin was recorded in a small subgroup of patients and was 14.3% and 28.6% for metronidazole. That can explain the still relatively good eradication results for 7 day triple therapy (TT). The PP eradication rate for PPI A C was 88.7% (72.0% mITT) and 85.2% PP for PPI C M (84.4% mITT). This is an acceptable eradication rate in PP analysis, but still not satisfactory, because it did not reach > 90% eradication rate. In some other parts of the world due to the increasing incidence of *H. pylori* resistance to clarithromycin, the cure rates of 7 day triple therapy (TT) have decreased to less than 80%, which is

TABLE 4. First line treatment results for treatment regimens with more than 15 patients

	mITT			PP		
Treatment	**N**	**Success % (95% C.I.)**		**N**	**Success % (95% C.I.)**	
Clarythromycin, amoxicillin, PPI, 7 days	664	**72.0%**	(68.6%–75.4%)	538	**88.7%**	(85.9%–91.3%)
Clarythromycin, metronidazole, PPI,7 days	486	**84.4%**	(81.2%–87.5%)	481	**85.2%**	(82.0%–88.4%)
Clarythromycin, amoxicillin, PPI, 10 days	38	**55.3%**	(39.1%–71.1%)	27	**77.8%**	(60.7%–92.9%)
Clarythro., amoxicillin., metro., PPI, 7 days	17	**88.2%**	(70.6%–100%)	15	**93.3%**	(77.8%–100%)

metro. = metronidazole; mITT = modified intention to treat; PP = per protocol; PPI = proton pump inhibitor

TABLE 5. Second line treatment results for treatment regimens with more than 15 patients

		mITT			PP	
Treatment	**N**	**Success % (95% C.I.)**		**N**	**Success % (95% C.I.)**	
Amoxicillin, Levofloxacin, PPI, 14 days	70	**87.1%**	(78.8%–94.6%)	65	**92.3%**	(85.3%–98.3%)
Amoxicillin, Levofloxacin, PPI, 10 days	24	**91.7%**	(78.6%–100%)	23	**95.7%**	(85.7%–100%)
Amoxicillin, Metronidazole, PPI, 7 days	18	**44.4%**	(21.1%–68.4%)	17	**47.1%**	(23.1%–72.2%)
Amoxicillin, Metronidazole, PPI, 10 days	16	**87,5%**	(68.4%–100%)	15	**93.3%**	(77.8%–100%)

C. I. = confidence interval; mITT = modified intention to treat; PP = per protocol; PPI = proton pump inhibitor

considered to be unacceptably low (14). Maastricht IV suggest not to use 7 day triple therapy in countries with *H. pylori* resistance to clarithromycin over 15%. Our *H. pylori* resistance rate to clarithromycin is still under this value, but we must continue to audit eradication rates with triple therapies in Slovenia as well as continuously measure primary *H. pylori* resistance rate to clarithromycin and other antibiotics.

Ten different 7-14 days triple combinations were used as a first line therapy. In our last *H. pylori* treatment guidelines[7] only two TT (PPI A C and PPI C M) were recommended. This shows us that real clinical practice in Slovenia is not ideal, which was also recognized in some other countries shown in Hp-EuReg data.[10]

We did not show any benefits of esomeprazole over other PPIs in the eradication rates as was shown in some other studies.[10,15] Because Caucasians have higher prevalence of high metabolizers (56%-81%) compared to Asians, higher doses of esomeprazole or rabeprazole are recommended, as they can control gastric pH adequately and allow better antibiotic efficacy.[16,17]

When *H. pylori* infection is found, it is very important to control the eradication rate and prescribe second or even further treatments to cure the infection.[2] In our data, dropout rate for second line therapy is still too high (6.3%). Results in Hp-EuReg are even worse with only 27% of first line eradication failures being retreated.[10] In Maastricht IV quadruple bismuth therapy is recommended as the second line treatment in low clarithromycin resistant regions.[2] The fact is that this therapy is not available in Slovenia at this moment. That is why the majority of second line treatments were 14 days PPI A L. In the National recommendation[7] only 14 day therapy should be used as a second line treatment. But in real practice, gastroenterologists use therapies from 7-14 days. This variations need to be corrected, because longer duration of second line therapies mean also better cure rates.[2,18] Our eradication rate for PPI A L is 92.3% in PP group and 87.1% in mITT group, which is a satisfactory result. We know that this is due to low *H. pylori* resistance to quinolones in Slovenia (3.1–4.4%).[19,20]

Other possible second line treatment could also be sequential or non-bismuth concomitant therapy with PPI and all three antibiotics (C, M, E). This therapy has been proven to be very effective (> 90% by ITT) in Slovenia[10] but is not used at the moment in clinical practice. These therapies can be effective also in the regions with *H. pylori* resistance to clarithromycin > 15%.[21-23] Only if dual resistance to clarithromycin and metronidazole is > 15%, the eradication rate of non-bismuth quadruple therapies will be impaired and bismuth quadruple therapies should be used.[24]

In the third and fourth line treatment PPI A L was used in some patients not treated with this regimen before, as well as bismuth quadruple therapies. Some patients were treated with 14 day therapies, but not all, which should also be corrected.

In Maastricht recommendations culture and antibiotic susceptibility should be done after two unsuccessful therapeutic attempts[2], but we seldom use this approach. The reason for this is non-reimbursement for culture by our National health fund.

One patient has been treated for the fifth time and one for the sixth time, both successfully. So finally all patients who were compliant with the prescribed therapeutic regimens were eradicated of *H. pylori* infection in the end, which is similar to our and international previously published data.[13,25]

Conclusions

Hp-EuReg is a very important clinical registry which helps us audit real clinical practice in the field of *H. pylori* eradication as well as collect eradication rates for different first, second line

and beyond treatments. From the analysis of our Slovenian data we can figure out some clinically important conclusions:

Seven days PPI A/M /C results has unacceptable low mITT eradication rates. Treatment duration should be prolonged to 14 days.

Dropout rate is too high. We must provide all general practitioners with the possibility to use urea breath test or monoclonal stool antibody test in all patients with *H. pylori* eradication therapies. No patients should be without confirmation of eradication success.

Treatment failures of the first line regimen should be retreated according to National guidelines, that is with 14 day PPI A L regimen

Primary *H. pylori* resistance to antibiotics and treatment results should be continuously monitored

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References

1. Hunt RH, Xiao SD, Megraud F, Leon-Barua R, Bazzoli F, van der Merwe S, et al. World Gastroenterology Organization. Helicobacter pylori in developing countries. World Gastroenterology Organisation Global Guideline. *J Gastrointestin Liver Dis* 2011; **20:** 299-304. doi: 10.1097/MCG.0b013e31820fb8f6
2. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, et al. Management of Helicobacter pylori infection – the Maastricht IV/Florence Consensus Report. *Gut* 2012; **61:** 646-64. doi: 10.1136/gutjnl-2012-302084
3. International Agency for Research on Cancer. Infection with Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61:** 177-240.
4. IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* Eradication as a Strategy for Preventing Gastric Cancer. Lyon, France: International Agency for Research on Cancer IARC Working Group Reports 2014; **8:** 1-181.
5. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012; **13:** 607-15. doi: 10.1016/S1470-2045(12)70137-7
6. Asaka M, Kato M, Takahashi S, Fukuda Y, Sugiyama T, Ota H, et al. Japanese Society for Helicobacter Research. Guidelines for the management of Helicobacter pylori infection in Japan: 2009 revised edition. *Helicobacter* 2010; **15:** 1-20. doi: 10.1111/j.1523-5378.2009.00738.x
7. Tepeš B, Štabuc B. [Slovenian Society for Gastroenterology and Hepatology Guidelines on the management of Helicobacter pylori infection]. Guidelines on the management of Helicobacter pylori infection. [Slovenian]. *Zdrav Vestn* 2011; **80:** 647-56.
8. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al**.** Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015; **64:** 1353-67. doi: 10.1136/gutjnl-2015-309252
9. Graham DY, Dorea MP. Helicobacter pylori therapy: a paradigm shift. *Expert Rev Anti-infe* 2016; **14:** 577-85. doi: 10.1080/14787210.2016.1178065
10. McNicholl AG, Gasbarrini A, Tepeš B, Bordin DS, Lerang F, Leja M, et al. Pan-European registry on *H. pylori* management (HP-EUREG). *Gastroenterology* 2016; **150:** S875-76. doi: 10.1016/S0016-5085(16)32952-3
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377-81. doi: 10.1016/j.jbi.2008.08.010
12. Tepeš B, Vujasinović M, Šeruga M, Stefanovič M, Forte A, Jeverica S. Randomized clinical trial comparing 10-day sequential, 7-day concomitant and 7-day standard triple therapies for Helicobacter pylori eradication. *Eur J Gastroenterol Hepatol* 2016; **28:** 676-83. doi: 10.1097/MEG.0000000000000590
13. Tepeš B, Zvezdana O. [Cumulative Helicobacter pylori eradication rates in Slovenia in the year 2008]. [Slovenian]. *Zdrav Vestn* 2010; **79:** 19-24.
14. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59:** 1143-53. doi: 10.1136/gut.2009.192757
15. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2012; **36:** 414-25. doi: 10.1111/j.1365-2036.2012.05211.x
16. Serrano D, Torrado S, Torrado-Santiago S, Gisbert J P. The influence of CYP2C19 genetic polymorphism on the pharmacokinetics/- pharmacodynamics of proton pump inhibitor-containing Helicobacter pylori treatments. *Curr Drug Metab* 2012; **13:** 1303-12. doi: 10.2174/138920012803341393
17. Tang HL, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of *H. pylori* infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS One* 2013; **8:** e62162. doi: 10.1371/journal.pone.0066730
18. Tai WC, Lee CH, Chiou SS, Kuo CM, Kuo CH, et al. The clinical and bacteriological factors for optimal levofloxacin-containing triple therapy in second-line Helicobacter pylori eradication. *PLoS One* 2014; **9:** e105822. doi: 10.1371/journal.pone.0105822
19. Jeverica S, Tepeš B, Ihan A, Skvarč M. [Primary resistance of Helicobacter pylori]. [Slovenian]. *Zdrav Vestn* 2010; **79:** 25-30.
20. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; **62:** 34-42. doi: 10.1136/gutjnl-2012-302254
21. Molina-Infante J, Lucendo AJ, Angueira T, Rodriguez-Tellez M, Perez-Aisa A, *et al.* Optimised empiric triple and concomitant therapy for Helicobacter pylori eradication in clinical practice: the OPTRICON study. *Aliment Pharmacol Ther* 2015; **41:** 581-9. doi: 10.1111/apt.13069
22. McNicholl AG, Marin AC, Molina-Infante J, Castro M, Barrio J, Ducons, et al. Randomised clinical trial comparing sequential and concomitant therapies for Helicobacter pylori eradication in routine clinical practice. *Gut* 2014; **63:** 244-9. doi: 10.1136/gutjnl-2013-304820
23. Molina-Infante J, Gisbert JP. Optimizing clarithromycin-containing therapy for Helicobacter pylori in the era of antibiotic resistance. *World J Gastroenterol* 2014; **20:** 10338-47. doi: 10.3748/wjg.v20.i30.10338
24. Graham DY, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014; **12:** 177-86. doi: 10.1016/j.cgh.2013.05.028
25. Rokkas T, Sechopoulos P, Robotis I, MargantinisG, Pistiolas D. Cumulative *H. pylori* eradication rates in clinical practice by adopting first and second line regimens proposed by Maastricht III consensus and a third line empirical regimen. *Am J Gastroenterol* 2009; **104:** 21-5. doi: 10.1038/ajg.2008.87

research article

Premalignant gastric lesions in patients included in National colorectal cancer screening

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Background. Gastric cancer is the fifth most common malignancy in the world with almost one million new cases annually. Helicobacter pylori infection causes 89% of all gastric cancers. Premalignant lesions (atrophy and intestinal metaplasia) develop after several decades of inflammation. Secondary prevention with gastroscopy is possible, but it is costly and has a low compliance rate. Alternative procedures like serology testing for pepsinogen I and II and pepsinogen I/II ratio are available to select patients for surveillance gastroscopies.

Patients and methods. In seven outpatient endoscopic units, 288 patients (154 men; 53.5%), average age 60.68 years, tested positive in National colorectal cancer screening programme SVIT, were included in the study. Gastropanel (BioHit, Finland) was used as a serologic biopsy method.

Results. We found 24 patients (12 men, mean age 63.7 years) with pepsinogen (pepsinogen I/II < 3 and/or pepsinogen I < 30 µg/L). Premalignant changes were found on gastric biopsies in 21 patients (7.3% incidence). Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) ≥ 1 was found in 20 patients; Operative Link for Gastritis Assessment (OLGA) ≥ 1 was found in 19 patients. Combined accuracy for preneoplastic lesions in Gastropanel positive patients was 87.5%. H. pylori seropositivity was found in 219 patients (76%). Only 24% of our population had normal results.

Conclusions. Gastropanel test has proven to be a reliable non-invasive test for advanced gastric preneoplastic lesions that can select patients for further gastroscopy. We found high H. pylori seropositivity in older age groups in Slovenia.

Key words: gastropanel; Helicobacer pylori; atrophy; intestinal metaplasia; gastric cancer

Introduction

Gastric cancer (GC) remains the fifth most common malignancy with almost one million new cases annually and is responsible for 9% of all cancer related deaths in the world (third place).[1] In Slovenia, the average incidence of gastric cancer in the period from 2009 to 2013 was 479 new cases of gastric cancer per year. The incidence rate was higher for men (29.1/100,000) than for women (17.8/100,000), with only 28% five-year survival rate.[2]

Helicobacter pylori (H. pylori) is grade I carcinogen and responsible for 89% of all gastric cancers.[3] Several decades of infection with H. Pylori can cause some preneoplastic changes, atrophy and intestinal metaplasia, in half of the infected patients.[4] Primary gastric cancer prevention program would be a National screening program for H. pylori infection with eradication of those infected. Secondary gastric cancer prevention program would be possible if we could find patients with severe preneoplastic changes in the stomach and offer them regular upper gastrointestinal endoscopies. Population-based screening by endoscopy for detection of these preneoplastic lesions is not feasible, except in Japan and Korea.[5,6] In Western countries, regular endoscopic follow-up is offered to patients with endoscopically visible preneoplastic lesions according to MAPS recommendations[7,8], but this represents only opportunistic secondary prevention.

Serologic biopsy – measuring pepsinogen I and pepsinogen II (PGI, PGII), Gastrin 17 (G 17) and H. pylori antibodies in the serum can select those patients with preneoplastic gastric lesions. In case of corpus atrophy and intestinal metaplasia, the production of pepsinogen I goes down more than pepsinogen II, which is produced also in antrum. Gastropanel (Biohot Ojy, Finland) has set cut-off for corpus atrophy at PGI/PGII < 3 and/or PGI < 30 μg/L).

If a patient is not on PPI therapy, increased Gastrin 17 can be another marker of low gastric acid secretion and corpus atrophy. Gastrin 17 is lower than normal in case of atrophy in antrum, or in case of gastric hypersecretion.[9] H. pylori seropositivity is a risk factor for gastric cancer and up to 2.9% of infected patients can develop gastric cancer in their lifetime.[10]

Serologic biopsy is more accurate in the diagnosis of corpus atrophic gastritis (CAG) than antral atrophic gastritis (AAG) with 70.2% *vs.* 51.6% pooled sensitivity and 93.9% *vs.* 84.1% pooled specificity.[11] The serologic biopsy can be of help in finding those patients in the population who have advanced premalignant gastric lesions. This method is already used in Japan, China and Finland.[12-15]

In our multicenter prospective study, we wanted to assess the accuracy of serologic biopsy (Gastropanel) in the diagnosis of premalignant gastric lesions (primary objective of the study) as well as the prevalence of H. pylori infection (secondary objective of the study) in a population of patients included in a National colorectal cancer screening program (age 50 to 74 years) who are FIT positive and thus referred to coloscopy.

Patients and methods

Patients included in the National colorectal cancer screening, tested FIT positive, and scheduled for screening colonoscopy in seven outpatient endoscopic units were invited to participate in the study. Exclusion criteria were use of PPI or H2 blockers in the previous two weeks. Those that fulfilled the criteria and signed the Informed Consent Statement were included.

Fasting serum with EDTA (2 X 5ml) were frozen to -20°C and transported on dry ice to Central laboratory at the Institute for Microbiology and Immunology at the Medical Faculty in Ljubljana, where it was frozen and stored at -80°C. Byohit Elisa test was used for PGI and PGII, G 17, and anti-H. pylori antibodies (IgG-Hp). According to producer data, normal values are: PGI 30–165 μg/L, PGII 3–15μg/L, PGI/PGII 3–20, G 17 < 5 pmol/L, H. pylori antibodies < 30 EIU. If PGI/PGII was < 3 and/or PGI < 30 μg/L, patients were invited to upper gastrointestinal endoscopy.[16,17]

Five biopsies (two from the lower and upper curvature 3 cm from the pylorus, one from incisura angularis, and two from lower and upper curvature of middle corpus) and two biopsies (from antrum and corpus) for rapid urease test (RUT) were taken. According to updated Sydney protocol and Operative Link for Gastritis Assessment (OLGA) / Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) classification, the histopathological analysis was performed by expert gastrointestinal pathologist.[18-20]

Patients who were H. pylori positive (positive anti-H. pylori antibodies or histology) and have normal pepsinogen levels took the urea breath test; according to national recommendations. If the result was positive, they received a 7-day triple regimen.[21]

The primary objective of the study was to detect patients with preneoplastic conditions (*i.e.* atrophic gastritis/intestinal metaplasia) in stomachs of fecal immunochemical test (FIT) positive patients included in National colorectal cancer screening with serologic biopsiy (GastroPanel®, Byohit, Helsinki, Finland).

The secondary objective of the study was to determine the prevalence of H. pylori infection in the age group from 50 to 74 years.

TABLE 1. Demographic data of patients included

Patients	Number	Percentage
Men	154	53.5%
Women	134	46,5%
Total	288	100%
50–60 years	134	46.5
61–70 years	120	41.7
70 +	34	11.8

Statistical analysis

The results of the Gastropanel testing (in Excel format) were submitted to Biohit Oyj (Helsinki, Finland) for final analysis using the GastroSoft® (Biohit Oyj) interpretation software.[16,22] All statistical analyses were performed using the SPSS 23.0.0.2 for Windows (IBM, Armonk, NY, USA) and STATA/SE 14.1 software (Stata Corp., College Station, TX, USA). Frequency tables were analyzed using the Chi-square test, with likelihood ratio (LR) or Fischer's exact test being used to assess the significance levels between the categorical variables. Using the exact method, odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated where appropriate. Differences in the means of continuous variables were analyzed using the non-parametric tests (Mann-Whitney, Kruskal-Wallis), with the mean (95% CI) values being derived from analysis of variance (ANOVA).

Ethics

The study was registered at the National Ethical Committee of the Ministry of Health under number 158/07/13 and was conducted in accordance with the Declaration of Helsinki, consistent with Good Clinical Practices recommendations.

Results

In seven SVIT endoscopic units, 288 patients, 154 men (53.5%) and 134 women (46.6%), average age 60.68 years (from 50–75), were included (Table 1). Results of Gastropanel for different age groups and sex are shown in Tables 2 and 3.

After data (in Excel) have been processed by using the GastroSoft®(Biohit Oyj) interpretation software, 4 different phenotypes of gastric histology by serologic biopsies (Gastropanel) have been found (normal Gastropanel, H. pylori gastritis, Corpus atrophic gastritis, Antrum atrophic gastritis) (Table 4).

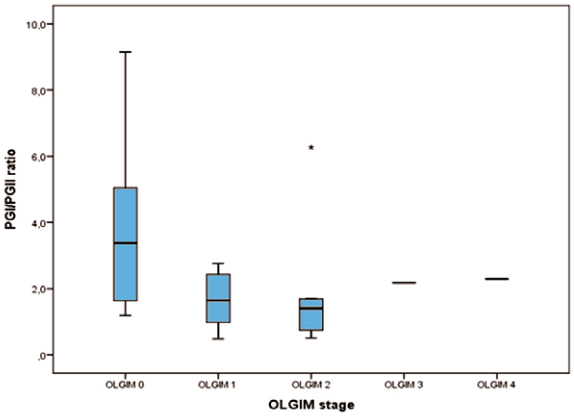

FIGURE 1. Prostaglandin I (PGI) / Prostaglandin II (PGII) ratio according to Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) stage.

Only 24% of our population had a normal Gastropanel test (no premalignant lesions and

TABLE 2. Gastropanel data for different age groups

	Age range	N	Mean	Std. Deviation	Std. Error
G 17 basal (pmol/L)	50–59 years	105	7.1860	8.6474	0.8439
	60–69 years	99	17.8350	99.0131	9.9512
	70+ years	32	8.9800	10.7870	1.9069
	Total	236	11.8970	64.5188	4.1998
PGI (µg/L)	50–59 years	134	95.9870	42.1806	3.6438
	60–69 years	120	97.9820	42.5086	3.8805
	70+ years	34	87.4010	53.5304	9.1804
	Total	288	95.8050	43.7446	2.5777
PGII (µg/L)	50–59 years	134	11.7030	10.3706	0.8959
	60–69 years	120	12.1780	9.4390	0.8617
	70+ years	34	12.9740	9.4896	1.6275
	Total	288	12.0480	9.8640	0–0581
PGI/PGII ratio	50–59 years	134	10.0840	4.4246	0.3822
	60–69 years	120	9.6950	4.6364	0.4232
	70+ years	34	7.6100	3.7772	0.6478
	Total	288	9.6300	4.4953	0.2849
Helicobacter pylori Ab titre (EIU)	50–59 years	134	72.9270	46.5802	4.0239
	60–69 years	120	80.8910	42.3679	3.8676
	70+ years	34	91.2500	51.0485	8.7547
	Total	288	78.4090	45.6677	2.2610

G 17 = Gastrin 17; PGI = Prostaglandin I; PGII = Prostaglandin II

TABLE 3. Gastropanel data for men and women

	N	Mean	Std. Deviaton	Std. error
G 17 basal (pmol/L)	W 109	16.4890	94.3688	9.0389
	M 127	7.9550	9.8272	0.8720
	T 236	11.8670	64.5188	4.1998
PGI (µg/L)	W 134	95.4210	44.0496	3.8053
	M 154	96.1380	43.6186	3.5149
	T 288	95.8050	43.7446	2.5777
PGII (µg/L)	W 134	13.1840	12.5659	1.0855
	M 154	11.0600	6.5683	0.5293
	T 288	12.0480	9.8640	0.5812
PGI/PGII ratio	W 134	9.4370	4.5881	0.3963
	M 154	9.7980	4.4210	0.3563
	T 288	9.6300	4.4953	0.2649
Helicobacter pylori Ab titre (EIU)	W 134	75.8700	47.1760	4.0754
	M 154	80.6170	44.3496	3.5738
	T 288	78.4090	45.6677	2.6910

G 17 = Gastrin 17; PGI = Prostaglandin I; PGII = Prostaglandin II

no H. pylori infection). The vast majority of them (70.5%) had H. pylori gastritis with no premalignant lesions and they were all asymptomatic. According to GastroSoft®, only 5.2% of the population had corpus atrophic gastritis (CAG) and 0.3% had antral atrophic gastritis (AAG).

Differences among age groups or sex were not statistically significant. Only PGI/PGII (p = 0,016) as well as PGI (p = 0,019) was significantly lower in older age group. PGI/PGII as well as PGI was lower in higher OLIM stage (Figure 1).

H. pylori seropositivity was found in 219 patients (76%; Table 5). Patients in younger age groups have lower seropositivity for H. pylori (70.1%) than older age groups. The oldest age group has the highest H. pylori seropositivity (85.3%); the differences between groups were statistically significant (P = 0.005).

Gastropanel test found only 24 patients (12 women, 12 men, mean age 63.5; from 50 – 75 years) with PGI/PGII < 3 and/or PGI < 30 µg/L. Those patients were examined by upper gastrointestinal endoscopy.

Premalignant changes (intestinal metaplasia/atrophy) was found in 21 patients. In 5 of those 21 patients no H. pylori infection could be found. Atrophic gastritis - OLGIM ≥ 1 was found in 20 patients; OLGA ≥ 1 was found in 19 patients. Combined accuracy for preneoplastic lesions in Gastropanel positive patients was 87.5%.

Incidence rate of OLGIM/OLGA ≥ 1 as criteria for atrophic gastritis in our study population was 7.3% (6.9% for OLGIM and 6.6% for OLGA). We found 3 patients with CAG, 1 patient with AAG, and 17 patients with chronic atrophic pangastritis.

Discussion

In countries with high incidence rate of gastric cancer, national programs for secondary prevention and early gastric cancer detection have been put in place. In Japan, they use barium double-contrast radiography combined with endoscopy from 1960, or direct gastroscopy in recent years. A total of 3,000 to 6,000 gastric cancer cases are detected annually. Among these cases, EGC (early gastric cancer) accounts for approximately 50% to 70%. An estimated 50% of patients undergo resection or delamination of the gastric mucosa through endoscopy.[23] In Korea, the direct upper gastrointestinal series, or endoscopic detection (or a combination) was adopted above the age of 40 as a way of gastric cancer screening and takes place every two years. Owing to the early diagnosis and treatment of gastric cancer, the 5-year survival rate of gastric cancer in Korea gradually increased from 40% during the 1990s to more than 60% at the beginning of this century.[24]

To improve the compliance and to reduce the costs, serologic biopsy has been introduced in Asia. It allows selection of patients with higher risk for preneoplastic gastric changes and reduces the endoscopic workload and costs. Since the 1990s, the detection of serum PG combined with endoscopy has been conducted in Japan to screen for gastric cancer. Miki *et al*. reported that among 101,892 Japanese, 125 cases of gastric cancer were detected using serum PG and endoscopy, with a detection rate for cancer of 0.12%. Among these cases, EGC accounted for 80% (25). This combined approach is now in place also in some regions of China.[13,14,28,29]

Gastric cancer incidence is the most prevalent in certain countries of East Asia, but Eastern and Central parts of Europe are on the second place regarding incidence of gastric cancer. In Slovenia, average gastric cancer incidence is 23.4/100,000 with -0.3% change in incidence per year in the last 10 years.[2]

H. pylori is the main carcinogen in gastric carcinogenesis responsible for 89% of all gastric cancers.[3] Slovenian Association for Gastroenterology

and Hepatology Recommendations for H. pylori diagnosis and treatment clearly stated that we should start with primary prevention in a way of screen and treat for H. pylori in population between 20 and 30 years before preneoplastic conditions develop.[28] At the moment, we practice opportunistic prevention for our elderly population according to MAPS (Management of precancerous conditions and lesions in the stomach) recommendations.[4,7]

The prevalence of preneoplasic changes in the stomach is 2%–5% in the developed world[29], but it is much higher in the developing world. The prevalence of preneoplastic lesions in St Petersburg study was 10.8% [30], while in our study it was 7.3%. The real prevalence is probably slightly higher, because we know that sensitivity of Gastropanel is 70.2% for CAG. Gastropanel missed some, especially early preneoplastic stages, so absolute numbers of preneoplastic changes in the population are higher. In some well conducted European studies, the sensitivity and specificity of the serologic biopsy to diagnose normal stomach mucosa in the population-based sample of the 1,000 subjects were 89% (95% CI 86–92%) and 92% (90–95%), respectively.[31]

Gastropanel software analysis found one patient with AAG and 15 patients with CAG. According to definite hystopathologic analysis, 1 patient had AAG, 3 CAG, and all the other Chronic atrophic pangastritis.[17] In our opinion, accuracy of Gastropanel for any Chronic atrophic gastritis is good, but this test is not very accurate in distinguishing between fenotipic chronic atrophic gastritis subtypes. The problem partially lies in specificity of G 17 as a marker of antrum atropy. G 17 can be low in patients with antral atrophy, but also in case of high gastric acid output. On the other hand, high G 17 is present in patients with corpus atrophy as well as in patients on PPIs.[11]

Our study was not designed in a way to be able to calculate sensitivity and specificity of Gastropanel for chronic atrophic changes in the stomach. On the other hand, the majority of patients tested positive for preneoplastic conditions in the stomach by gastropanel were also positive with histology. In our study, the accuracy of Gastropanel for detection of preneoplastic condition in the stomach was 87.5%. This makes Gastropanel a suitable first step test in secondary prevention of gastric cancer; positive patients can then be sent to endoscopy.

Worldwide, the age-specific incidence of gastric cancer of intestinal type is approximately twice as high in males as in females. We did not find statistically significant difference in H. pylori infection rate in our study, neither in preneoplastic changes of stomach mucosa between men and women. There are evidences that this difference in gastric cancer incidence can be caused by hormonal influences.[32,33]

TABLE 4. Histologic phenotypes of gastric mucosa according to Gastropanel results

	Frequency	Percent	Valid percent	Cumulative percent
Normal panel	73.00	25.30	25.30	25.30
HP gastritis	199.00	69.10	69.10	94.40
AGA	1.00	0.30	0.30	94.80
AGC	15.00	5.20	5.20	100.00
Total	288	100	100	

AGA = Atrophic gastritis of antrum; AGC = Atrophic gastritis of corpus

TABLE 5. Age Group H. pylori positive vs. negative

Age Group		Hp positive vs negative		Total
		HP+	Hp-	
50-59	Count	94	40	134
	% within Age Group	70.1%	29.9%	100.0%
60-69	Count	96	24	120
	% within Age Group	80,0%	20.0%	100.0%
70+	Count	29	5	34
	% within Age Group	85.3%	14.7%	100.0%
Total	Count	219	69	288
	% within Age Group	76.0%	24.0%	100.0%

The incidence of gastric cancer increases exponentially with age. However, in multivariate analyses, age is not an independent risk factor for gastric cancer, it is only a surrogate marker for H. pylori infection rate which is a birth cohort effect.[34,34] We found lower PGI and PGI/PGII ratio in older age groups. We also found that values of PGI and the PGI/PGII ratio were lover in the higher stage of OLGIM, what has also been previously reported.[36]

The secondary objective of the study was to determine the prevalence of H. pylori infection in the age group from 50 to 74 years. Gubina *et al*. published H. pylori epidemiologic study in 2005.[37] The average prevalence of H. pylori infection in Slovenia was 25.1%, while the highest prevalence rate was 54% in the age group > 60 years. We were surprised that in our study H. pylori seropositivity was 76% and significantly increasing with age. In our epidemiologic study[37], number of patients

older than 60 years was low (76 participants), what can represent a selection bias to the study and partially explain lower H. pylori seropositivity in older population.

In five of those patients with preneoplastic lesions, H. pylori was negative. This was found also in other studies.[17,25] When preneoplastic changes are diffused, H. pylori could not persist in the stomach anymore, but this does not prove that those patients were not infected previously in their lives.

This high H. pylori prevalence in our study population is comparable to the prevalence of H. pylori in St Petersburg study (76.7%) and in Astana study (76.5%)[38], albeit their population was younger than in our study. The high prevalence of H. pylori in Slovenia goes in parallel with medium high gastric cancer prevalence rate and with predictions that our prevalence of gastric cancer will stay high in the future.[2] This prediction speaks for itself that a program for secondary gastric cancer should be put in place in Slovenia. The most feasible program would be a two-step program with serologic gastric biopsy and gastroscopy for those tested positive.

Conclusions

Gastropanel test has proved to be a reliable non-invasive test for advanced gastric preneoplastic lesions that can select patients for further gastroscopy and biopsy in a National secondary gastric cancer prevention program. H. pylori prevalence rate in the age group 50–74 is with 76% still very high.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C,Rebelo M. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136:** E359-386. doi: 10.1002/ijc.29210
2. Zadnik V, Primic Zakelj M, Lokar K, Jarm K, Ivanus U, Zagar T. Cancer burden in Slovenia with the time trends analysis. *Radiol Oncol* 2018; 52(1): 7-13.; **51:** 47-55. doi: 10.1515/raon-2017-0008
3. IARC/WHO. Helicobacter pylori eradication as a strategy for preventing gastric cancer. International Agency for Research on Cancer/ World Health Organisation; 2014. [citated 2017 Avg 15]. Available at http://www.iarc.fr/en/publications/pdfs-online/wrk8/ or www.iarc.fr/en/ publications/pdfs-online/wrk8/. ISBN 978-92-832-2454-9
4. Malfertheiner P, Megraud F, O 'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. *Gut* 2017; **66:** 6-30. doi: 10.1136/gutjnl-2012-302084
5. Nakajima S. Gastric cancer screening in Japan, now and tomorrow. *Nihon Rinsho* 2012; **70:** 1686-93. doi: 10.1007/s101200200000
6. Choi IJ. Screening and surveillance of gastric cancer. *Korean J Gastroenterol* 2007; **49:** 15-22. doi: 10.4166/kjg.2009.54.2.67
7. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O Connor A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). *Endoscopy* 2012; **44:** 74-94. doi: 10.1055/s-0031-1291491
8. Tepeš B. Kavalar R. [Gastric cancer, screening possibilities and proposals for endoscopic and histologic follow-up of premalignant gastric lesions]. [Slovenian]. *Zdrav Vestn* 2010; **79:** 366-74. doi: https://doi.org/10.6016/290
9. Yuan Y. A survey and evaluation of population-based screening for gastric cancer. *Cancer Biol Med* 2013; **10:** 72-80. doi: 10.7497/j.issn.2095-3941.2013.02.002
10. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345:** 784-9. doi: 10.1056/NEJMoa001999
11. Syrjänen K. A Panel of Serum Biomarkers (GastroPanel®) in Non-invasive diagnosis of atrophic gastritis. Systematic review and meta-analysis. *Anticancer Res* 2016; **36:** 5133-44. doi: 10.21873/anticanres.11083
12. Matsushima M, Miki K, Ichinose M, Kakei N, Yahagi N, Suzuki T, et al. The clinical application of the serum pepsinogen I and II levels as a mass screening method for gastric cancer. In: Takahashi K, editor. *Aspartic proteinases: advances in experimental medicine and biology.* New York: Plenum Press; 1995. p. 139-43.
13. *Screening, early detection and treatment of cancer in China*. Dong ZW, editor. Beijing: People's Medical Publishing House; 2009.
14. Early detection and treatment of cancer committee. *Technical solution on early detection and treatment of cancer in China.* Beijing: People's Medical Publishing House; 2011.
15. Sipponen P. Biomarkers in clinical practice: a tool to find subjects at high risk for stomach cancer. A personal view. *Adv Med Sci* 2006; **51:** 51-3.
16. Väänänen H, Vauhkonen M, Helske T, Kääriäinen I, Rasmussen M, Tunturi-Hihnala H, et al. Nonendoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. *Eur J Gastroenterol Hepatol* 2003; **15:** 885-91. doi: 10.1097/01.meg.0000059169.46867.01
17. Agréus L, Kuipers EJ, Kupcinskas L, Malfertheiner P, Di Mario F, Leja M, et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. *Scand J Gastroenterol* 2012; **47:** 136-47. doi: 10.3109/00365521.2011.645501
18. Dixon M, Genta R, Yardley J, Correa P. Classification and grading of gastritis: the updated Sydney System. *Am J Surg Pathol* 1996; **10:** 1161-81.
19. Rugge M, Meggio A, Pennelli G, Piscioli F, Giacomelli L, De Pretis G, et al. Gastritis staging in clinical practice: the OLGA staging system. *Gut* 2007; **56:** 631-6. doi: 10.1136/gut.2006.106666
20. Capelle LG, de Vries AC, Haringsma J. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. *Gastrointest Endosc* 2010; **71:** 1150-8. doi: 10.1016/j.gie.2009.12.029

21. Tepeš B, Štabuc B. Slovenian society for gastroenterology and hepatology guidelines on the management of Helicobacter pylori infection. [Slovenian]. *Zdrav Vestn* 2011; **80:** 647-56. doi: https://doi.org/10.6016/216

22. Syrjänen KJ, Sipponen P, Härkönen M, Peetsalu A and Korpela S. Accuracy of GastroPanel testing in detection of atrophic gastritis. *Eur J Gastroenterol Hepatol* 2015; **27:** 102-4. doi: 10.1097/MEG.0000000000000215

23. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 2008; **38:** 259-67. doi: 10.1093/jjco/hyn017

24. Jung KW, Park S, Kong HJ, Won YJ, Boo YK, Shin HR, et al. Cancer statistics in Korea: incidence, mortality and survival in 2006-2007. *J Korean Med Sci* 2010; **25:** 1113-21. doi: 10.3346/jkms.2010.25.8.1113

25. Miki K, Ichinose M, Kawamura N, Matsushima M, Ahmad HB, Kimura M, et al. The significance of low serum pepsinogen levels to detect stomach cancer associated with extensive chronic gastritis in Japanese subjects. *Jpn J Cancer Res* 1989; **80:** 111-4.

26. Zhang X, Xue L, Xing L, Wang J, Cui J, Mi J, et al. Low serum pepsinogen I and pepsinogen I/II ratio and Helicobacter pylori infection are associated with increased risk of gastric cancer: 14year follow up result in a rural Chinese community. *Int J Cancer* 2012; **130:** 1614-9. doi: 10.1002/ijc.26172

27. Yuan Y. Population-based gastric cancer screening in Zhuanghe, Liaoning, from 1997 to 2011. *Zhonghua Zhong Liu Za Zhi* 2012; **34:** 538-42.

28. Tepeš B, Štabuc B. Slovenian Association for Gastroenterology and hepatology recommendations for the management of patients infected with Helicobacter pylori. *Zdrav Vestn* 2017 (in press).

29. Sipponen P, Graham DY. Importance of atrophic gastritis in diagnostics and prevention of gastric cancer: application of plasma biomarkers. *Scand J Gastroenterol* 2007; **42:** 2–10. doi: 10.1080/00365520600863720

30. Roman LD, Lukyanchuk R , Sablin OA, Araslanova,EI, Eklund C, Hendolin P, et al. Prevalence of H. pyloriInfection and atrophic gastritis in a population-based screening with serum biomarker panel (GastroPanel®) in St. Petersburg. *Anticancer Res* 2016; **36:** 4129-38.

31. Storskrubb T, Aro P, Ronkainen J, Sipponen P, Nyhlin H, Talley NJ, et al. Serum biomarkers provide an accurate method for diagnosis of atrophic gastritis in a general population: the Kalixanda study. *Scand J Gastroenterol* 2008; **43:** 1448-55. doi: 10.1080/00365520802273025

32. Sipponen P, Correa P. Delayed rise in incidence of gastric cancer in females results in unique sex ratio (M/F) pattern: etiologic hypothesis. *Gastric Cancer* 2002; **5:** 213-9. doi: 10.1007/s101200200037

33. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2012; **21:** 20-38. doi: 10.1158/1055-9965.EPI-11-0834

34. Sipponen P, Kekki M, Haapakoski J, Ihamäki T, Siurala M. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. *Int J Cancer* 1985; **35:** 173-7.

35. Roosendaal R, Kuipers EJ, Buitenwerf J, van Uffelen C, Meuwissen SG, van Kamp GJ, Vandenbroucke-Grauls CM. Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am J Gastroenterol* 1997; **92:** 1480-2.

36. Väänänen H, Vauhkonen M, Helske T, Kääriäinen I, Rasmussen M, Tunturi-Hihnala H, et al. Nonendoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. *Eur J Gastroenterol Hepatol* 2003; **15:** 885-91. doi: 10.1097/01.meg.0000059169.46867.01

37. Gubina M, Tepeš B, Vidmar G, Logar J, Wraber B, Poljanec J, Bricelj I, et al. The prevalence of Helicobacter pylori infection in Slovenia in 2005. *Zdrav Vestn* 2006; **75:** 169-73.

38. Benberin V , Bektayeva R, Karabayeva R, Lebedev A, AkemeyevaK , Paloheimo L, et al. Prevalence of H. pylori infection and atrophic gastritis among asymptomatic and dyspeptic adults in Kazakhstan. A Hospital-Based screening with a panel of serum biomarkers. *Anticancer Res* 2013; **33:** 4595-602.

research article

Computed tomographic perfusion imaging for the prediction of response and survival to transarterial chemoembolization of hepatocellular carcinoma

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Background. The purpose of this retrospective cohort study was to evaluate the clinical value of computed tomographic perfusion imaging (CTPI) parameters in predicting the response to treatment and overall survival in patients with hepatocellular carcinoma (HCC) treated with drug-eluting beads transarterial chemoembolization (DEBTACE).

Patients and methods. Between December 2010 and January 2013 eighteen patients (17 men, 1 woman; mean age 69 ± 5.8 years) with intermediate stage HCC underwent CTPI of the liver prior to treatment with DEBTACE. Treatment response was evaluated on follow-up imaging according to modified Response Evaluation Criteria in Solid Tumors. Pre-treatment CTPI parameters were compared between patients with complete response and partial response with a Student t-test. We compared survival times with Kaplan-Meier method.

Results. CTPI parameters of patients with complete response and others did not show statistical significant difference. The mean survival time was 25.4 ± 3.2 months (95%; CI: 18.7-32.1). Survival was statistically significantly longer in patients with hepatic blood flow (BF) lower than 50.44 ml/100 ml/min ($p = 0.033$), hepatic blood volume (BV) lower than 13.32 ml/100 ml ($p = 0.028$) and time to peak (TTP) longer than 19.035 s ($p = 0.015$).

Conclusions. CTPI enables prediction of survival in patients with intermediate stage HCC, treated with DEBTACE based on the pre-treatment values of BF, BV and TTP perfusion parameters. CT perfusion imaging can't be used to predict treatment response to DEBTACE.

Key words: hepatocellular carcinoma; computed tomography perfusion imaging; drug-eluting beads transarterial chemoembolization; response to treatment; survival

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer mortality in the world.[1] Patients with HCC are divided into five stages by the Barcelona Clinic Liver Cancer (BCLC) staging system according to pre-established prognostic variables. Those classified as intermediate or BCLC B stage present a mean 2-year survival of 49%. Transarterial chemoembolization (TACE) is the standard treatment for such patients.[1,2] Lately a new embolization agent called drug-eluting bead (DEB) has been introduced and several clinical studies have confirmed the benefits of DEBTACE with respect to

improved tumor response, reduced adverse effects and improved survival.[2-8]

The European Association for the Study of Liver (EASL) has proposed to assess response to loco-regional treatments by assessing the decrease in viable tumor volume, seen as a decrease in contrast-enhancing areas at conventional contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) (modified Response Evaluation Criteria in Solid Tumors (mRECIST)).[1,9] The number of treatment sessions with DEBTACE depends on the response of the tumor. As the therapy may be repeated and interchangeably applied, early assessment of treatment response is crucial. Early prediction of treatment response makes it possible to prevent unnecessary side effects and modify treatment plan or replace it with other more effective treatment modalities before tumor progression. Due to heterogeneity of the BCLC B stage patient population survival rates are variable and scattered across the literature.[1,3-6,10-12] Therefore, not all patients with intermediate stage HCC will derive similar benefit from TACE. Some may benefit from other treatment options which are currently approved or being explored. These include different TACE modalities, such as selective TACE or DEBTACE, transarterial radioembolization (TARE), combined approaches with radiofrequency ablation (RFA) or sorafenib.[1-4,13]

Current prognostic factors for the prediction of treatment response and survival in patients treated with TACE such as clinical performance, status of patient, number and size of tumors, presence of macrovascular invasion, extrahepatic spread and grade of hepatic damage are mainly based on clinical assessment and are included in BCLC classification.[1,13] However, the malignant nature of the tumor as well as other characteristics are not generally considered. Apart from well-known clinical factors related to tumor stage and liver function, remarkably few data are available upon other measurable predictive or prognostic factors for TACE treatment response and survival in intermediate stage HCC. Thus, careful selection of patients likely to respond and benefit from TACE using a noninvasive imaging biomarker seems important.[13,14]

Functional imaging techniques are technical improvement of conventional morphological techniques that can provide both qualitative and quantitative information on tumors.[15-17] Perfusion parameters are therefore theoretically good candidates for the evaluation of microscopic vascular differences between lesions with different pathological grade and for the assessment of treatment response, especially after chemoembolization, or during treatments with anti-angiogenic drugs.[18-26]

Computed tomographic perfusion imaging (CTPI) is a dynamic, contrast-enhanced, minimally invasive functional radiologic imaging technique. It allows for an objective, quantitative evaluation of tissue perfusion.[16] The basis for the use of CTPI in oncology is that the microvascular changes in angiogenesis are reflected by increased tumor vascularization in vivo.[18] High tumor angiogenesis activity is associated with distant metastases and is an adverse prognostic factor in cancers.[27,28] We can identify the degree of angiogenesis in tumors with invasive histologic biomarkers such as microvessel density (MVD) and vascular endothelial growth factor (VEGF). Many studies have shown a direct correlation between these invasive histologic biomarkers and tumor CTPI parameters.[15,20,29-31]

The purpose of this retrospective cohort study was to estimate the clinical value of CTPI parameters in predicting the response and survival to DEBTACE of patients with intermediate stage HCC.

Patients and methods

This retrospective cohort study took place at Clinical Institute of Radiology (CIR), University Medical Centre Ljubljana (UMCL). It was performed in accordance with the Helsinki declaration ethical standards for biomedical studies on human beings on the basis of patient charts held at Clinical Department of Gastroenterology and CIR UMCL. It was approved by Republic of Slovenia National Medical Ethics Committee on the 19th of August 2014 (118/08/14).

Study population and study design

From all the patients with HCC who had CTPI before treatment with TACE between December 2010 and January 2013 (the total number of patients was 38) only the patients with intermediate stage HCC treated with DEBTACE were selected. Examinations where CTPI analysis could not be performed due to technical reasons (the section of portal vein was not visible on recordings) were excluded from the study. We also excluded the patients whose perfusion parameters were not indicating an active HCC because of previous TACE treatments.

Thus, the final study cohort comprised 18 patients (17 men, 1 woman: mean age, 69 ± 5.8

years) who all underwent CTPI before treatment with DEBTACE. All patients were examined using a 64-slice dual-source CT (Siemens Medical Systems®, Erlangen, Germany) and after the examination data was transferred to outside work station (MultiModality Workplace; Siemens Healthcare). Treatment with DEBTACE was based on the consensus of the Liver Multidisciplinary Team Meeting, held weekly at our institution. All patients underwent at least two sessions of DEBTACE. It was performed in local anesthesia with superselective microcatheter technique with 2.4 F microcatheter (Progreat®, Terumo Europe N.V, Belgium). DEBs with a diameter of 100-300 μm (DC Beads®, Terumo Europe N.V, Belgium) were loaded with 50 -100 mg of doxorubicin. In patients with multifocal tumors, the position of the microcatheter was changed within the same session if necessary to ensure superselective DEB delivery in each lesion. Radiological follow up was performed every 3 months. Follow up imaging was performed with contrast enhanced four-phase CT or MRI of the liver enhanced with contrast medium specific for the liver. 64- and 16–slice multidetector CT (Siemens Medical Systems®, Erlangen, Germany) and 3 T MRI (Siemens Medical Systems®, Erlangen, Germany) were used. Treatment was repeated on demand, that is, in patients with residual or recurrent tumors observed by CT or MRI, according to the mRECIST and in agreement with recent expert opinions. Data from patient charts was inserted into clinical protocols. The following data were collected: age at CTPI, sex, clinical status of patient, etiology of liver cirrhosis, stage of liver cirrhosis according to Child-Pugh, size, number and position of lesions, laboratory parameters (blood screen, bilirubin, transaminase, urea, creatinine), portal vein permeability, extrahepatic spread of the disease, perfusion parameters (hepatic blood flow (BF), hepatic blood volume (BV), time to peak (TTP), permeability (PMB), arterial liver perfusion (ALP), portal venous perfusion (PVP) and hepatic perfusion index (HPI)) in target lesion, selectiveness of TACE, the use of microcatheter, the use of ConeBeam CT technology, type and size of embolization particles, the dose of chemotherapeutic (doxorubicin), number of DEBTACE procedures, response to treatment according to mRECIST criteria and survival.

CTPI protocol

CTPI was performed by using a 64-slice dual-source CT (Siemens Medical Systems®, Erlangen, Germany). The scan region of the tumor was based on the CT scan of the abdomen (120 kV, 180 mA) obtained without contrast medium during a breath hold at the end of expiration. The scanned region with CTPI consisted of 4 adjacent 6 mm thick sections. For lesions larger than 24 mm in diameter, the levels with the largest tumor diameter were selected. A dynamic study of the selected area was performed in a single breath hold at the end of expiration with the administration of 50 ml non-ionic contrast agent (Visipaque 320®, GE Healthcare) at a rate of 6 ml/s via a power injector by using a bolus tracking algorithm through an 18-gauge intravenous cubital cannula. CTPI scanning (100 mA, 80 kV, section thickness of 6 mm, rotation time 1 second, matrix 512 × 512 mm) was initiated 6 seconds after the injection start, and 4 contiguous sections of tissue were scanned every second for 55 seconds. The contrast agent administration was followed by a power injection of 20 ml of saline (at the same injection rate).

Computed tomographic perfusion analysis

Quantitative analysis of CTPI data was performed using commercially available software (Syngo Volume Perfusion CT Body; Siemens Healthcare). An integrated motion correction algorithm for anatomic alignment was applied. Volumes of interest were manually drawn around the target lesion, spleen, portal vein and aorta. For better determination of target lesion images of the target lesions in the baseline CT were used. The software then created quantitative maps of perfusion and calculated CTPI parameters and standard deviations. The parameters were calculated on the basis of the method described by Blomley *et al.* and Tshusima *et al*.[17,21] CTPI parameters were calculated in the volume of interest drawn around the borders of the tumor and in the tumor-free parenchyma. Several parameters can be derived from CTPI studies. Hepatic blood flow (BF), representing the flow rate through vasculature; Hepatic blood volume (BV), representing the volume of flowing blood; Time to peak (TTP), defined as the time from arrival of the contrast medium in major arterial vessels to the peak enhancement; Permeability (PMB), representing the total flow from plasma to interstitial space; Arterial liver perfusion (ALP), representing the flow rate through arterial vasculature; Portal venous perfusion (PVP), representing the flow rate through venous vasculature and Hepatic perfusion index (HPI), defined as the ratio

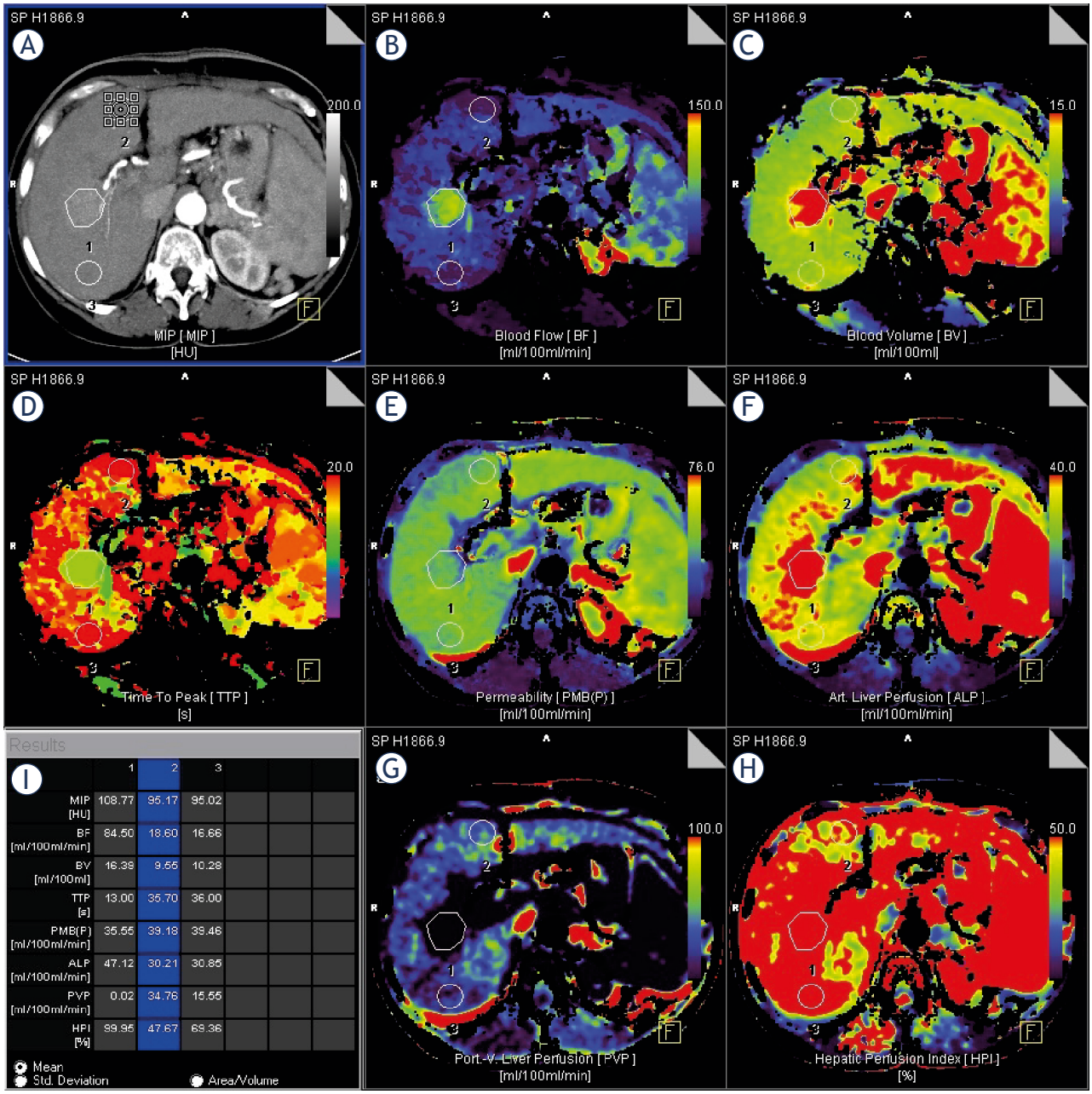

FIGURE 1. Computed Tomographic Perfusion Imaging of the liver. Image of a 65-year-old woman with hepatocellular carcinoma. **(A)** HCC in the segment VIII of the liver (1 – volume of interest in the the tumor, 2 – volume of interest in the normal liver parenchyma, 3 – volume of interest in the normal liver parenchyma). **(B)** Higher BF values in the tumor (84.50 ml/100ml/min) in comparison with normal liver parenchyma (18.60 and 16.66 ml/100ml/min). **(C)** Higher BV values in the tumor (16.39 ml/100ml) in comparison with the normal liver parenchyma (9.55 and 10.28 ml/100ml). **(D)** Lower TTP values in the the tumor (13.00 s) in comparison with the normal liver parenchyma (35.70 and 36.00 s). **(E)** Lower PMB values in the tumor (35.55 ml/100ml/min) in comparison with the normal liver parenchyma (39.18 and 39.46 ml/100ml/min). **(F)** Higher ALP in the tumor (47.12 ml/100ml/min) in comparison with the normal liver parenchyma (30.21 and 30.85 ml/100ml/min). **(G)** Lower PVP values in the tumor (0.02 ml/100ml/min) in comparison with the normal liver parenchyma (34.76 and 15.55 ml/100ml/min). **(H)** Higher HPI values in the tumor (99.95 %) in comparison with the normal liver parenchyma (47.67 and 69.36 %). **(I)** Calculation of perfusion parameters.

between arterial liver perfusion and total liver perfusion. Hepatic drawing was done by one reader in the presence of an experienced abdominal radiologist (Figure 1).

Statistical analysis

Statistical analysis was performed with IBM® SPSS® Statistics 20 (International Business Machines

Corp., Armonk, New York) for Windows software. Kolmogorov-Smirnov test was used to determine normality of our data. The Student t test for independent samples was used for comparing CTPI parameters between lesions with complete response and those with partial response. The threshold values for CTPI parameters used for survival analysis were established by using receiver operating characteristic (ROC). ROC analysis tested the ability of each CTPI parameter to help identify patients surviving longer than the follow-up period of two years. The point on the ROC curve furthest from the line of no discrimination was considered the optimum threshold value. Survival time was defined as the time between the date of first TACE and the date of death. A patient was considered lost to follow-up for all time points that exceeded the follow-up period for that patient. The Kaplan-Meier curves were used to illustrate the overall survival rates. Statistical significance was interfered at p less than 0.05. Categorical variables are expressed as frequencies and percentages. Quantitative variables are expressed as means and standard deviations (SD).

Results

Patient characteristics

The baseline demographic, clinical, laboratory and tumor staging characteristics of the patients included in the analysis are summarized in Table 1. Patients underwent CTPI 22 ± 49.7 days before treatment with DEBTACE. They were treated with a total of 62 DEBTACE procedures. The mean number of procedures per patient was 3.4 ± 1.5. Follow-up imaging was performed 4.9 ± 3.3 months after the first DEBTACE.

Computed tomographic perfusion and morphologic treatment response

We divided our target lesions on the basis of treatment response to DEBTACE determined at the follow-up imaging. Treatment response was described as complete or partial by mRECIST criteria. Lesions with complete response to treatment were in the first group, lesions with partial response in the second group. In the first group there were nine lesions, and in the second there were ten. We compared these groups with the use of Student t test for independent variables. Our results showed no statistically significant difference between our groups (Table 2).

TABLE 1. Baseline characteristics of the patients

Age [years]	**68.8 ± 5.8**
Sex (M/F), n [%]	17/1 [94.4/5.6]
Cirrhosis (yes/no), n [%]	16/2 [88.9/11.1]
Aetiology of cirrhosis, n [%] Alcohol HBV HCV Other	 7 [43.8] 3 [18.8] 1 [6.3] 5 [31.3]
Albumin [g/l]	38.3 ± 5.1
INR	1.2 ± 0.3
Total bilirubin [mmol/l]	23.6 ± 18.8
Child-Pugh score (points) A, n [%] B, n [%]	5.7 ± 0.8 14 [77.8] 4 [22.2]
Creatinine [μmol/l]	87.8 ± 22.8
AST [μkat/l]	1.1 ± 0.9
ALT [μkat/l]	0.9 ± 0.8
γGT [μkat/l]	1.9 ± 1.1
AFP [kIE/l]	174.5 ± 279.3
Portal vein thrombosis (yes/no), n [%]	3/15 [16.7/83.3]
Bilobar disease, n [%]	4 [22.2]
Unilobar disease, n [%] Right lobe, n [%] Left lobe, n [%]	14 [77.8] 13 [92.9] 1 [7.1]
Overall number of lesions, n Average number of nodules per patient	56 3.1 ± 2.1
Average of HCC nodule diameters [cm]	4.4 ± 1.8

AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = International normalized ratio; γGT = gamma-glutamyltranspeptidase. Quantitative variables are expressed as means and standard deviations. Categorical variables are expressed as frequencies and percentages

Patient outcome

The follow-up time from the first DEBTACE was on average 24.3 ± 13.1 months and 10 patients died in this time. The mean survival time was 25.4 ± 3.2 months (95% CI: 18.7-32.1). One-year and two-year survival was 83.3% and 50% respectively. Kaplan-Meier curves were used to illustrate overall survival rates. Patients were divided into two groups on the basis of threshold values for each CTPI parameter. Patients with a CTPI parameter value lower than the threshold value were placed in the "group 1" and patients with higher CTPI parameter value in "group 2". Threshold values were set at BF 50.4 ml/100ml/min (88.9% sensitivity, 66.7% specificity), BV 13.3 ml/100ml (88.9% sensitivity, 55.6% specificity), TTP 19 s (100% sensitivity, 44.4% specificity), PMB 40.2 ml/100ml/min (88.9%

sensitivity, 44.4% specificity), ALP 33.1 ml/100ml/min (55.6% sensitivity, 55.6% specificity), PVP 1.8 ml/100ml/min (88.9% sensitivity, 33.3% specificity), HPI 82.7% (77.8% sensitivity, 66.7% specificity). The number of patients in groups varies with different CTPI parameters. Statistically significant differences in mean survival times were seen at CTPI parameters BF, BV and TTP (p = 0.033, p = 0.028 in p = 0.015 respectively) (Table 3, Figure 2). There was no statistically significant difference in mean survival times with other CTPI parameters (PMB (p = 0.079), ALP (p = 0.691), PVP (p = 0.400) and HPI (p = 0.244)) (Table 3).

TABLE 2. CTPI Parameters of target lesions before treatment with TACE

	Complete response (n = 9)	Partial response (n = 10)	P
BF [ml/100ml/min]	36.3 ± 23.2	51 ± 31.6	0.271
BV[ml/100ml]	11.6 ± 5	14.4 ± 4.8	0.240
TTP [s]	26.3 ± 8.3	24 ± 7.8	0.551
PMB [ml/100ml/min]	37.3 ± 19.3	33.6 ± 10.9	0.616
ALP [ml/100ml/min]	38.7 ± 22.2	49 ± 28.9	0.400
PVP [ml/100ml/min]	20.8 ± 22.7	13 ± 17	0.404
HPI [%]	65.1 ± 30.7	78.6 ± 27.4	0.322

ALP = arterial liver perfusion; BF = hepatic blood flow; BV = hepatic blood volume; HPI = hepatic perfusion index; p = statistical significance; PMB = permeability; PVP = portal vein perfusion; TTP = time to peak. Quantitative variables are expressed as means with standard deviation.

Discussion

The BCLC guidelines for the treatment of HCC recommend TACE for patients with intermediate-stage HCC. Due to heterogeneity of the patient population tumor response and survival rates are variable.[1,4,5,9-11] The overall response rate for TACE treatment is about 50%, with the lowest reported around 15% and the highest around 85.6%.[1-8] Reported 1-, 2- and 3-year survival rates range from 37% to 91.5%, 14% to 75% and 58.8% to 71.4%, respectively.[1,3,4] Current prognostic factors for determination of treatment response and survival in patients treated with TACE are mainly based on clinical assessment and are included in the BCLC classification.[1,13] However, the malignant nature of the tumor, as well as its other characteristics, are not considered. Apart from the well-known clinical factors related to tumor stage and liver function, remarkably few data are available upon other measurable prognostic or predictive factors for TACE treatment response and survival of patients with intermediate stage HCC. Thus, careful selection of patients likely to respond and benefit from TACE using a noninvasive imaging biomarker seems important.[13,14] In the present study, we used pre-treatment CTPI parameters to determine if they could be used as predicting factors for treatment response and prognostic factors for survival.

We were not able to demonstrate a significant correlation between the values of pre-treatment CTPI parameters and the type of response to DEBTACE according to mRECIST criteria, although the mean values of CTPI parameters in the two groups do show some promise for future studies. Target lesions with complete response had lower pre-treatment mean values of BF, BV, ALP and HPI and higher pre-treatment mean values of TTP and PVP than target lesions with partial response, although these differences were not statistically significant.

TABLE 3. Patients' survival. Group 1 – patients with the value of CTPI parameter lower than the threshold value, group 2 – patients with the value of CTPI parameter higher than the threshold value

	Threshold value	Group 1 mean survival [months]	Group 2 mean survival [months]	P
BF	50.4 ml/100ml/min	35.6 ± 5	18.8 ± 2.7	0.033
BV	13.3 ml/100ml	35.2 ± 4.3	18.8 ± 4.1	0.028
TTP	19 s	16.4 ± 0.8	33.2 ± 4.7	0.015
PMB	40.2 ml/100ml/min	33.8 ± 4.2	15.9 ± 5.4	0.079
ALP	33.1 ml/100ml/min	30.2 ± 6.6	27.1 ± 3.8	0.691
PVP	1.8 ml/100ml/min	23.5 ± 5.5	30.8 ± 4.7	0.400
HPI	82.7 %	32.8 ± 6	24 ± 3.8	0.244

ALP = arterial liver perfusion; BF = hepatic blood flow; BV = hepatic blood volume, HPI = hepatic perfusion index; p = statistical significance in mean survival between group 1 and group 2; PMB = permeability; PVP = portal vein perfusion, TTP = time to peak, Quantitative variables are expressed as means with standard deviation.

When comparing the overall survival of patients, we were able to demonstrate a correlation between pre-treatment CTPI parameter values and overall survival in patients with intermediate stage HCC. To our knowledge, this is the first time this finding has been reported in patients with HCC undergoing TACE. Patients with pre-treatment CTPI parameter BF lower than 50.4 ml/100ml/min, BV lower than 13.3 ml/100ml and TTP longer than 19 s had significantly longer survival (35.6 *vs.* 18.8 months, 35.2 *vs.* 18.8 months and 33.2 *vs.* 16.4 months, respectively). Although we could not demonstrate significant difference in mean survival values between groups when testing other CTPI parameters, the results show some promise for future studies. Survival was longer in the group

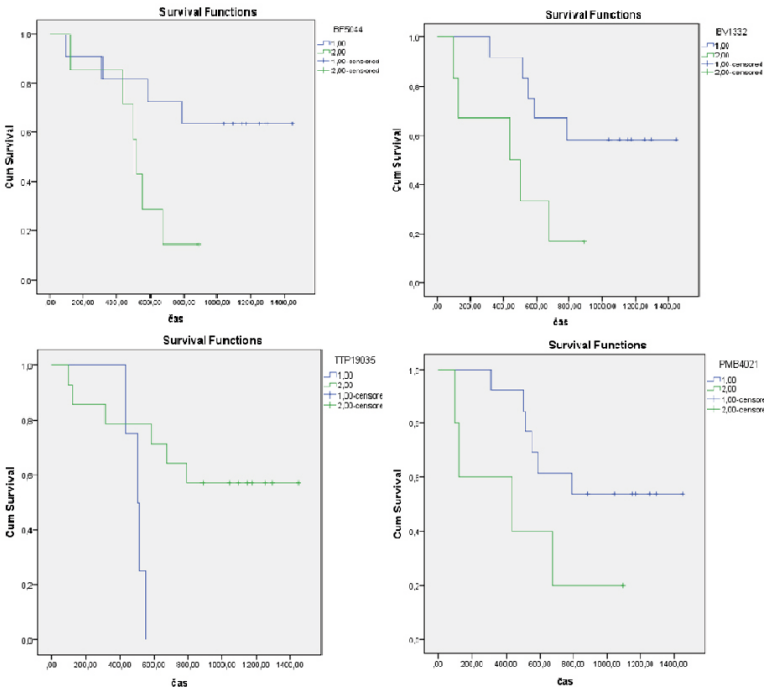

FIGURE 2. Kaplan-Meier survival curves. Patients with BF lower than 50.4 ml/100ml/min, BV lower than 13.3 ml/100ml, TTP longer than 19 s have statistically significant longer survival (p = 0.033, p = 0.028, p = 0.015). Čas = Time in days. Blue line - Group 1, Green line - Group 2.

of patients with values of pre-treatment CTPI parameter PMB lower than 40.2 ml/100ml/min, ALP lower than 33.1 ml/100ml/min, PVP values higher than 1,8 ml/100ml/min, and HPI values lower than 82,7%.

CTPI of the liver provides functional information about the microcirculation of normal parenchyma and focal neoplastic lesions of the liver and has already been studied as a possible prognostic biomarker in other malignancies.[16-18] Results of these studies show that response to treatment with chemotherapy, radiotherapy and anti-angiogenic drugs is better when the values of BF and BV are high.[32-37] A possible explanation for this is that well-perfused tumors allow better delivery of chemotherapy. They may also have better oxygenation and thus potentially have greater radiosensitivity.[38] Similar results were found by Morsbach *et al*.[16] They were able to demonstrate that the ALP of liver metastases before treatment with TARE enables the prediction of morphologic response and survival to therapy. Responders to therapy regarding tumor size reduction showed significantly higher ALP values as compared with those not responding to TARE. Differences in the therapeutic option used in our study and the fact that HCC is a highly vascular tumor with different degree of tumor arterial perfusion, different pathological grade and clinical behavior during hepatocarcinogenesis might well account for differences between our results and the results of these studies. However, results of our study are similar to those reported by Jiang *et al*.[39] and Petralia *et al*.[40] in trials of 23 and 12 patients with advanced HCC treated with a combination of anti-angiogenic treatment and chemotherapy. They reported that tumors with poor prognosis tend to show higher baseline BF and BV, suggesting higher vascularity along with extensive intratumoral arteriovenous shunts. Results of our study also show similarity with a study conducted by Michielsen *et al*.[41] in patients undergoing TACE for inoperable HCC. Patients with higher vascularized lesions had shorter progression-free survival after TACE, indicating higher malignancy potential of highly vascularized tumors.

HCC is a highly vascular tumor and the source of intranodular blood supply changes during carcinogenesis. Early stage HCC still has some supply from the portal vein, and when it reaches the stage of moderately differentiated HCC, it receives all the arterial blood supply from abnormal arteries formed during carcinogenesis. For this reason, the arterial blood supply tends to increase during hepatocarcinogenesis.[42] Perfusion imaging techniques would be ideal for the prediction of the pathological grade and clinical behavior of HCC, but literature data on this topic is relatively poor. Yang HF *et al*.[15] investigated the value of CTPI for assessment of angiogenesis in liver cancer and concluded that BF and ALP might be useful parameters in assessing angiogenesis in liver cancer. The values of these two parameters correlated with microvascular density. And since the degree of tumor perfusion is potentially associated with tumor aggressiveness our hypothesis was that patients with lower values of BF and ALP in the tumor should have a better response to treatment and longer overall survival than those with high values of these perfusion parameters.[18] Furthermore, treatment response with necrosis is based on local chemoembolization of feeding vessels, and there could be a correlation between the embolization of all feeding vessels and the success of DEBTACE. On the other hand Ippolito *et al*.[43] did not report any significant correlation between CTPI parameters and pathological grade and Sahani *et al*.[44] found that well-differentiated HCC had significantly higher CTPI parameter values (higher BF, BV and PMB) than moderately and poorly differentiated HCC. Sahani concluded that relatively larger tumor diameter (mean >

9 cm) and the presence of tumor necrosis in the high-grade tumor group could account for these observations. However, in our study, we did not include any patients with a large central necrosis that would produce such results.

The results from our study using CTPI, representing an objective, quantitative imaging tool, showed a predictive value of pre-treatment BF, BV and TTP of HCC for overall survival of patients treated with DEBTACE. As previously discussed, these parameters could be used as predictive biomarkers. Higher values of BF, BV and on the other hand lower values of TTP could represent a highly vascularized tumor.[15,20,29-31,41,42,45] Patients with such tumors may benefit from treatments that work better with high CTPI parameter values, such as TARE or anti-angiogenic therapies.[13,33,34,46]

When working with CTPI the radiation dose is an important aspect that needs to be considered. It is normally equal or higher to that of multiphase CT acquisitions. The radiation dose is estimated to be from 7.3 to 30.6 mSv and depends on the technology used. It is especially important to consider this with oncologic patients that undergo several CT scans before and after treatment.[47]

Our study has some limitations. First, our study is a retrospective study. Therefore, we had to work with the available data, instead of carefully planning the timing of procedures. Second, we included a limited number of patients. Future studies should aim at the inclusion of a larger group of patients, preferably in a multicentric fashion. Third, histopathologic correlation with CT or MR imaging regarding tumor necrosis after treatment with DEBTACE was not performed since previous reports already showed good correlation between the percentage of tumor necrosis obtained at the histopathologic examination and the tumor enhancement assessed with imaging. Fourth, the reading of CTPI was only done once, so we had no data to compare unbiased inter-reader variability. Fifth, we did not take into account different determinants of therapeutic response to DEBTACE, such as liver cirrhosis, gender, age, number and size of tumors, invasion of the portal vein, dosage of chemotherapeutic, but rather only correlated CTPI parameters with different treatment responses to DEBTACE. Finally, the results of this study are not directly transferable when using other software. The difference in values of perfusion parameters could be up to 46 % when using different software.[48]

In conclusion, our results suggest that pre-treatment CTPI parameters BF, BV and TTP measured in HCC are related to overall survival of patients treated with DEBTACE. Thus, CTPI has the potential to become a new imaging biomarker for selecting patients who will benefit from treatment with DEBTACE. Our study and most previous studies investigating the CTPI parameters were based on retrospectively acquired data, further large-scale prospective clinical trials are required.

References

1. European Association for the Study of the Liver, European Organisation for Research and Treatement of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56:** 908-43. doi: 10.1016/j.jhep.2011.12.001
2. Lammer J, Malagari K, Vogl T,Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010; **33:** 41–52. doi: 10.1007/s00270-009-9711-7
3. Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS, et al. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocelluar carcinoma (HCC). *J Surg Oncol* 2010; **101:** 476-80. doi: 10.1002/jso.21522
4. Malagari K, Pomoni M, Moschouris H,Bouma E, Koskinas J, Stefaniotou A, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. *Cardiovasc Intervent Radiol* 2012; **35:** 1119-28.
5. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007; **46:** 474-81.
6. Popovic P, Stabuc B, Jansa R, Garbajs M. Survival of patients with intermediate stage hepatocellular carcinoma treated with superselective transarterial chemoembolization using doxorubicin-loaded DC Bead under cone-beam computed tomography control. *Radiol Oncol* 2016; **50:** 418-26. doi: 10.1515/raon-2015-0045
7. Kettenbach J, Stadler A, Katzler IV, Schernthaner R, Blum M, Lammer J, et al. Drug-loaded microspheres for the treatment of liver cancer: review of current results. *Cardiovasc Intervent Radiol* 2008; **31:** 468-76. doi: 10.1007/s00270-007-9280-6
8. Malgari K, Chatzimichael K, Alexopöulou E, Kelekis A, Hall B, Dourakis S, et al. Transarterial chemoembolisation of unresectable hepatocelular carcinoma with drug eluting beads: results of an open-label study of 62 patients. *Cardiovasc Interv Radiol* 2008; **31:** 269-80.
9. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Sem Liver Disease* 2010; **30:** 52-60. doi: 10.1055/s-0030-1247132
10. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003; **37:** 429-42.
11. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology* 2006; **131:** 461-9.
12. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol* 2012; **56:** 1330-5. doi: 10.1016/j.jhep.2012.01.008
13. Fatourou EM, Tsochatzis EA. ART and science in using transarterial chemoembolization for retreating patients with hepatocellular carcinoma. *Hepatobiliary Surg Nutr* 2014; **3:** 415-8. doi: 10.3978/j.issn.2304-3881.2014.07.01
14. Tsochatzis EA, Fatourou E, O'Beirne J, Meyer T, Burroughs AK. Transarterial chemoembolization and bland embolization for hepatocellular carcinoma. *World J Gastroenterol* 2014; **20:** 3069-77. doi: 10.3748/wjg.v20.i12.3069

15. Yang HF, Du Y, Ni JX, Zhou XP, Li JD, Zhang Q, et al. Perfusion computed tomography evaluation of angiogenesis in liver cancer. *Eur Radiol* 2010; **20:** 1424-30. doi: 10.1007/s00330-009-1693-y

16. Morsbach F, Pfammatter T, Reiner CS, Fischer MA, Sah BR, Winklhofer S, et al. Computed tomographic perfusion imaging for the prediction of response and survival to transarterial radioembolization of liver metastases. *Invest Radiol* 2013; **48:** 787-94. doi: 10.1097/RLI.0b013e31829810f7

17. Blomley MJ, Coulden R, Dawson P, Kormano M, Donlan P, Bufkin C, et al. Liver perfusion studied with ultrafast CT. *J Comput Assist Tomogr* 1995; **19:** 424-33.

18. Garcia-Figueiras R, Goh VJ, Padhani AR, Baleato-González S, Garrido M, León L, et al. Ct perfusion in oncologic imaging: A useful tool? *AJR Am J Roentgenol* 2013; **200:** 8-19. doi: 10.2214/AJR.11.8476

19. Avsenik J, Bisdas S, Popovic KS. Blood-brain barrier permeability imaging using perfusion computed tomography. *Radiol Oncol* 2015; **49:** 107-14. doi: 10.2478/raon-2014-0029

20. Goh V, Halligan S, Daley F, Wellsted DM, Guenther T, Bartram CI. Colorectal tumor vascularity: quantitative assessment with multidetector CT--do tumor perfusion measurements reflect angiogenesis? *Radiology* 2009; **249:** 510-7. doi: 10.1148/radiol.2492071365

21. Tsushima Y, Funabasama S, Aoki J,Sanada S, Endo K. Quantitative perfusion map of malignant liver tumors, created from dynamic computed tomography data. *Acad Radiol* 2004; **11:** 215-23.

22. Yang L, Zhang XM, Tan BX, Liu M, Dong GL, Zhai ZH. Computed tomographic perfusion imaging for the therapeutic response of chemoembolization for hepatocellular carcinoma. *J Comput Assist Tomogr* 2012; **36:** 226-30. doi: 10.1097/RCT.0b013e318245c23c

23. Chen G, Ma DQ, He W, Zhang BF, Zhao LQ. Computed tomography perfusion in evaluating the therapeutic effect of transarterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2008; **14:** 5738-43.

24. Sahani D, Holalkere DS, Mueller PR, Zhu AX. Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue-initial experience. *Radiology* 2007; **243:** 736-43.

25. Zhou ZF, Huang HL, Xu B, et al. Clinic application with MSCT perfusion in liver tumor. *Linchuang Fangshexue Zazhi* 2006; **25:** 233-7.

26. Komemushi A, Tanigawa N, Kojima H, Kariya S, Sawada S. CT perfusion of the liver during selective hepatic arteriography: pure arterial blood perfusion of liver tumor and parenchyma. *Radiat Med* 2003; **21:** 246-51.

27. Ebos JM, Kerbel RS. Antiangiogenic therapy: impact on invasion, disease progression, and metastasis. *Nat Rev Clin Oncol* 2011; **8:** 210-21. doi: 10.1038/nrclinonc.2011.21

28. De Robertis R, Tinazzi Martini P, Demozzi E, Puntel G, Ortolani S, Cingarlini S, et al. Prognostication and response assessment in liver and pancreatic tumors: the new imaging. *World J Gastroenterol* 2015; **21:** 6794-808. doi: 10.3748/wjg.v21.i22.6794

29. Ash L, Teknos TN, Gandhi D, Patel S, Mukherji SK. Head and neck squamous cell carcinoma: CT perfusion can help noninvasively predict intratumoral microvessel density. *Radiology* 2009; **251:** 422-8. doi: 10.1148/radiol.2512080743

30. Chen Y, Zhang J, Dai J, Feng X, Lu H, Zhou C. Angiogenesis of renal cell carcinoma: perfusion CT findings. *Abdom Imaging* 2010; **35:** 622-8. doi: 10.1007/s00261-009-9565-0

31. D'Assignies G, Couvelard A, Bahrami S, Vullierme MP, Hammel P, Hentic O, et al. Pancreatic endocrine tumors: tumor blood flow assessed with perfusion CT reflects angiogenesis and correlates with prognostic factors. *Radiology* 2009; **250:** 407-16. doi: 10.1148/radiol.2501080291

32. Fournier LS, Oudard S, Thiam R,Trinquart L, Banu E, Medioni J, et al. Metastatic renal carcinoma: evaluation of anti-angiogenic therapy with dynamic contrast enhanced CT. *Radiology* 2010; **256:** 511-8. doi: 10.1148/radiol.10091362

33. Bellomi M, Petralia G, Sonzogni A, Zampino MG, Rocca A. CT perfusion for the monitoring of neo-adjuvant chemoradiation therapy in rectal carcinoma. *Radiology* 2007; **244:** 486-93.

34. Han KS, Jung DC, Choi HJ, Jeong MS, Cho KS, Joung JY, et al. Pretreatment assesment of tumor enhancement on contrast-enhanced computed tomography as a potential predictor of treatment outcome in metastatic renal cell carcinoma patients receiving antiangiogenic therapy. *Cancer* 2010; **116:** 2332-42. doi: 10.1002/cncr.25019

35. Bisdas S, Surlan-Popovic K, Didanovic V, Vogl TJ. Functional CT of squamous cell carcinoma in the head and neck: repeatability of tumor and muscle quantitative measurements, inter- and intra-observer agreement. *Eur Radiol* 2008; **18:** 2241-5. doi: 10.1007/s00330-008-0990-1

36. Gandhi D, Chepeha DB, Miller T, Carlos RC, Bradford CR, Karamchandani R, et al. Correlation between initial and early follow-up CT perfusion parameters with endoscopic tumor response in patients with advanced squamous cell carcinomas of the oropharynx treated with organ-preservation therapy. *AJNR Am J Neuroradiol* 2006; **27:** 101–6.

37. Surlan-Popovic K, Bisdas S, Rumboldt Z, Koh TS, Strojan P. Changes in perfusion CT of advanced squamous cell carcinoma of the head and neck treated during the course of concomitant chemoradiotherapy. *AJNR Am J Neuroradiol* 2010; **31:** 570-5. doi: 10.3174/ajnr.A1859

38. Wang J, Wu N, Cham MD, Song Y. Tumor response in patients with advanced non-small cell lung cancer: perfusion CT evaluation of chemotherapy and radiation therapy. *AJR* 2009; **193:** 1090-6. doi: 10.2214/AJR.08.1367

39. Jiang T, Kambadakone A, Kulkarni NM, Zhu AX, Sahani DV. Monitoring response to antiangiogenic treatment and predicting outcomes in advanced hepatocellular carcinoma using image biomarkers, CT perfusion, tumor density, and tumor size (RECIST). *Invest Radiol* 2012; **47:** 11-7. doi: 10.1097/RLI.0b013e3182199bb5

40. Petralia G, Fazio N, Bonello L, D'Andrea G, Radice D, Bellomi M. Perfusion computed tomography in patients with hepatocellular carcinoma treated with thalidomide: initial experience. *J Comput Assist Tomogr* 2011; **35:** 195–201. doi: 10.1097/RCT.0b013e31820ccf51

41. Michielsen K, De Keyzer F, Verslype C, Dymarkowski S, van Malenstein H, Oyen R, et al. Pretreatment DCE-MRI for prediction of PFS in patients with inoperable HCC treated with TACE. *Cancer Imaging* 2011; **11:** 114.

42. Visualization of multistep hepatocarcinogenesis using various imaging biomarkers [internet]. ECR 2014. C-0120. Retrieved from: http://posterng.netkey.at/esr/viewing/index.php?module=viewing_poster&task=viewsection&pi=119549&ti=394293&searchkey=

43. Ippolito D, Capraro C, Casiraghi A, , Cestari C, Sironi S. Quantitative assessment of tumour associated neovascularisation in patients with liver cirrhosis and hepatocellular carcinoma: role of dynamic-CT perfusion imaging. *Eur Radiol* 2012; **22:** 803-11. doi: 10.1007/s00330-011-2307-z

44. Sahani DV, Holalkere NS, Mueller PR, Zhu AX. Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue--initial experience. *Radiology* 2007; **243:** 736-43.

45. Frampas E, Lassau N, Zappa M, Vullierme MP, Koscielny S, Vilgrain V. Advanced hepatocellular carcinoma: early evaluation of response to targeted therapy and prognostic value of perfusion CT and dynamic contrast enhanced-ultrasound. Preliminary results. *Eur J Radiol* 2013; **82:** 205-11. doi: 10.1016/j.ejrad.2012.12.004

46. Schmitz S, Rommel D, Michoux N, Lhommel R, Hanin FX, Duprez T, et al. Dynamic contrast-enhanced computed tomography to assess early activity of cetuximab in squamous cell carcinoma of the head and neck. *Radiol Oncol* 2015; **49:** 17-25. doi: 10.2478/raon-2014-0030

47. Kim SH, Kamaya A, Willmann JK. CT perfusion of the liver: principles and applications in oncology. *Radiology* 2014; **272:** 322-44. doi: 10.1148/radiol.14130091

48. Mazzei MA, Preda L, Cianfoni A, Volterrani L. CT Perfusion: Technical developments and current and future applications. *Biomed Res Int* 2015; **2015:** 397521. doi: 10.1155/2015/397521

research article

Preoperative intensity-modulated chemoradiation therapy with simultaneous integrated boost in rectal cancer: 2-year follow-up results of phase II study

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Background. The aim of the study was to investigate the feasibility and safety of experimental fractionation using intensity modulated radiation therapy with a simultaneous integrated boost (IMRT-SIB) to shorten the overall treatment time without dose escalation in preoperative radiochemotherapy of locally advanced rectal cancer.

Patients and methods. Between January 2014 and November 2015, a total of 51 patients with operable stage II-III rectal adenocarcinoma were treated. The preoperative treatment with intensity modulated radiation therapy (IMRT) and a pelvic dose of 41.8 Gy and simultaneously delivered 46.2 Gy to T2/3 and 48.4 Gy to T4 tumour in 22 fractions, with standard concomitant capecitabine, was completed in 50 patients out of whom 47 were operated. The median follow-up was 35 months.

Results. The rate of acute toxicity G ≥ 3 was 2.4%. The total downstaging rate was 89% and radical resection was achieved in 98% of patients. Pathologic complete response (pCR) was observed in 25.5% of patients, with 2-year local control (LC), disease free survival (DFS), and overall survival (OS) of 100% for this patient group. An intention-to-treat analysis revealed pN to be a significant prognostic factor for DFS and OS (P = 0.005 and 0.030, respectively). LC for the entire group was 100%, and 2-year DFS and OS were 90% (95 % CI 98.4–81.6) and 92.2% (95% CI 99.6–84.7), respectively.

Conclusions. The experimental regime in this study resulted in a high rate of pCR with a low acute toxicity profile. Excellent early results translated into encouraging 2-year LC, DFS, and OS.

Key words: rectal cancer; intensity modulated radiation therapy; simultaneous integrated boost; preoperative radiochemotherapy; acute toxicity; pathologic complete response

Introduction

With standard preoperative treatment of locally advanced rectal cancer (LARC), we can achieve excellent local control; but long term survival is still poor due to a high rate of distant metastases.[1,2] To target distant microscopic disease, an additional drug has been added to the preoperative treatment in several studies, but with conflicting results of treatment outcome and high acute toxicity.[3-5]

Since dosimetric studies on preoperative intensity-modulated radiotherapy (IMRT) showed a better sparing of organs at risk compared with standard 3-dimensional conformal radiotherapy (3D CRT) in rectal cancer[6-9], this novel radiation technique has been used in several prospective phase II studies with the aim of improving the treatment outcome in LARC. The treatment intensification consisted of a dose escalation with a simultaneous integrated boost (SIB), with or without the use of

an additional drug alongside standard concomitant capecitabine.[10-15] Researchers report an encouraging rate of pathologic complete response (pCR) and local control (LC), but with substantial acute toxicity with oxaliplatin addition[12] and non-negligible late toxicity with dose escalation.[11]

Because of a promising impact on clinical outcome, but, conflicting toxicity results with dose escalation in preoperative treatment of LARC, we conducted a phase II trial, testing the experimental fractionation with the use of IMRT-SIB in order to shorten the overall treatment time with a biologically effective dose (BED) similar to the one used in standard 3D CRT. In recently published early results from our trial, we demonstrated that preoperative radiochemotherapy with IMRT-SIB without dose escalation, concomitantly with capecitabine, can achieve a high rate of pCR, a downstaging with a very low acute toxicity profile, and excellent compliance.[16] After the 2-year follow-up, we analysed the impact of experimental fractionation on LC, disease-free survival (DFS), and overall survival (OS).

Patients and methods

Study design and inclusion criteria

The trial design, eligibility criteria, and treatment details have been published previously in detail.[16] In brief, patients had to present with histologically confirmed, operable adenocarcinoma, located within 15 cm from the anal verge. Patients with locally advanced, non-metastatic disease (cT ≥ 3 and/or cN ≥ 1 on magnetic resonance imaging (MRI) and M0 on CT thorax/abdomen) without contraindications for chemotherapy were included.

TABLE 1. Biologic effective dose (BED) comparison for standard 3-dimensional conformal radiotherapy (3D CRT) and intensity modulated radioation therapy with simultaneous boost (IMRT-SIB) as experimental fractionation

Treatment	Pelvis TD/d/BED (Gy)	Tumour T≤3 TD/d/BED (Gy)	Tumour T4 TD/d/BED (Gy)
3D CRT	45 / 1.8 / **37.5**	50.4 / 1.8 / **40.9**	54 / 1.8 / **43.9**
IMRT-SIB	41.8 / 1.9 / **35.9**	46.2 / 2.1 / **42.1**	48.4 / 2.2 / **45.2**

BED is calculated as BED = TD x (d + α/β) / (2 + α/β) – (T - t) x D_{prolif} in which TD is the total dose, d dose (Gy) per fraction, α/β is the common linear-quadratic quotient (set to 10 Gy), D_{prolif} is the dose recovered due to proliferation (set to 0.6 Gy/day), T = total treatment time and t = initial delay time (days, set to 7 days)data from 36 prospective studies, 7 retrospective studies and 17 other articles were used. A total of 131 scientific articles are included, involving 25 351 patients. The results were compared with those of a similar overview from 1996 including 15 042 patients. The conclusions reached can be summarized thus: The results after rectal cancer surgery have improved during the past decade. It is likely that local failure rates after 5 years of follow-up at hospitals adopting the TME-concept (TME = total mesorectal excision.[20] Standard fractionation for preoperative rectal cancer treatment with 3D CRT consists of 45 Gy in 25 fractions to the tumour and regional lymph nodes (pelvis) and additional boost 3 x 1.8 Gy (TD 50.4 Gy) in T ≤3 and 5 x 1.8 Gy (TD 54 Gy) in T4 tumour.

Prior to treatment, all patients received detailed oral and written information, and signed an informed consent form. The trial was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 41/12/13) and was in agreement with the Declaration of Helsinki. The study was registered in the ClinicalTrials.gov database (NCT02268006).

Treatment protocol

The target volumes and dose prescription were defined according to ICRU Reports 50, 62[17], and 83.[18] The gross tumour volume (GTV) encompassed all visible primary tumours. GTV + 1 cm represented a boost volume (CTV2), and the clinical target volume 1 (CTV1) contained CTV2, mesorectum, and regional lymph nodes from L5/S1 to 4 cm below the tumour or *musculus levator ani*. The nodes along *arteria iliaca externa* were included in case of substantial genitourinary structure infiltration, and the *ishiorectal fossa* and anal canal in the case of *musculus levator ani* or anal canal involvement. The internal target volume (ITV) extended up to 0.5 cm anteriorly in the lower half and up to 1.5 cm anteriorly in the upper half of the mesorectum.[19] The planning target volume (PTV) was extended from ITV for 7 mm posteriorly and laterally, and 10 mm in other directions.

PTV 1 received 41.8 Gy in 22 fractions and SIB was prescribed to tumour (PTV 2) concomitantly to doses of 46.2 Gy and 48.4 Gy to T ≤ 3 and T4 tumours in 22 fractions, respectively, 5 times per week (Monday to Friday) (Table 1). The main constraints for organs at risk were: V_{45Gy} < 195 cc and D_{max} ≤ 50 Gy; anal canal V_{40Gy} ≤ 40% and D_{max} ≤ 55 Gy; iliac crests V_{30Gy} < 50 %, V_{40Gy} < 35%; bladder V_{30Gy} < 50% and V_{35Gy} < 35%; and penile bulb $D_{90\%}$ < 50 Gy [16] (Figure 1).

The treatment was delivered on Clinac 2100 CDI (Varian, Palo Alto, USA) using the dynamic multileaf collimator technique with 6MV photons and a daily position verification (ExacTrac X-ray 6D system, BrainLAB AG, Feldkirchen, Germany).

Patients received concomitant chemotherapy with capecitabine from the first to last day of the radiation treatment (including weekends) at a daily dose of 825 mg/m^2/12 h. One dose was taken 1 hour prior to irradiation. The treatment compliance and acute toxicity were evaluated weekly according to the common terminology criteria for adverse events (CTCAE) v.4.0.[21]

Surgery was scheduled 6–8 weeks after the completion of chemoradiotherapy, pathologic stage

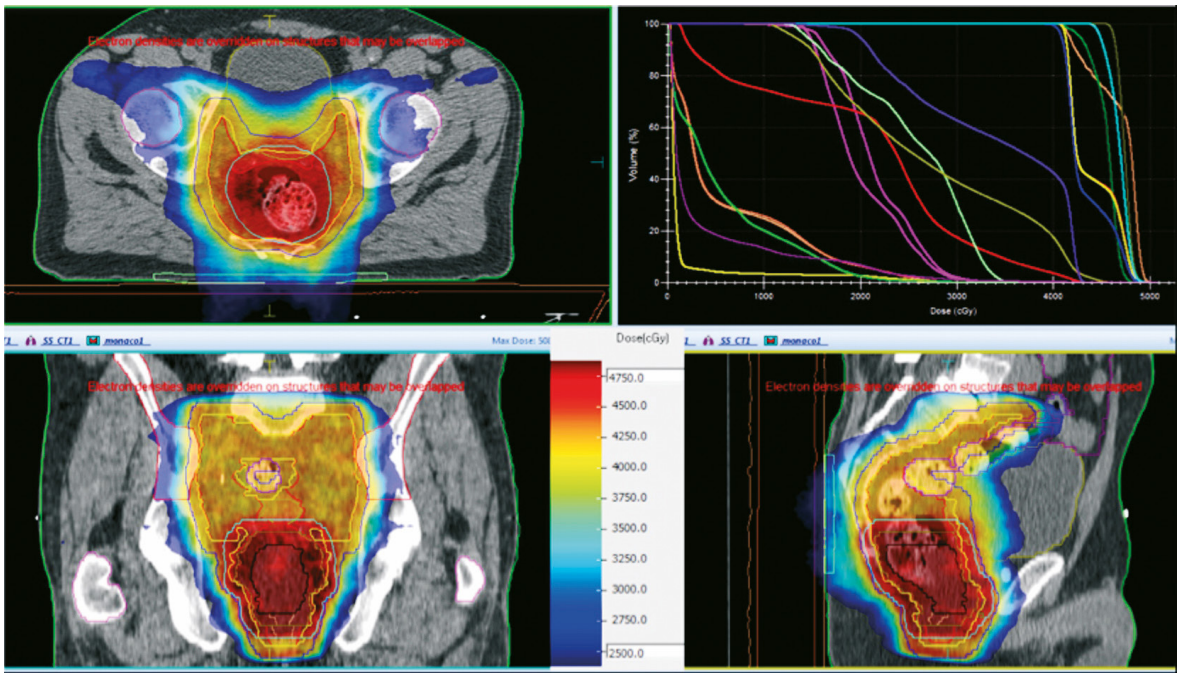

FIGURE 1. Intensity modulated radiation therapy plan met the planning goals.

recorded according to the AJCC 7th edition[22], and tumour regression grade according to the criteria by Dworak *et al*.[23]

Six cycles of adjuvant chemotherapy with capecitabine were offered to patients with residual tumour on pathologic examination. After treatment, the follow-up consisted of clinical and serum CEA evaluation every 3 months for two years, and later on a bi-annual basis with abdominal ultrasound every 6 months and a chest radiograph annually.

Statistics

This was a prospective phase II study on patients with locally advanced rectal cancer, designed to evaluate the pathologic complete response after experimental preoperative treatment as a primary endpoint. The key secondary endpoints were to evaluate the acute toxicity of preoperative treatment, tumour response, LC, DFS, and OS. Late toxicity and the quality of life will be analysed after a 5-year follow-up.

All time intervals were calculated from the date of operation or date of chemoradiotherapy completion (for non-operated patients). The end dates for time calculations were the dates of the last follow-up or death for OS, and for DFS the dates of detected local/distant relapse, last follow-up, or death. In the patient with primary lung metastasis and in non-operated patients, we counted the DFS time as 0 months.

A statistical analysis was performed using the Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for presenting general data. Patients surgically treated after chemoradiotherapy completion (N = 47) entered treatment response analysis. Fisher's exact test was used for tumour regression grade prognostic group comparison. The survival curves were calculated with the Kaplan-Maier method and the influence of the possible prognostic factors on survival was verified by means of the log-rank test.

Results

Between January 2014 and November 2015, a total of 51 patients were treated (Figure 2). Patients and tumour characteristics were described in detail elsewhere[16], but, briefly – the median age of the group was 66 years (range, 30–81 years) and two thirds were men. Nearly half of the tumours were located in the lower third of the rectum and 20 patients had positive mesorectal fascia (MRF+). According to AJCC 7th edition[22], the clinical stages of the disease were as follows: T2N1M0 (n = 1), T3N0M0 (n = 6), T3N1M0 (n = 15), T3N2M0 (n = 22), T4N1M0 (n = 4),T4N2M0 (n = 2), and T3N1M1 (n = 1). One patient had a small lung lesion prior to

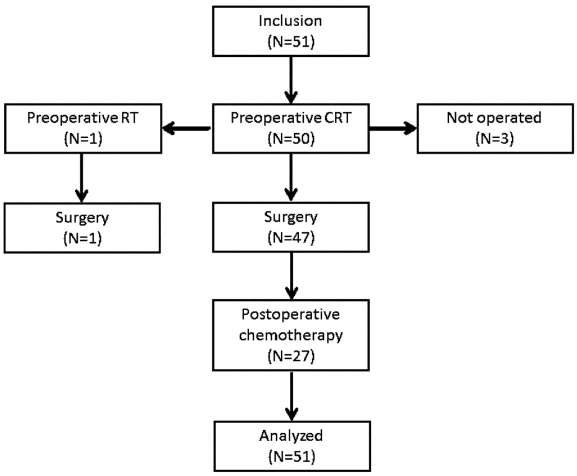

FIGURE 2. Distribution of patients through the trial.

CRT = radiochemotherapy; RT = radiotherapy

treatment, but control CT following the treatment revealed a primary metastatic disease with lung metastasis in his case.

Treatment

Preoperative radiochemotherapy according to protocol was completed by 50 patients in a median of 31 days (range 29–36 days), and one received preoperative short-course radiotherapy (25 Gy in 5 fractions) due to ischemic stroke in the first week of experimental treatment. The acute toxicity of preoperative treatment was mild, with only two G3 acute adverse events with infectious enterocolitis and radiodermatitis.

Surgery was performed in 48 patients and operation was omitted in three due to the patient's refusal, metachronous pancreatic carcinoma, and serious bleeding from rectal varices. Low anterior resection was performed in 40 patients, abdominoperineal resection in 7, and pelvic exenteration in 1. Radical resection (R0) was achieved in 47 patients and one had a microscopic carcinoma focus in the circumferential margin (R1). Major complications (CTCAE v.4.0 G ≥ 3) occurred in 4 out of 48 patients. A rescue surgery with pelvic exenteration was performed in the patient with rectal varices due to tumour progression 35 months after chemoradiotherapy completion. She is disease-free 4 months after R0 resection.

Adjuvant chemotherapy was given to patients who did not achieve pCR. In four patients, adjuvant treatment was omitted due to preoperative adverse events (ischemic stroke in two patients and infectious enterocolitis G3 in one), and one patient refused it.

TABLE 2. Influence of potential prognostic factors on overall survival (OS) and disease free survival (DFS)

Prognostic factor	OS	DFS
Age	ns	ns
Gender	ns	ns
WHO PS	ns	ns
Tumour grade	ns	ns
cTumour stage[a]	ns	ns
cNodal stage[a]	ns	ns
TRG	ns	ns
TRG prognostic group	ns	ns
pTumour stage[d]	ns	ns
pNodal stage[d]	p = 0.005	p = 0.039
pCR[f]		
Adjuvant chemotherapy[g]	ns	ns
5-6 vs. ≤4 cycles*	p = 0.009	p = 0.012

TRG = tumour regression grade[23]; WHO PS = WHO performance status; f – pathologic complete response; g – chemotherapy; * calculated for 36 patients with indication for adjuvant chemotherapy; ns = not specific (p > 0.05).

[a] according the AJCC, 7th edition[22]

Treatment response

Among 47 operated patients who completed preoperative treatment according to protocol, 12 achieved pathologic complete response (25.5%). The total downstaging rate was 89% (42 of 47 patients), with a decrease in T and N stages observed in 32 (68%) and in 39 (83%) patients, respectively. According to the Dworak criteria[23], the tumour regression grades (TRG) were TRG 4, TRG 3, TRG 2, TRG 1, and TRG 0 in 12, 16, 13, 6, and 0 patients, respectively.

Survival

An intention-to-treat analysis was performed on all 51 patients. In the median follow-up time of 35 months (range, 14–43 months), we recorded no local relapses and 4 distal relapses (two patients with lung metastases and two with both liver and paraaortic lymph node metastases). To date, 44 patients are alive without rectal cancer; two patients are alive with primary disease (one with an intact primary tumour and one with liver metastases). Three patients have died because of primary rectal cancer disease and two of other causes (myocardial infarction and pancreatic cancer).

Cumulative 2-year LC, DFS, and OS were 100%, 90% (95% CI 98.4–81.6), and 92.2% (95% CI 99.6–

TABLE 3. Comparison of tumour regression grade in patients with R0 resection

	IMRT-SIB But-Hadzic *et al.*[16] N = 46	3D CRT Focas *et al.*[32] N = 385	p	IMRT-SIB But-Hadzic *et al.*[16] N = 46	IMRT-SIB Li *et al.*[10] N = 58	p
TRG 4	12 (26%)	40 (10%)	**0.004**	12 (26 %)	19 (33 %)	0.302
TRG 2–3	29 (63%)	254 (66%)	0.404	29 (63 %)	20 (35 %)	**0.003**
TRG 0–1	5 (11%)	91 (24%)	**0.031**	5 (11 %)	19 (32 %)	**0.007**

3D CRT = 3D conformal radiotherapy; IMRT-SIB = intensity modulated radiation therapy with simultaneous boost; TRG = tumour regression grading[23]

84.7), respectively. The possible influence of potential prognostic factors on OS and DFS was determined by means of the log-rank test (Table 2). There was no link between gender, age, performance status, cT, cN, pT, or TRG and survival. Patients with pN2 had significantly worse OS and DFS (Figure 3). In the group of 36 patients that had an indication for adjuvant chemotherapy, we found that the patients who received 5–6 cycles of chemotherapy had significantly better OS and DFS compared with ≤ 4 cycles of chemotherapy (Figure 3). We found a trend toward different OS for patients in different TRG prognostic group, although non-significant. Two-year OS's for good (TRG 4), intermediate (TRG 2–3,) and bad (TRG 0–1) prognostic groups were 100%, 93.3%, and 83.3%, respectively (p = 0.426). Local control, 2-year OS, and 2-year DFS were all 100% for 12 patients with pCR.

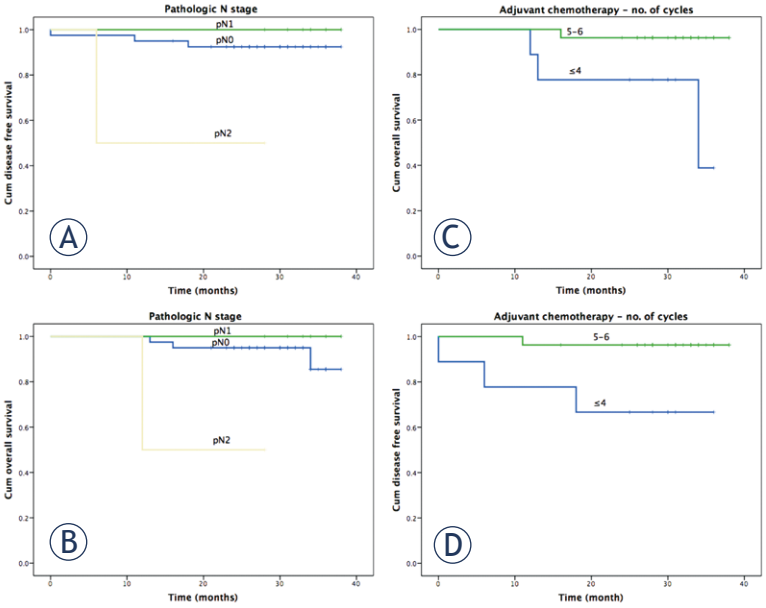

FIGURE 3. Prognostic significance of pathologic nodal stage (pN) on 2-year disease-free survival[a], overall survival[b], prognostic significance of the received number of adjuvant chemotherapy cycles in patients without pCR on 2-year disease-free survival[c], and overall survival[d] in rectal cancer after preoperative radiochemotherapy and surgery.

Discussion

The main limiting factor in the preoperative treatment of locally advanced rectal cancer is acute toxicity – mainly gastrointestinal – which has been preventing the intensification of standard radiochemotherapy for rectal cancer in the last decade. To date, only few prospective studies have used the dosimetric advantage of IMRT-SIB for preoperative treatment intensification of locally advanced rectal cancer.[10-15] With our experimental preoperative fractionation regime without dose escalation, with standard capecitabine, we report lower acute toxicity rates and comparable treatment results to these dose-escalated studies.

In a previous publication, we reported a very low acute toxicity profile with only 2.4% G3 acute toxicities[16], which is lower than two comparable studies with capecitabine. In a Chinese study, 41.8 Gy was delivered to an elective volume in 22 fractions and the tumour-involved lymph nodes received 50.6 Gy.[10] The pelvis received 46 Gy in 23 fractions in a Spanish study with simultaneous dose escalation to 57.5 Gy to macroscopic disease.[12] Authors reported 14% and 7.6% G ≥ 3 acute toxicity rates, respectively. In two drug concomitant chemotherapy (oxaliplatin/capecitabine) dose-escalation trials, the toxicity rates were even higher, up to 44.4%.[13-15]

The shorter treatment time in our trial resulted in 25.5% pCR and excellent downstaging rates of 68% and 83% for T and N stages, respectively. In our historic cohort with 3D CRT rates of pCR, T, and N downstaging were 9%, 40%, and 52.9%, respectively.[24] Our pCR rate did not significantly differ from the 31% and 30,6% rates in the Chinese and Spanish trials, but was significantly higher compared to our historic cohort.

We observed improved results with a BED similar to standard preoperative treatment. Because of a strong positive correlation between pCR and the

dose of radiation[25], we believe that there are multiple factors positively influencing the results of our trial. Firstly, if the time factor in our calculations is underestimated due to a short lag-period[26], the BED of our fractionation regime is higher and improvement is achieved due to a steep dose response curve. Secondly, in historic 3D CRT trials, pretreatment pelvic MRI was not mandatory[27] and the clinical stage was unreliable. Even in the era of MRI, only recently has cN begun being determined according to morphology.[28] Thirdly, there was a huge improvement in the precision of the radiotherapy process in recent years. In our study protocol, we tried to minimize the dosimetric impact of inter-observer variability[29] by using detailed contouring guidelines and a co-registered planning MRI[30] when available. A non-uniform safety margin was applied and IGRT was used. In our previous 3D CRT trial, the contouring guidelines were more loose and GTV was contoured according to CT, since MRI was done only in 5% of patients.[24] A uniform 1 cm safety margin was used, not counting for organ motion, and the patient position was verified with weekly portal films only. Consequently, systematic errors were substantial and could have contributed to poorer results.

Our tumour downstaging rate is comparable to the Chinese trial; but in a Spanish trial, the rate was higher (76.4%) with a higher dose escalation.[10,12] In both studies, an additional boost was applied to the involved lymph nodes with only a 5 mm margin and position verification with weekly portal films in the Chinese and a daily cone beam CT in the Spanish trial. Our N-downstaging rate is similar to that in the Chinese research and higher than the Spanish trial despite lower BED, which suggests that an additional boost to the involved lymph nodes is not mandatory. Another explanation of these results would be that the 5 mm margin around the nodal GTV that was used in both of the other trials was not sufficient to adequately cover the affected nodes with the boost dose and the N downstaging rate could have been higher.

Since the pCR rate has a poor treatment prognostic value[31] and the downstaging comparison with historic trials is not reliable, we performed a comparison of three prognostic groups according to late results of CAO/ARO/AIO-94 trial. They found a significant impact on 10-year DFS for the good (TRG 4), intermediate (TRG 2–3), and bad (TRG 0–1) response groups. We compared the proportions from our study to comparable preoperative studies with concomitant capecitabine (Table 3). In comparison to 3D CRT[32], we achieved a higher pCR rate (TRG 4; $p = 0.004$) and observed less bad responses to treatment (TRG 0–1; $p = 0.031$) with an equal proportion of patients in the intermediate prognostic group. In comparison with dose-escalation IMRT-SIB preoperative treatment[10], we didn't find a significant difference in the good prognostic group, but the proportion of patients with an intermediate response was higher ($p = 0.003$) with fewer patients exhibiting a bad response in our study ($p = 0.007$), which could be a consequence of a more precise radiotherapy procedure.

We report an excellent 2-year LC of 100%, and 2-year DFS and OS of 90% and 92,2%, respectively. The results are comparable to more intensified preoperative treatment regimes with reported 2-3-year LC 70–100%, DFS 86–95% and OS 64–96%. In concordance with other studies, we found pN to be the main prognostic factor on OS and DFS[27]; no association between pCR and survival; and an excellent prognosis for pCR group of patients (2-year LC, DFS, and OS all 100%). The main limitations of our study are the lack of randomization, the small sample size, and no long-term follow-up. Longer follow-up of the patients is needed to determine if excellent early results will translate to improved long-term results, and to determine the impact of our treatment protocol on late toxicity and QoL.

In conclusion high rate of pCR and downstaging after preoperative treatment of LARC with IMRT-SIB in 22 fractions without dose escalation, concomitant with capecitabine, translated into excellent 2-year LC, DFS, and OS (100%, 90%, and 92.2%, respectively). With the presented results, we have confirmed the superiority of our study to the conventional preoperative regimen.[5,24] Because of similar results to other IMRT trials and lower acute toxicity profile, our experimental regime is eligible for testing treatment intensification with a second drug in order to further improve the treatment efficacy.

References

1. Bujko K, Michalski W, Kepka L, Nowacki MP, Nasierowska-Guttmejer A, Tokar P, et al. Association between pathologic response in metastatic lymph nodes after preoperative chemoradiotherapy and risk of distant metastases in rectal cancer: an analysis of outcomes in a randomized trial. *Int J Radiat Oncol Biol Phys* 2007; **67:** 369-77. doi: 10.1016/j.ijrobp.2006.08.065

2. Leibold T, Shia J, Ruo L, Minsky BD, Akhurst T, Gollub M J, et al. Prognostic implications of the distribution of lymph node metastases in rectal cancer after neoadjuvant chemoradiotherapy. *J Clin Oncol* 2008; **26:** 2106-11. doi: 10.1200/JCO.2007.12.7704

3. Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Lafay I, Hennequin C, Etienne PL, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *J Clin Oncol* 2012; **30:** 4558-65. doi: 10.1200/JCO.2012.42.8771

4. Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *Lancet Oncol* 2012; **13:** 679-87. doi: 10.1016/S1470-2045(12)70187-0

5. Velenik V, Ocvirk J, Music, M, Bracko M, Anderluh F, Oblak I, et al. Neoadjuvant capecitabine, radiotherapy, and bevacizumab (CRAB) in locally advanced rectal cancer: results of an open-label phase II study. *Radiat Oncol*. 2011; **6:** 105. doi: 10.1186/1748-717X-6-105

6. Arbea L, Ramos, LI, Martínez-Monge R, Moreno M, Aristu, J. Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications, *Radiat Oncol* 2010; **5:** 17. doi: 10.1186/1748-717X-5-17

7. Guerrero Urbano MT, Henrys AJ, Adams EJ, Norman AR, Bedford JL, Harrington KJ, et al. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. *Int J Radiat Oncol Biol Phys* 2006; **65:** 907-16. doi: 10.1016/j.ijrobp.2005.12.056

8. Engels B, De Ridder M, Tournel K, Sermeus A, De Coninck P, Verellen D, et al. Preoperative helical tomotherapy and megavoltage computed tomography for rectal cancer: impact on the irradiated volume of small bowel. *Int J Radiat Oncol Biol Phys* 2009; **74:** 1476-80. doi: 10.1016/j.ijrobp.2008.10.017

9. Mok H, Crane CH, Palmer MB, Briere TM, Beddar S, Delclos ME, et al. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. *Radiat Oncol* 2011; **6:** 63. doi: 10.1186/1748-717X-6-63

10. Li JL, Ji JF, Cai Y, Li XF, Li YH, Wu H, et al. Preoperative concomitant boost intensity-modulated radiotherapy with oral capecitabine in locally advanced mid-low rectal cancer: a phase II trial". *Radiother Oncol* 2012; **102:** 4-9. doi: 10.1016/j.radonc.2011.07.030

11. Engels B, Platteaux N, Van den Begin R, Gevaert T, Sermeus A, Storme,G, et al. Preoperative intensity-modulated and image-guided radiotherapy with a simultaneous integrated boost in locally advanced rectal cancer: report on late toxicity and outcome. *Radiother Oncol* 2014; **110:** 155-9. doi: 10.1016/j.radonc.2013.10.026

12. Hernando-Requejo O, López M, Cubillo A, Rodriguez A, Ciervide R, Valero J, et al. Complete pathological responses in locally advanced rectal cancer after preoperative IMRT and integrated-boost chemoradiation. *Strahlenther Onkol* 2014;1**90:** 515-20. doi: 10.1007/s00066-014-0650-0

13. Picardi V, Macchia G, Guido A, Giaccherini L, Deodato F, Farioli A, et al. Preoperative chemoradiation with VMAT-SIB in rectal cancer: a phase II study. *Clin Colorectal Cancer 2016*. doi: 10.1016/j.clcc.2016.06.004

14. Hong TS, Moughan J, Garofalo MC, Bendell J, Berger AC, Oldenburg NBE, et al. NRG Oncology Radiation Therapy Oncology Group 0822: a phase 2 study of preoperative chemoradiation therapy using intensity modulated radiation therapy in combination with capecitabine and oxaliplatin for patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2015; **93:** 29-36. doi: 10.1016/j.ijrobp.2015.05.005

15. Zhu J, Liu F, Gu W, Lian P, Sheng W, Xu J, et al. "Concomitant boost IMRT-based neoadjuvant chemoradiotherapy for clinical stage II/III rectal adenocarcinoma: results of a phase II study. *Radiat Oncol* 2014; **9:** 70. doi: 10.1186/1748-717X-9-70

16. But-Hadzic J, Anderluh F, Brecelj E, Edhemovic I, Secerov-Ermenc A, Hudej R, et al. Acute toxicity and tumor response in locally advanced rectal cancer after preoperative chemoradiation therapy with shortening of the overall treatment time using intensity-modulated radiation therapy with simultaneous integrated boost: a phase 2 trial. *Int J Radiat Oncol Biol Phys* 2016; **96:** 1003-10. doi: 10.1016/j.ijrobp.2016.08.031

17. ICRU. Prescribing, recording and reporting photon beam therapy (ICRU report 50). *ICRU Report* 1993: 357-60. doi: 10.2307/3578862

18. Gregoire V, Mackie TR. Dose prescription, reporting and recording in intensity-modulated radiation therapy: a digest of the ICRU Report 83. *Imaging Med* 2011; **3:** 367-73. doi: 10.2217/iim.11.22

19. Van Triest B, Nijkamp J, van Herk M, Sonke JJ, de Jong R, Hollmann B, et al. Repeat CT assessed CTV variation and PTV margins for short- and long-course pre-operative RT of rectal cancer. *Radiother Oncol* 2012; **102:** 399-405. doi: 10.1016/j.radonc.2011.11.011

20. Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E, Grönberg H, et al. A systematic overview of radiation therapy effects in rectal cancer. *Acta Oncol* 2003; **42:** 476-92.

21. U. S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE), Version 4.0 (CTCAE). May 28, 2009: Available at: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. [Citated 2017 Jun 15].

22. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17:** 1471–4. doi: 10.1245/s10434-010-0985-4

23. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis*. 1997; **12:** 19-23.

24. Velenik V, Oblak I, Anderluh F. Long-term results from a randomized phase II trial of neoadjuvant combined-modality therapy for locally advanced rectal cancer. *Radiat Oncol* 2010; **5:** 88. doi: 10.1186/1748-717X-5-88

25. Burbach JPM, den Harder AM, Intven M, van Vulpen M, Verkooijen HM, Reerink O. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis. *Radiother Oncol* 2014; **113:** 1-9. doi: 10.1016/j.radonc.2014.08.035

26. Suwinski R, Taylor JM, Withers HR. Rapid growth of microscopic rectal cancer as a determinant of response to preoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 1998; **42:** 943-51. doi: http://dx.doi.org/10.1016/S0360-3016(98)00343-5

27. Fokas E, Liersch T, Fietkau R, Hohenberger W, Beissbarth T, Hess C, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. *J Clin Oncol* 2014; **32:** 1554-62. doi: 10.1200/JCO.2013.54.3769

28. Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. *Radiology* 2003; **227:** 371-7. doi: 10.1148/radiol.2272011747

29. Lobefalo F, Bignardi M, Reggiori G, Tozzi A, Tomatis S, Alongi F, et al. Dosimetric impact of inter-observer variability for 3D conformal radiotherapy and volumetric modulated arc therapy: the rectal tumor target definition case. *Radiat Oncol* 2013; **8:** 176. doi: 10.1186/1748-717X-8-176

30. O'Neill BD, Salerno G, Thomas K, Tait DM, Brown G. MR vs CT imaging: low rectal cancer tumour delineation for three-dimensional conformal radiotherapy. *Br J Radiol* 2009; **82:** 509-13. doi: 10.1259/bjr/60198873

31. Glynne-Jones R, Mawdsley S, Pearce T, Buyse M. Alternative clinical end points in rectal cancer - are we getting closer? *Ann Oncol* 2006; 17: 1239-48. doi: 10.1093/annonc/mdl173

32. Rödel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005; **23:** 8688-96. doi: 10.1200/JCO.2005.02.1329

research article

Prognostic significance of tumor regression in locally advanced rectal cancer after preoperative radiochemotherapy

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Background. The majority of rectal cancers are discovered in locally advanced forms (UICC stage II, III). Treatment consists of preoperative radiochemotherapy, followed by surgery 6–8 weeks later and finally by postoperative chemotherapy. The aim of this study was to find out if tumor regression affected long-term survival in patients with localy advanced rectal cancer, treated with neoadjuvant radiochemotherapy.

Patients and methods. Patients with rectal cancer stage II or III, treated between 2006 and 2010, were included in a retrospective study. Clinical and pathohistologic data were acquired from computer databases and information about survival from Cancer Registry. Survival was estimated according to Kaplan-Meier method. Significance of prognostic factors was evaluated in univariate analysis; comparison was carried out with log-rank test. The multivariate analysis was performed according to the Cox regression model; statistically significant variables from univariate analysis were included.

Results. Two hundred and two patients met inclusion criteria. Median follow-up was 53.2 months. Stage ypT0N0 (pathologic complete response, pCR) was observed in 14.8% of patients. Pathohistologic stage had statistically significant impact on survival ($p = 0.001$). 5-year survival in patients with pCR was>90%. Postoperative T and N status were also found to be statistically significant ($p = 0.011$ for ypT and $p < 0.001$ for ypN). According to multivariate analysis, tumor response to neoadjuvant therapy was the only independent prognostic factor ($p = 0.003$).

Conclusions. Pathologic response of tumor to preoperative radiochemotherapy is an important prognostic factor for prediction of long-term survival of patients with locally advanced rectal cancer.

Key words: rectal cancer; tumor regression; preoperative radiochemotherapy; prognosis

Introduction

Combined chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the standard treatment for patients with locally advanced rectal cancer.[1] This approach led to significantly enhanced tumor control, with local recurrence rates of < 10%.

Preoperative chemotherapy induces changes in both gross appearance of the surgical specimen and its pathological features. Pathologic tumor response to therapy is an important prognostic factor for long-term prognosis. Moreover, patients with complete pathologic response to neoadjuvant treatment have much better prognosis than patients with less or no response.[2] The rate of response is better in neoadjuvant CRT compared with long course RT, and possibly absent in short course RT with immediate surgery. In fact, maximal response of the radiation occurs only several weeks after its end.[3] For that reason surgery has been delayed until 6–12 weeks following neoadjuvant CRT.[4,5] The use of neoadjuvant CRT leading to tumor shrinkage increases the likelihood of performing a sphincter preserving surgery and increases circumferential and distal margins in surgical specimen with

reduction of lymphatic and vascular invasion.[6-9] Chemoradiation induces a tumor downstaging effect, which potentially improves the feasibility of a complete resection with benefits in local disease control. However, the type and remission rate to neoadjuvant CRT remains considerably variable. While some patients may not respond, others may even have progression of disease. Other group of patients experiences downstaging and 15–25% has surgical specimens without any viable tumor cells, a condition referred to as pathologic complete response (ypCR).[10,11,12]

The aim of this study was to find out if tumor regression affected long-term survival in patients with localy advanced rectal cancer, treated with neoadjuvant radiochemotherapy.

Patients and methods

Our retrospective research included patients with locally advanced rectal cancer (stage II, III), treated in Clinical Department of Abdominal Surgery, University Medical Centre Ljubljana between 2006 and 2010. The study was approved by institutional board, informed consent was obtained from all patients and all procedures were performed according to the guidelines of the Helsinki Declaration.

After analysing available medical documentation and considering exclusion criteria (stage I or IV at diagnosis; noninvasive tumors, tumors *in situ*, inoperable tumors, nonradical resection (R1, R2), reoperation because of tumor recurrence), two hundred and two patients were selected for analysis.

Relevant patients' data were: age, sex, type of operation, survival, preoperative stage established by MRI (cTNM), type of neoadjuvant therapy and pathohistological findings. The latter allowed for a classification of the anatomical extent of the disease according to the 7th ed. of the UICC TNM classifiation.[13] Histopathological regression grade of the primary tumor after neoadjuvant radiochemotherapy, was assessed according to Dworak regression scale.[14]

Survival data were provided by Cancer registry. Kaplan-Meier method was used to analyse survival. Significance of prognostic factors was evaluated with univariate analysis and log-rank test. Statistically sigificant variables from univariate analysis were used in multivariate analysis; with Cox regression model independent variables with effect on long-term survival of rectal cancer patients were pointed out.

All statistical analyses were carried out with statistical program SPSS 19.0.0 (SPSS Inc, Chicago, USA). A p value < 0.05 was considered statistically significant.

Results

Two hundred and two rectal cancer patients were included in the research. There were 114 (56.4%) male and 88 (43.6%) female. The median age was 62.5 years (range 33–86). Median follow up was 53.2 months (range 29–88). According to preoperative diagnostics (physical examination, laboratory tests, chest radiography, ultrasound of abdomen and MRI of pelvis) TNM stage was established. Thyrty eight patients (18.5%) had stage II and 164 (81.5%) stage III of the disease. They all received neoadjuvant treatment: long-course radiotherapy (radiation of totally 50.4–54 Gy) and most of them additional chemotherapy (5-fluorouracil or capecitabine). Six to eight weeks after finishing preoperative treatment all patients underwent total mesorectal excision (TME) surgery. One hundred and fifty-two (75%) patients had low anterior resection, of which 2 were without creating anastomosis (Hartmann resection) and 1 was laparoscopic. Fifty-two (25%) patients underwnet abdominoperineal excision. One hundred and sixty-eight (83%) patients received postoperative 5-FU based chemotherapy. The rest 17% of patients did not receive adjuvant therapy because of postoperative complications, preexisting comorbidities or favourable patohistological results.

Pathohistological findings of resected specimens revealed: 31 patients (15.3%) with complete tumour response in rectal wall (ypT0). Other results were: ypT1 in 13 patients (6%), ypT2 in 46 (23%), ypT3 in 104 (52%) and ypT4 in 7 patients (4%), respectively.

Lymph nodes in resected specimens: in 133 patients (66%) no tumor cells were found in them (ypN0) and in the 69 patients (34%), the lymph nodes were positive.

After neoadjuvant therapy, TNM stage was reassessed. thirty patients (14.8%) achieved final stage 0 (ypT0N0), which means complete pathologic response to preoperative treatment. Other tumors responded as follows: pooperative stage I was achieved in 45 patients (22.3%), stage II in 52 (25.8%), stage III in 63 (31.2%) and stage IV in 12 patients (5.9%).

Analysing closely the group of patients with complete pathological response (ypT0N0), 17 of them (57%) had preoperatively stage II disease and

TABLE 1. Results of survival analysis

	Median survival [years]	95% confidence interval	p (log rank)
Pooperative stage 0	6.6	6.1–7.1	
pooperative stage I	6.4	5.8–6.9	
Pooperative stage II	5.5	4.9–6.1	0.001
Pooperative stage III	4.9	4.3–5.6	
Pooperative stage IV	3.7	2.8–4.6	
ypT0	6.6	6.1–6.7	
ypT1	6.0	5.2–6.9	
ypT2	6.1	5.5–6.7	0.011
ypT3	5.3	4.8–5.8	
ypT4	3.9	2.0–5.8	
ypN0	6.1	5.8–6.5	
ypN1	5.2	4.4–6.0	< 0.001
ypN2	3.7	3.0–4.4	
Preoperative stage II	5.8	5.0–6.6	0.389
Preoperative stage III	5.6	5.1–6.0	

TABLE 2. Results of multivariate analysis

	Hazard ratio	95% confidence interval	p
ypT	1.307	0.847–2.014	0.226
ypN	1.507	0.935–2.428	0.092
Postoperative stage	1.268	0.793–2.027	0.793
Downstaging (response to preoperative therapy)	2.725	1.4–5.3	0.003

13 (43%) stage III. Preoperative stage T was following: cT2 in 6 patients (20%), cT3 23 (77%) and cT4 1 patient (3%). Lymh nodes were preoperatively negative in 17 patients (57%) and cN1 was established in 13 (43%). In none of the patients with pathological complete response cN2 was detected preoperatively, (Table 1, Figure 1).

The results show that patients with complete pathological response (ypT0N0) have excellent prognosis, as 5-year survival rate exceeds 90%, (72% in postoperative stage II ad 57% in postoperative stage III). Statistically significant are also differences in survival according to preoperative T stage ($p = 0.011$) and preoperative N stage ($p < 0.001$). If tumor cells are found in resected specimens, it means worse prognosis, as 5-year survival rate falls from 80 % in ypN0 to 65% in ypN1 and only 30% in ypN2.

According to univariate analysis, statistically important variables were pooperative stage and pooperative T and N. We used proportional hazards model or the Cox regression to check, if any of aforementioned variables, including response to preoperative therapy (considered as postoperative downstaging), act as independent prognostic factors in predicting survival in patients after neoadjuvant therapy. The results are shown in Table 2. ypT, ypN and postoperative stage do not act as independent variables. The only statistically significant independent prognostic factor is the response to neoadjuvant therapy ($p < 0.003$).

Figure 2 shows differences in survival according to response to neoadjuvant therapy in group of patients with preoperative stage II, compared to group of patients with preoperative stage III. Survival is statistically significantly better if patients respond to neoadjuvant therapy.

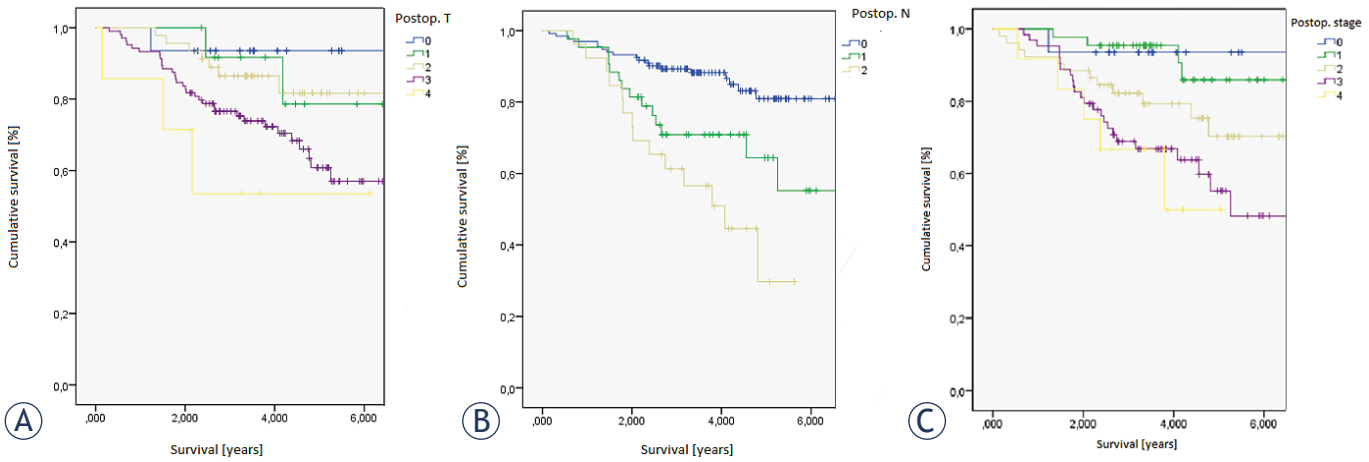

FIGURE 1. Survival according to **(A)** postoperative T (ypT), **(B)** postoperative N (ypN) and **(C)** postoperative stage (yS).

Discussion

Evaluating tumor response to neoadjuvant radiochemotherapy only on the basis of downstaging can be misleading. Tumor can decrease in size significantlly (for example from preoperative T3 to postoperative T2), but there may be no evident tumor regression, which means considerable mass of tumor cells in macroscopically small tumor. On the other hand, despite of no downsizing after neoadjuvant therapy, there may be good regression and very few or no tumor cells are found in the resected surgical specimen.[10,14]

Complete pathologic response (pCR), which means stage ypT0N0 or in other words no tumor cells in resected surgical specimen, can be detected in 7–30% of patients with locally advanced rectal cancer, treated with neoadjuvant therapy.[2,7,8] Our results are comparable with those studies, as we detected 14.8% of pCR. Using statistical analysis, we found out that pCR means excellent prognosis, as 5-year survival rate turned out to be >90% (p = 0.001). Meta analysis of 12 larger studies worldwide reports 90.2% 5-year survival rate in pCR patients (p = 0.0001)[15]; similar percentage (90% or more) is mentioned in various other studies[2,4,16], while others failed to prove relation between pCR and better survival.[15] In the literature, strong evidence exists that patients with pCR have very few local recurrences (2–5% in 5 years) and that there are statistically significant differences, if groups of patients with pCR are compared to those who failed to respond to preoperative treatment.[4,16] It is important to state that in some no local recurrences at all were found in groups of pCR patients.[6,17] Nevertheless, regardless of no local recurrences, chance of distant metastases still exists. Primary tumor can completely respond to neoadjuvant therapy, but the problem is distant micrometastatic focuses, which can stay undetected in the time of primary diagnostics. They can respond to neoadjuvant therapy or not, in the latter case they remain the source of tumor cells even after successful neoadjuvant treatment at the site of primary tumor.[15,18]

According to our research, pT, pN and postoperative stage all importantly affect survival. Lower pT, no tumor cells in resected lymph nodes and lower postoperative stage mean better prognosis (p = 0.011; < 0.001 and 0.001 for pT, pN and postoperative stage, respectivelly). Nevertheless, none of mentioned variables proved to be statistically significant in multivariate analysis. The only prognostic factor, which acts as independend variable, was response to neoadjuvant therapy, in other words downstaging (p = 0.003). Tumor deposits in local lymph nodes almost invariably mean worse prognosis.

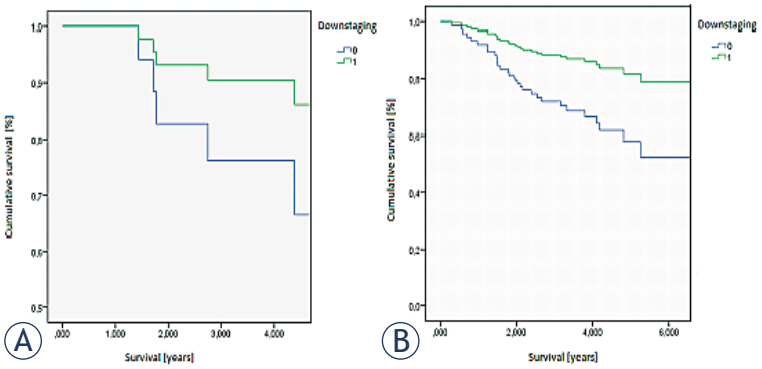

FIGURE 2. Survival according to response to neoadjuvant therapy (0: no response, 1: response): **(A)** group of patients with preoperative stage II, **(B)** group of patients with preoperative stage III.

An interesting finding is that in approximately 17% of patients with ypT0, tumor cells in perirectal lymph nodes can still be found. These patients act similar as group of patients with no response to neoadjuvant therapy.[6,19]

There remains an open question why achieving pCR means good prognosis. pCR is achieved in tumors, which themselves have a favourable biological profile with lesser susceptibility to local recurrences or distant metastases. Various trials tried to find possible biological markers for pCR.[2,11,19]

Considering data exist about excellent prognosis in patients with pCR but a question about most appropriate therapy in patients with pCR is still unanswered. Could neoadjuvant radiochemotherapy without surgery suffice or might less extensive operation, for example transanal local excision be a better option for them?[1,19,20] There are many reasons against TME: it is a mutilating procedure with significant mortality and many long-term consequences (fecal incontinence, urinary and sexual dysfunction). But on the other hand, without surgery we can not reliably assess pCR as accuracy of other methods for assesment of tumour response to preoperative treatment is low.[12]

Is there any possibility to assess preoperatively, whether patients responded to treatment completely and all tumor cells were destroyed? Clinical complete response (cCR) represents a list of clinical and endoscopic characteristics: whitening of rectal wall mucosa, telangiectasias within mucosa, scars in rectal wall, seen as light stiffness of the wall during the insuflation. If an ulceration, palpable node or stenosis are found during examination, it means incomplete clinical response.[12] Two different terms

are used: *initial cCR*, which is assessed immediately after neoadjuvant therapy, and *sustained cCR*, when cCR is mantained for 10 weeks – 12 months after completing chemoradiotherapy. The problem of this approach is that we do not know anything about nodal status. Namely, in lymph nodes residual tumor cells may still be present.[18] Brasilian researchers were the first to introduce so-called »wait-and-see« approach in selected group of patients.[16,19] Those patients were not operated, yet were closely followed. Follow up consisted of clinical examination, rigid proctoscopy, biopsies and measurements of serum CEA levels. In this trial only 99 patients with sustained cCR were included. 5-year overall survival was 92.7% and 5-year disease free survival 85%, which is comparable with results in operated patients. According to the results of exsistent trial they concluded that »wait-and-see« is safe and successfull method, but only in carefully selected patients with low-rectal carcinoma and good response to neadjuvant therapy.[16,19]

Dutch research group defined cCR on the basis of MRI and endoscopy as follows: on MRI no residual tumor is detected or only fibrosis is present; there are no suspicious lymh nodes; endoscopically there can be no residual tumor seen; biopsy must be negative; if in the beginning tumor is palpable at the digitorectal examination, it should be undetectable at the same examination after neoadjuvant therapy. Their testing group numbered 21 patients: oncological outcome was comparable to the outcome in operated patients, 2-year survival was 100%, local recurrence was detected in 2%. Moreover, unoperated patients had significantly less functional complications. Researchers put stress on the importance of assessing nodal status after neoadjuvant therapy when making a decision whether certain patient is appropriate for »wait-and-see« approach. They used MRI to assess nodal status, which was not the case in Brasilian trial. Consequently, the latter included more patients with undetected residual tumor cells in lymph nodes. It might be the reason why oncological outcome in brasilian trial is worse than in the Dutch one.[21] Other trials did not present such good results of »wait-and-see« approach, in fact they noted significantly more local recurrences (23–83%) while long term survival could be compared to long term survival in operated patients.

One must point out the limitations of current researches: many of them are small, retrospective studies with relative short follow-up, therefore more extensive trial should be carried out in the future. The most appropriate would be a prospective randomised clinical trial to compare »wait-and-see« approach to standard neoadjuvant radiochemotherapy with total mesorectal excision of rectal cancer. However, random patient assignment to either of research groups could be questionable. An American retrospective trial, which assessed the percentage of patients with preoperatively determined cCR that actually achieved pCR, determined postoperatively. Only a fourth of cCR patients achieved also pCR, what points out, how important is careful selection of patients, suitable for nonoperative treatment.[12,22]

Our research allowed us to demonstrate that patients with good response to preoperative radiochemotherapy have better prognosis and less recurrences or distant metastases. For them, benefits of neoadjuvant therapy are indisputable. Existent research should be a basis for further researches, with which predictive factors of good or poor respose to radiochemotherapy in a population of patients with locally advanced rectal cancer could be defined. In a population there are always patients with poor or no response to neodjuvant therapy. It is proven that preoperative radiochemotherapy generally (except for patients with pCR) does not improve overall survival. It certainly diminishes possibility of local recurrences, but the main cause of death in rectal cancer patients are usually distant metastases, which can not always be prevented by neoadjuvant therapy.[18] Many studies show that high quality of radical total mesorectal excisions overweights multimodal treatment. The question remains whether chemotherapeutics and radiation are really so vital for rectal cancer patients. The fact is that with quality radical mesorectal excision all tumor tissue and lymph nodes are removed.[23] TME is mutilating procedure which causes many functional disabilities, but on the other hand radiochemotherapy also has its side effects. One of them are long-term effects because of nerve and vascular damage in perirectal area, which means worsening of anorectal function. It can be much worse after radiochemotherapy than after TME alone.[24,25] In the future surveys on posttreatment quality of life is necessary to define most appropriate approach with best oncological and functional outcome in patients, who respond to treatment poorly or do not respond at all.

References

1. Trakarnsanga A, Ithimakin S, Weiser MR. Treatment of locally advanced rectal cancer: controversies and questions. *World J Gastroenterol* 2012; **18:** 5521-32. doi: 10.3748/wjg.v18.i39.5521

2. Ferrari L, Fichera A Neoadjuvant chemoradiation therapy and pathological complete response in rectal cancer. *Gastroenterology Report* 2015; **3:** 277-88. doi: 10.1093/gastro/gov039

3. Peeters KC, van de Velde CJH, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients – a Dutch colorectal cancer group study. *J Clin Oncol* 2005; **23:** 6199-206. doi: 10.1200/JCO.2005.14.779

4. Guillem JG, Chessin DB, Cohen AM, Shia J, Mazumdar M, Enker W, et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. *Ann Surg* 2005; **241:** 829-36. doi: 10.1097/01.sla.0000161980.46459.96

5. García-Aguilar J, Hernandez de Anda E, Sirivongs P, Lee SH, Madoff RD, Rothenberger DA. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. *Dis Colon Rectum* 2003; **46:** 298-304. doi: 10.1097/01.DCR.0000054637.75996.DF

6. Hughes R, Glynne-Jones R, Grainger J, Richman P, Makris A, Harrison M, et al. Can pathological complete response in the primary tumour following pre-operative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for sterilisation of pelvic lymph nodes, a low risk of local recurrence and the appropriateness of local excision? *Int J Colorectal Dis* 2006; **21:** 11-7. https://doi.org/10.1007/s00384-005-0749-y

7. Huebner M, Wolff BG, Smyrk TC, Aakre J, Larson DW. Partial pathologic response and nodal status as most significant prognostic factors for advanced rectal cancer treated with preoperative chemoradiotherapy. *World J Surg* 2012; **36:** 675-83. doi: 10.1007/s00268-011-1409-8

8. Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg* 2009; **250:** 582-9. doi: 10.1097/SLA.0b013e3181b91e63

9. Huh JW, Kim HR, Kim YJ. Clinical prediction of pathological complete response after preoperative chemoradiotherapy for rectal cancer. *Dis Colon Rectum* 2013; **56:** 698-703. doi: 10.1097/DCR.0b013e3182837e5b

10. Hermanek P, Merkel S, Hohenberger W. Prognosis of rectal carcinoma after multimodal treatment: ypTNM classification and tumor regression grading are essential. *Anticancer Res* 2013; **33:** 559-66. doi: 10.4143/crt.2015.254

11. Kawai K, Ishihara S, Nozawa H, Hata K, Kiyomatsu T, Morikawa T, et al. Prediction of pathological complete response using endoscopic findings and outcomes of patients who underwent watchful waiting after chemoradiotherapy for rectal cancer. *Dis Colon Rectum* 2017; **60:** 368–375. doi: 10.1097/DCR.0000000000000742

12. Smith FM, Wiland H, Mace A, Pai RK, Kalady MF. Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy. *Dis Colon Rectum* 2014; **57:** 311–315. doi: 10.1097/DCR.0b013e3182a84eba

13. Sobin LH, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours*. 7th edition. New York: John Wiley & Sons; 2009.

14. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorect Dis* 1997; **12:** 19-23.

15. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg* 2012; **99:** 918-28. doi: 10.1002/bjs.8702

16. Fraser MS, Rao C, Perez RO, Bujko K, Habr-Gama A, Faiz O. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic mode. *Dis Colon Rectum* 2015; **58:** 159-171.

17. Kuo LJ, Liu MC, Jian JJ, Horng CF, Cheng TI, Chen CM, et al. Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy? *Ann Surg Oncol* 2007; **14:** 2766-72. doi: 10.1245/s10434-007-9471-z

18. Theodoropoulos G, Wise WE, Padmanabhan A, Kerner BA, Taylor CW, Aguilar PS, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. *Dis Colon Rectum* 2002; **45:** 895-903. doi.org/10.1007/s10350-004-6325-7

19. Sprenger T, Rothe H, Conradi CR, Beissbarth T, Kauffels A, Kitz J, et al. Stage-dependent frequency of lymph node metastases in patients with rectal carcinoma after preoperative chemoradiation: results from the CAO/ARO/AIO-94 trial and from a comparative prospective evaluation with extensive pathological workup. *Dis Colon Rectum* 2016; **59:** 377-385. doi: 10.1097/DCR.0000000000000570

20. Kong JC, Guerra RG, Warrier SK, Ramsay RG, Heriot AG. Outcome and salvage surgery following "Watch and Wait" for rectal cancer after neoadjuvant therapy: a systematic review. *Dis Colon Rectum* 2017; **60:** 335-345. doi: 10.1097/DCR.0000000000000754

21. Kim NK, Kim MS, Al-Asari SF. Update and debate issues in surgical treatment of middle and low rectal cancer. *J Korean Soc Coloproctol* 2012; **28:** 230-240. doi: 10.1097/SLA.0b013e31829068c5

22. Maas M, Beets-Tan RG, Lanbregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. Wait-and-see policy for clinical complete responders after chemoradioation for rectal cancer. *J Clin Oncol* 2011; **29:** 4633-40. doi: 10.1200/JCO.2011.37

23. Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 448 patients. *J Am Coll Surg* 2002; **194:** 131-5.

24. Chang KH, Smith MJ, McAnena OJ, Aprjanto AS, Dowdall JF. Increased use of multidisciplinary treatment modalities adds little to the outcome of rectal cancer treated by optimal total mesorectal excision. *Int J Colorectal Dis* 2012; **27:** 1275-83. doi: 10.1007/s00384-012-1440-8

25. Loos M, Quentmeier P, Schuster T, Nitsche U, Gertler R, Keerl A, et al. Effect of preoperative radio(chemo)therapy on long term functional outcome in rectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol* 2013; **20:** 1816-28. doi: 10.1245/s10434-012-2827-z

research article

Laparoscopic parenchyma-sparing liver resection for colorectal metastases

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Background. Laparoscopic liver resection (LLR) of colorectal liver metastases (CLM) is increasingly performed in specialized centers. While there is a trend towards a parenchyma-sparing strategy in multimodal treatment for CLM, its role is yet unclear. In this study we present short- and long-term outcomes of laparoscopic parenchyma-sparing liver resection (LPSLR) at a single center.

Patients and methods. LLR were performed in 951 procedures between August 1998 and March 2017 at Oslo University Hospital, Oslo, Norway. Patients who primarily underwent LPSLR for CLM were included in the study. LPSLR was defined as non-anatomic hence the patients who underwent hemihepatectomy and sectionectomy were excluded. Perioperative and oncologic outcomes were analyzed. The Accordion classification was used to grade postoperative complications. The median follow-up was 40 months.

Results. 296 patients underwent primary LPSLR for CLM. A single specimen was resected in 204 cases, multiple resections were performed in 92 cases. 5 laparoscopic operations were converted to open. The median operative time was 134 minutes, blood loss was 200 ml and hospital stay was 3 days. There was no 90-day mortality in this study. The postoperative complication rate was 14.5%. 189 patients developed disease recurrence. Recurrence in the liver occurred in 146 patients (49%), of whom 85 patients underwent repeated surgical treatment (liver resection [n = 69], ablation [n = 14] and liver transplantation [n = 2]). Five-year overall survival was 48%, median overall survival was 56 months.

Conclusions. LPSLR of CLM can be performed safely with the good surgical and oncological results. The technique facilitates repeated surgical treatment, which may improve survival for patients with CLM.

Key words: laparoscopic parenchyma-sparing liver resection; colorectal cancer; liver metastases; survival

Introduction

Colorectal cancer is the third most common cancer worldwide.[1] Liver resection is considered the only curative treatment for colorectal liver metastases (CLM), with postoperative 5-year survival rates of 30–58%.[2-5] Parenchyma-sparing liver resection (PSLR) has, in many centers, become an essential part of multimodal treatment of CLM. The parenchyma-sparing approach allows radical resection with maximum preservation of liver parenchyma, thereby decreasing the risk of postoperative liver failure and facilitating repeated resections in the case of liver recurrence.[6-13]

Laparoscopic liver resection (LLR) has progressively developed during the past two decades and the advantages are well-known.[14-20] Our experience in LLR has been reported previously.[18,21-27] The

short- and long-term outcomes after laparoscopic parenchyma-sparing liver resection (LPSLR) for CLM have been minimally reported in the literature.[28-30] In this study we report short and long-term outcomes after 18 years of LPSLR for CLM in a single center.

Patients and methods

Rikshospitalet is the tertiary referral center for hepato-pancreato-biliary surgery for the South-Eastern Regional Health Authority in Norway. Between August 1998 and March 2017, LLRs were performed in 951 procedures. Of these, patients who primarily underwent LPSLR for CLM between August 1998 and March 2016 were identified from the continuously updated database and included in the study. Patients who previously underwent open liver resections were excluded from the study. LPSLR was defined as non-anatomic laparoscopic liver resections. In one case LPSLR was performed in a patient with a transplanted liver. Patients who underwent hemihepatectomy or sectionectomy were excluded, as were patients with planned two-stage procedures. Data were collected from Electronic Health Records. The study was performed in accordance with the Declaration of Helsinki, and all patients signed informed consent for the procedures.

Standard preoperative investigations included contrast-enhanced X-ray computed tomography (CT) scans of the thorax and abdomen, clinical biochemistry, magnetic resonance imaging (MRI) of the liver (if required) and positron emission tomography (PET) scan (if required).

Synchronous CLM was defined as liver metastases detected within 12 months of diagnosis of the primary CRC, otherwise metastases were defined as metachronous.

The surgical technique for LLR at our centre has been described previously.[18,21] Laparoscopic ultrasonography and advanced laparoscopic equipment were preconditions. The main dissection instruments were LigaSure® (Covidien, Mansfield, MA, USA), Thunderbeat® (Olympus, Tokyo, Japan) or Cayman® (B.Braun, Melsungen, Germany), sometimes assisted by ultrasonic aspirators, mainly CUSA® (Integra, Cincinnati, OH, USA), SonoSurg aspirator® (Olympus, Tokyo, Japan) and Söring aspirator® (Söring, Quickborn, Germany). Ultrasonic dissectors, as Sonicision® (Covidien, Mansfield, MA, USA) or Harmonic Scalpel® (Ethicon, Sommerville, NJ, USA) were mostly used to achieve a superficial parenchymal transection. Surgical clips and the LigaSure® were used in small and medium-sized vessel transections, whereas the Endo-GIA®(Covidien, Inc.) was applied for transection of major vessels.

Non-steroidal anti-inflammatory drugs and intravenous paracetamol were used for postoperative analgesia. Opioids were given if required. Patients were encouraged to mobilize early and resume oral intake as soon as tolerated.

Tumor size was measured following specimen fixation in formaldehyde during the histopathologic analyses of resected specimens. The distance from the tumor to the resection margin was measured macroscopically and microscopically after fixation. All resection margins were assessed microscopically with regard to tumor tissue, a resection margin of less than 1 mm was defined as positive (R1). In cases where multiple resections were performed, the narrowest resection margin was recorded.

Postoperative complications were categorized in accordance to the Accordion classification.[31,32]

Patients were treated with neoadjuvant and adjuvant chemotherapy following national guidelines. The data are presented as median (range) and/or number (percentage). Overall survival was estimated from liver resection until death and recurrence-free survival was estimated from liver resection until the first registered recurrence of the disease or progression in cases with extrahepatic metastases. Survival probabilities were calculated using the Kaplan–Meier method. SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, USA: IBM corp) was used for statistical analysis.

Results

Perioperative data

Between August 1998 and March 2016, a total of 296 patients underwent LPSLR as the primary surgical treatment for CLM at Oslo University Hospital. Baseline characteristics are summarized in Table 1. Resection of solitary metastases was performed in 204 patients (69%), multiple resections were performed in the remaining 92 patients (31%). Two concomitant liver resections were performed in 66 cases, three resections in 12 cases, four resections in 12 cases, five and seven resections in the two remaining cases. In total, 432 liver specimens were resected in 296 procedures. Median resection margin was 3 mm (range 0 to 30 mm). The total

TABLE 1. Patient characteristics (N = 296)

Age, years, median (range)	66 (29–89)
Gender (female/male)	110/186
BMI, kg, median, (range)	25 (16–42)
ASA score	2 (1–3)
Synchronous/metachronous	224/72
Neoadjuvant chemotherapy yes/no/no information	122/168/6
Preoperative CEA, median (range)	12 (1–498)
Extrahepatic disease at the time of liver resection, n (%)	21 (7.1)
Liver involvement (unilobar/bilobar)	233/63

ASA = American Society of Anestesiology; BMI = body mass index; CEA = carcino-embryonic antigen

TABLE 2. Intraoperative details and postoperative complications

Operative time, min, median (range)	134 (20-373)
Blood loss, ml, median (range)	200 (<50-4000)
No. of resected specimens pr. procedure, 1/ 2/ 3/ 4/ 5/ 7 Total	204/ 66/ 12/ 12/ 1/ 1 432
Total No. of removed lesions	448
Max diameter of lesions, mm, median d (range)	22 (4-80)
Resection margin, R0 / R1 (n=294) Median, mm (range)	239 / 55 3 (0-30)
Conversion to open access, n (%)	5 (1.7)
Combination with RFA or cryoablation, n (%)	20 (6.7)
Simultaneous resection with primary, n (%)	11 (3.7)
Postoperative complications, Accordion, n (%) Grade 2 / Grade 3 / Grade 4 / Grade 5	43 (14.5) 19/ 14/ 8/ 2
Postoperative hospital stay, days, median (range)	3 (1-35)

RFA = Radiofrequency ablation

TABLE 3. Long-term outcomes

Disease recurrence, n (%)	189 (64)
Liver recurrence, n (%)	146 (49.3)
Isolated liver recurrence, n (%)	75 (25.3)
Recurrence in resection bed, n (%)	7 (2.3)
Repeat liver resection, n (%)	69 (23.3)
Secondary RFA, n (%)	14 (4.7)
Median overall survival, months (95% confidential interval)	56 (46-66)
3-year overall survival rate, %	68
5-year overall survival rate, %	48
3-year recurrence-free survival rate, %	36
5-year recurrence-free survival rate, %	34

RFA = Radiofrequency ablation

number of removed lesions was 448 and the median diameter was 22 mm (range: 4 to 80 mm). The resected tumors were located in all liver segments (Table 2).

Five procedures (1.7%) were converted to open surgery. The reason for conversion was hemorrhage (n = 3), unfavorable location of tumor (n = 1) and small intestine perforation (n = 1). In 20 cases LPSLR was combined with ablation (n = 18) or cryoablation (n = 2). 11 patients underwent synchronous resections for colorectal cancer. Median operative time was 134 min (20–373), while median blood loss was 200 ml (<50–4000). Postoperative complications developed in 43 patients (14.5%) and were graded according to the expanded Accordion classification (Table 2). The median hospital stay was 3 days (range: 1–35). There was no 90-day mortality in this study. Perioperative adverse events are described in Table 2.

Long-term outcomes

Median observation time was 40 months (4 to 191). Twenty-one patients had extrahepatic metastases (16 with lung metastases, two with metastases on the peritoneum, two with the metastases in the brain and the lungs, and one with metastasis in the spine) at the time of liver resection.

Disease recurrence or progression of extrahepatic metastases occurred in 189 (64%) patients on a median follow-up of 6 months. Recurrence in the liver occurred in 146 (49.3%) patients with a median follow-up of 6 months, including 7 patients (2.3%) who experienced local recurrence. Isolated hepatic recurrences developed in 75 patients. The most common sites of recurrence were liver, lungs, peritoneum and brain. A total of 69 patients underwent repeated liver resections, of whom 43 had laparoscopic and 26 had open resections. Additionally, 14 patients underwent secondary radiofrequency ablation and two patients had liver transplantation for liver recurrences (Table 3).

Median overall survival was 56 months One-, three- and five-year overall survival rates were 97%, 68% and 48%, respectively (Figure 1).

One-, three- and five-year recurrence-free survival was 50%, 36% and 34%, while the median recurrence-free survival was 12 months (Table 3).

Discussion

In this study, we report a single center experience of LPSLR for CLM. In 1960's and 1970's the major-

ity of patients with CLM (70–80%) were never candidates for resection, but nowadays a large portion of patients undergo surgery due to significant improvements in preoperative investigations, surgical techniques, anesthesia, chemotherapy regimens and the expansion of resectability criteria.[4,5] Based on oncologic reasoning at that time, hemihepatectomies were considered the only curative option in patients with CLM. Nevertheless, over the years, PSLR has increasingly been used for CLM.[6,33] There are two main reasons for this: the evolution of the concept of resectability and the increased knowledge on tumor biology.[34,35]

Over the past decades, the concept of tumor resectability in CLM has changed significantly. While in the 1970s, resection was considered only in patients with solitary liver metastasis, nowadays resection of CLM is considered regardless of tumor size and number, provided that a resection with negative margins is possible, that stable disease can be achieved, that the remaining parenchyma is sufficient to prevent liver failure, and that there is no unresectable extrahepatic disease.[36]

There are two known mechanisms for hepatic spread of colorectal cancer: metastasis from the primary tumor, and metastasis from other existing metastases. In contrast to hepatocellular carcinoma, tumor cells from CLM do not migrate into intrahepatic portal branches to form secondary intrahepatic metastases. Instead, intrahepatic lymphatic invasion can be responsible for ''remetastasis'' from liver metastases and may be a prognostic factor for CLM.[37-42]

PSLR is an essential part of multimodal treatment of CLM, as it avoids unnecessary removal of normal parenchyma and is associated with less surgical stress, fewer postoperative complications and feasibility of future resections.[6,33,43]

LLR is becoming an important alternative to conventional open surgery. In this study we included patients who primarily underwent LPSLR for CLM. All resections aimed to achieve complete tumor resection and to preserve as much liver parenchyma as possible. We report both perioperative and long-term oncologic outcomes. Five patients (1.7%) were converted to open surgery in our series, which is a lower conversion rate than reported for both minor and major laparoscopic hepatectomies by other groups.[16,28,29,44] Postoperative complications developed in 43 cases (14.5%) and the median postoperative length of stay was 3 days. Perioperative outcomes in this study are consistent with earlier reported surgical results after open and laparoscopic PSLR for CLM.[7,9-12,28,29]

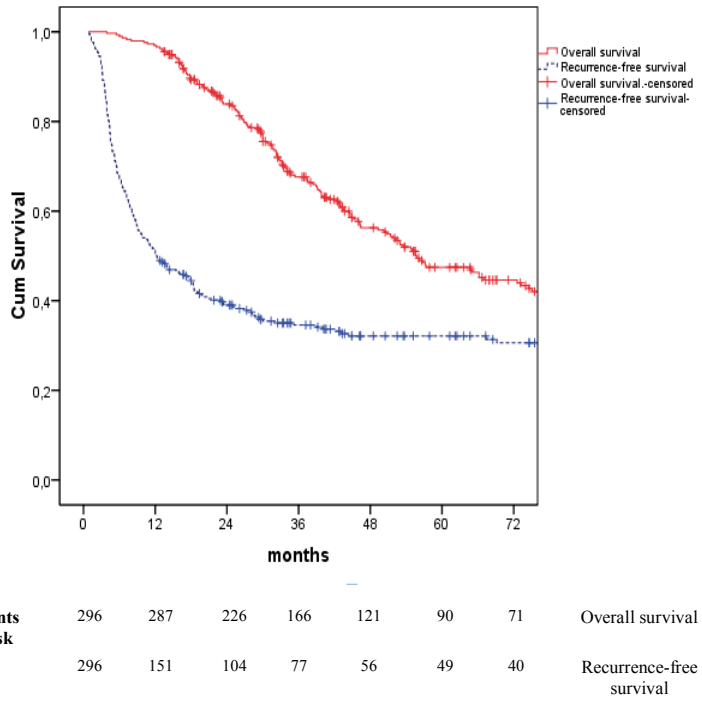

FIGURE 1. Kaplan-Meier survival curves.

Previous studies have indicated that survival rates were higher in patients with resection margins larger than 10 mm compared to those with the resection margins less than 10 mm.[45,46] Other studies have opposed these findings and indicate that predicted margins of less than 10 mm should not be an exclusion criteria for resection in these patients.[40,47] Moreover, recently two large studies suggested that a one mm cancer free margin can be considered oncologically adequate for resection of CLM.[27,48]

In the present study, isolated hepatic recurrence developed in 75 cases, for which repeated hepatectomy was performed in 68% (51 of 75) (18 open, 33 laparoscopic). Local recurrence developed in seven patients (2.3%), five following R1 resection (9%) and two following R0 resection (0.8%). The relatively low number of local recurrences after R1 resections can be explained by the use of energy-based surgical instruments for parenchyma transection, that induce thermal damage to the surrounding tissue and thus create an additional zone of tissue necrosis. As a result, the true resection margins may be several millimeters wider than those estimated by the pathologist.

In our study liver recurrences were frequently resectable. A total of 69 repeat liver resections (51 with isolated liver recurrence and 18 with extrahepatic resectable metastases) were performed.

Tanaka *et al.*[49] showed that minor resections may offer a long-term survival advantage compared to a major resection in patients with multiple CLM. In our study 80 patients received solely multiple LPSLR, and the five-year survival for this group was 44%.

In the study published in 2014, Evrard *et al.*[50] combined PSLR with RFA in 288 patients, five-year overall survival was 37%, compared to 39% for the 18 patients that underwent resection combined with local ablation in our study.

These outcomes demonstrate that multiple simultaneous LPSLRs are feasible and may be preferred over single major resection in a substantial portion of patients. In patients with additional unfavorable located lesions, PSLR can be combined with local ablation avoiding formal resections with acceptable oncological results. In addition, the patients with formal resections compared with parenchyma-sparing technique have reduced chance of further surgical treatment.[6]

Alvarez *et al.*[6] showed in a systematic review that five-year overall survival rates varied from 27% to 60% for anatomic and from 29% to 61% for non-anatomic liver resection, compared to 48% in our study.

In conclusion, outcomes after laparoscopic parenchyma-sparing liver resection are comparable to those after open major and minor hepatectomy. In centers with sufficient expertise, this may be a good treatment option for patients with CLM.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61:** 69-90. doi: 10.3322/caac.20107
2. Curley SA. Outcomes after surgical treatment of colorectal cancer liver metastases. *Sem Oncol* 2005; **32(Suppl 9):** S109-11. doi: 10.1053/j.seminoncol.2005.06.011
3. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008; **247:** 125-35. doi: 10.1097/SLA.0b013e31815aa2c2
4. Chiappa A, Makuuchi M, Lygidakis NJ, Zbar AP, Chong G, Bertani E, et al. The management of colorectal liver metastases: Expanding the role of hepatic resection in the age of multimodal therapy. *Crit Rev Oncol Hematol* 2009; **72:** 65-75. doi: 10.1016/j.critrevonc.2008.11.003
5. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Brit J Cancer* 2006; **94:** 982-99. doi: 10.1038/sj.bjc.6603033
6. Alvarez FA, Sanchez Claria R, Oggero S, de Santibanes E. Parenchymal-sparing liver surgery in patients with colorectal carcinoma liver metastases. *World J Gastrointest Surg* 2016; **8:** 407-23. doi: 10.4240/wjgs.v8.i6.407
7. Matsuki R, Mise Y, Saiura A, Inoue Y, Ishizawa T, Takahashi Y. Parenchymal-sparing hepatectomy for deep-placed colorectal liver metastases. *Surgery* 2016; **160:** 1256-63. doi: 10.1016/j.surg.2016.06.041
8. Matsumura M, Mise Y, Saiura A, Inoue Y, Ishizawa T, Ichida H, et al. Parenchymal-sparing hepatectomy does not increase intrahepatic recurrence in patients with advanced colorectal liver metastases. *Ann Surg Oncol* 2016; **23:** 3718-26. doi: 10.1245/s10434-016-5278-0
9. Memeo R, de Blasi V, Adam R, Goere D, Azoulay D, Ayav A, et al. Parenchymal-sparing hepatectomies (PSH) for bilobar colorectal liver metastases are associated with a lower morbidity and similar oncological results: a propensity score matching analysis. *HPB* 2016; **18:** 781-90. doi: 10.1016/j.hpb.2016.06.004
10. Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. *Ann Surg* 2016; **263:** 146-52. doi: 10.1097/sla.0000000000001194
11. Gold JS, Are C, Kornprat P, Jarnagin WR, Gonen M, Fong Y, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. *Ann Surg* 2008; **247:** 109-17. doi: 10.1097/SLA.0b013e3181557e47
12. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, et al. Anatomical major resection versus nonanatomical limited resection for liver metastases from colorectal carcinoma. *Am J Surg* 2001; **181:** 153-9. PubMed PMID: 11425058.
13. Guzzetti E, Pulitano C, Catena M, Arru M, Ratti F, Finazzi R, et al. Impact of type of liver resection on the outcome of colorectal liver metastases: a case-matched analysis. *J Surg Oncol* 2008; **97:** 503-7. doi: 10.1002/jso.20979
14. Reich H, McGlynn F, DeCaprio J, Budin R. Laparoscopic excision of benign liver lesions. *Obstet Gynecol* 1991; **78:** 956-8.
15. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. *Ann Surg* 2009; **250:** 825-30.
16. Reddy SK, Tsung A, Geller DA. Laparoscopic liver resection. *World J Surg* 2011; **35:** 1478-86. doi: 10.1007/s00268-010-0906-5
17. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg* 2015; **261:** 619-29. doi: 10.1097/sla.0000000000001184
18. Edwin B, Mala T, Gladhaug I, Fosse E, Mathisen Y, Bergan A, et al. Liver tumors and minimally invasive surgery: a feasibility study. *J Laparoendosc Adv Surg Tech A* 2001; **11:** 133-9. doi: 10.1089/10926420152389260
19. Cherqui D, Husson E, Hammoud R, Malassagne B, Stephan F, Bensaid S, et al. Laparoscopic liver resections: a feasibility study in 30 patients. *Ann Surg* 2000; **232:** 753-62.
20. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg* 2009; **250:** 831-41. doi: 10.1097/SLA.0b013e3181b0c4df
21. Mala T, Edwin B, Rosseland AR, Gladhaug I, Fosse E, Mathisen O. Laparoscopic liver resection: experience of 53 procedures at a single center. *J Hepatobiliary Pancreat Surg* 2005; **12:** 298-303. doi: 10.1007/s00534-005-0974-3
22. Kazaryan AM, Marangos IP, Rosok BI, Rosseland AR, Villanger O, Fosse E, et al. Laparoscopic resection of colorectal liver metastases: surgical and long-term oncologic outcome. *Ann Surg* 2010; **252:** 1005-12. doi: 10.1097/SLA.0b013e3181f66954
23. Kazaryan AM, Pavlik Marangos I, Rosseland AR, Rosok BI, Mala T, Villanger O, et al. Laparoscopic liver resection for malignant and benign lesions: ten-year Norwegian single-center experience. *Arch Surg* 2010; **145:** 34-40. doi: 10.1001/archsurg.2009.229
24. Barkhatov L, Fretland AA, Kazaryan AM, Rosok BI, Brudvik KW, Waage A, et al. Validation of clinical risk scores for laparoscopic liver resections of colorectal liver metastases: a 10-year observed follow-up study. *J Surg Oncol* 2016; **114:** 757-63. doi: 10.1002/jso.24391
25. Edwin B, Nordin A, Kazaryan AM. Laparoscopic liver surgery: new frontiers. *Scand J Surg* 2011; **100:** 54-65. doi: 10.1177/145749691110000110
26. Kazaryan AM, Rosok BI, Marangos IP, Rosseland AR, Edwin B. Comparative evaluation of laparoscopic liver resection for posterosuperior and anterolateral segments. *Surg Endosc* 2011; **25:** 3881-9. doi: 10.1007/s00464-011-1815-x

27. Postriganova N, Kazaryan AM, Rosok BI, Fretland A, Barkhatov L, Edwin B. Margin status after laparoscopic resection of colorectal liver metastases: does a narrow resection margin have an influence on survival and local recurrence? *HPB* 2014; **16:** 822-9. doi: 10.1111/hpb.12204

28. Cipriani F, Shelat VG, Rawashdeh M, Francone E, Aldrighetti L, Takhar A, et al. Laparoscopic parenchymal-sparing resections for nonperipheral liver lesions, the diamond technique: technical aspects, clinical outcomes, and oncologic efficiency. *J Am Coll Surg* 2015; **221:** 265-72. doi: 10.1016/j.jamcollsurg.2015.03.029

29. Conrad C, Ogiso S, Inoue Y, Shivathirthan N, Gayet B. Laparoscopic parenchymal-sparing liver resection of lesions in the central segments: feasible, safe, and effective. *Surg Endosc* 2015;**29:** 2410-7. doi: 10.1007/s00464-014-3924-9

30. D'Hondt M, Yoshihara E, Vansteenkiste F, Steelant PJ, Van Ooteghem B, Pottel H, et al. Laparoscopic parenchymal preserving hepatic resections in semiprone position for tumors located in the posterosuperior segments. *Langenbecks Arch Surg* 2016; **401:** 255-62. doi: 10.1007/s00423-016-1375-6

31. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. *Ann Surg* 2009; **250:** 177-86. doi: 10.1097/SLA.0b013e3181afde41

32. Porembka MR, Hall BL, Hirbe M, Strasberg SM. Quantitative weighting of postoperative complications based on the accordion severity grading system: demonstration of potential impact using the american college of surgeons national surgical quality improvement program. *J Am Coll Surg* 2010; **210:** 286-98. doi: 10.1016/j.jamcollsurg.2009.12.004

33. Moris D, Dimitroulis D, Vernadakis S, Papalampros A, Spartalis E, Petrou A, et al. Parenchymal-sparing hepatectomy as the new doctrine in the treatment of liver-metastatic colorectal disease: beyond oncological outcomes. Anticancer Res 2017; **37:** 9-14. doi: 10.21873/anticanres.11283

34. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127:** 2893-917. doi: 10.1002/ijc.25516

35. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62:** 10-29. doi: 10.3322/caac.20138

36. Adams RB, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. *HPB* 2013; **15:** 91-103. doi: 10.1111/j.1477-2574.2012.00557.x

37. Riihimaki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. *Scientific Rep* 2016; **6:** 29765. doi: 10.1038/srep29765

38. Jin K, Gao W, Lu Y, Lan H, Teng L, Cao F. Mechanisms regulating colorectal cancer cell metastasis into liver (Review). *Oncol Lett* 2012; **3:** 11-5. doi: 10.3892/ol.2011.432

39. Kokudo N, Miki Y, Sugai S, Yanagisawa A, Kato Y, Sakamoto Y, et al. Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. *Archives Surg* 2002; **137:** 833-40. doi: doi:10.1001/archsurg.137.7.833

40. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005; **241:** 715-22, discussion 22-4. doi: 10.1097/01.sla.0000160703.75808.7d

41. Lupinacci RM, Mello ES, Pinheiro RS, Marques G, Coelho FF, Kruger JA, et al. Intrahepatic lymphatic invasion but not vascular invasion is a major prognostic factor after resection of colorectal cancer liver metastases. *World J Surg* 2014; **38:** 2089-96. doi: 10.1007/s00268-014-2511-5

42. Korita PV, Wakai T, Shirai Y, Sakata J, Takizawa K, Cruz PV, et al. Intrahepatic lymphatic invasion independently predicts poor survival and recurrences after hepatectomy in patients with colorectal carcinoma liver metastases. *Ann Surg Oncol* 2007; **14:** 3472-80. doi: 10.1245/s10434-007-9594-2

43. Fretland AA, Sokolov A, Postriganova N, Kazaryan AM, Pischke SE, Nilsson PH, et al. Inflammatory response after laparoscopic versus open resection of colorectal liver metastases: data from the Oslo-CoMet Trial. *Medicine* 2015; **94:** doi: 10.1097/MD.0000000000001786

44. Pearce NW, Di Fabio F, Teng MJ, Syed S, Primrose JN, Abu Hilal M. Laparoscopic right hepatectomy: a challenging, but feasible, safe and efficient procedure. *Am J Surg* 2011; **202:** doi: 10.1016/j.amjsurg.2010.08.032

45. Are C, Gonen M, Zazzali K, Dematteo RP, Jarnagin WR, Fong Y, et al. The impact of margins on outcome after hepatic resection for colorectal metastasis. *Ann Surg* 2007; **246:** 295-300. doi: 10.1097/SLA.0b013e31811ea962

46. Wakai T, Shirai Y, Sakata J, Valera VA, Korita PV, Akazawa K, et al. Appraisal of 1 cm hepatectomy margins for intrahepatic micrometastases in patients with colorectal carcinoma liver metastasis. *Ann Surg Oncol* 2008; **15:** 2472-81. doi: 10.1245/s10434-008-0023-y

47. Hamady ZZ, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JP. Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: a critical appraisal of the 1cm rule. *EJSO* 2006; **32:** 557-63. doi: 10.1016/j.ejso.2006.02.001

48. Hamady ZZ, Lodge JP, Welsh FK, Toogood GJ, White A, John T, et al. One-millimeter cancer-free margin is curative for colorectal liver metastases: a propensity score case-match approach. *Ann Surg* 2014; **259:** 543-8. doi: 10.1097/SLA.0b013e3182902b6e

49. Tanaka K, Shimada H, Matsumoto C, Matsuo K, Takeda K, Nagano Y, et al. Impact of the degree of liver resection on survival for patients with multiple liver metastases from colorectal cancer. *World J Surg* 2008; **32:** 2057-69. doi: 10.1007/s00268-008-9610-0

50. Evrard S, Poston G, Kissmeyer-Nielsen P, Diallo A, Desolneux G, Brouste V, et al. Combined ablation and resection (CARe) as an effective parenchymal sparing treatment for extensive colorectal liver metastases. *PloS One* 2014; **9:** e114404. doi: 10.1371/journal.pone.0114404

research article

Simultaneous pure laparoscopic resection of primary colorectal cancer and synchronous liver metastases: a single institution experience with propensity score matching analysis

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Background. The aim of the study was to compare the outcome of pure laparoscopic and open simultaneous resection of both the primary colorectal cancer and synchronous colorectal liver metastases (SCLM).

Patients and methods. From 2000 to 2016 all patients treated by simultaneous resection were assessed for entry in this single center, clinically nonrandomized trial. A propensity score matching was used to compare the laparoscopic group (LAP) to open surgery group (OPEN). Primary endpoints were perioperative and oncologic outcomes. Secondary endpoints were overall survival (OS) and disease-free survival (DFS).

Results. Of the 82 patients identified who underwent simultaneous liver resection for SCLM, 10 patients underwent LAP. All these consecutive patients from LAP were matched to 10 comparable OPEN. LAP reduced the length of hospital stay (P = 0.044) and solid food oral intake was faster (P = 0.006) in this group. No patient undergoing the laparoscopic procedure experienced conversion to the open technique. No difference was observed in operative time, blood loss, transfusion rate, narcotics requirement, clinical risk score, resection margin, R0 resections rate, morbidity, mortality and incisional hernias rate. The two groups did not differ significantly in terms of the 3-year OS rate (90 *vs.* 75%; P = 0.842) and DFS rate (60 *vs.* 57%; P = 0.724).

Conclusions. LAP reduced the length of hospital stay and offers faster solid food oral intake. Comparable oncologic and survival outcomes can be achieved. LAP is beneficial for well selected patients in high volume centers with appropriate expertise.

Key words: colorectal cancer; synchronous liver metastases; laparoscopy; liver resection; colorectal resection

Introduction

Colorectal cancer is one of the most common causes of cancer related death in the Western world.[1] At the time of diagnosis of the primary tumor, up to 25% of patients present with synchronous colorectal liver metastases (SCLM).[2] Complete surgical resection of both primary tumor and SCLM remains the only treatment option providing long-term survival and chance for cure.[3]

Different oncological strategies have been described including traditional two-stage colon first approach,[4] liver first procedure[5] or a one-step surgical resection of both the primary tumor and

SCLM.[6] Several reports have shown the benefit of a simultaneous open resection of primary tumor and SCLM compared with a staged approach.[7-8]

Minimally invasive colorectal and liver surgery are both accepted worldwide.[9-11] Technical refinements and the development of advanced laparoscopic techniques has made simultaneous resection an attractive option. However, despite the increasing use of laparoscopy in colorectal and liver resections, simultaneous pure laparoscopic resection (SPLR) of the primary colorectal cancer and SCLM is still rarely performed.

Sporadic case reports and single institution series have shown the feasibility and safety of simultaneous laparoscopic resection of both primary CRC and SCLM.[12-28] Recently, two large international multicenter retrospective studies, which were published from the same group of surgeons, confirmed that in selected patient's laparoscopic surgery allowed similar outcomes compared with the traditional open approach.[29-30]

The aim of this study was to compare the surgical and oncological outcomes of patients undergoing simultaneous resection of primary colorectal cancer and SCLM by laparoscopic or open surgery using propensity score matching.

Patients and methods

Patient selection and study design

All patients with SCLM were discussed by the multidisciplinary team. Treatment decisions were based on location and complexity of resection of the primary tumor, extent of liver resection, liver function and physical condition of the patients. The policy of the institution is not to combine a simultaneous major liver resection (≥ 3 segments) with complex colorectal procedure (*e.g.* total colectomy, low anterior resection). The most ideal candidates for combined laparoscopic liver resection were patients with solitary, peripherally located metastasis in anterolateral segments.

Study subjects were identified from a prospectively maintained database of patients who underwent liver resections for CLM from January 2000 to December 2016 at the Department of Abdominal and General Surgery, University Medical Centre Maribor. This institution is a tertiary referral center with more than 15 years' experience in laparoscopic colorectal and with 8 years' experience in laparoscopic liver surgery. SCLM were defined as those identified at the time of diagnosis of the primary colorectal cancer. All patients gave their informed consent. Ethical approval for this study was obtained from the local institutional review board. Patient records were anonymized and de-identified prior to analysis.

All patients in the database who submitted to simultaneous laparoscopic resection of both the primary tumor and SCLM were selected and included in the study. Those laparoscopic patients were compared to patients that underwent open simultaneous liver and colorectal resection for stage IV colorectal cancer. A propensity score matching was applied to identify the most comparable patients from the open surgery group. Primary endpoints of the study were perioperative and oncologic outcomes. Secondary endpoints of the study were overall survival (OS) and disease-free survival (DFS).

Neoadjuvant and adjuvant therapy

Patients with rectal advanced local disease (≥ T3 and/or ≥ N1) and SCLM received short-course preoperative radiotherapy (5 x 5 Gy) and neoadjuvant systemic chemotherapy (3–6 courses) as a standard treatment protocol. However, neoadjuvant systemic therapy was not administered routinely for patients with colon cancer and SCLM. Adjuvant systemic therapy was administered at the discretion of the medical oncologist.

In general, chemotherapy included fluoropyrimidine-based therapies in combination with oxaliplatin or irinotecan. The different chemotherapy protocols included the FOLFOX (oxaliplatin, fluorouracil, and leucovorin), XELOX (capecitabin and oxaliplatin), XELIRI (capecitabin and irinotecan) and FOLFIRI (irinotecan, fluorouracil, and leucovorin) protocol, respectively. From year 2006, antiangiogenic agents (bevacizumab or cetuximab) were also added to these protocols.

Simultaneous liver and colorectal surgery: surgical technique

Surgical procedures were performed by one dedicated team and the liver resection was completed first. All liver resections (laparoscopic and open) were executed by at least one experienced senior HPB surgeon (SP or AI). A liver parenchymal sparing approach was applied in both groups. All laparoscopic colorectal resections were performed by one experienced senior colorectal surgeon (BK**).**

Laparoscopic procedure

Only pure laparoscopic liver and colorectal resections were performed. Generally, patients were

placed in the supine position, except for resection of posterosuperior segments of the liver when the left lateral decubitus position was used. For rectal resections a split leg position was used. Four 12 mm ports were always used and additional 5 mm ports were placed as necessary. Laparoscopic ultrasonography of the liver was routinely performed to complete staging, locate the metastases, and accurately assess its margins and also to locate any adjacent biliary/vascular structures. It was also used to mark the plane of transection. Carbon dioxide pressure for pneumoperitoneum was kept at 12–14 mmHg during hepatic parenchymal transection. Pressures higher than this are generally avoided to reduce the risk of gas embolism but a slight rise during bleeding can aid hemostasis. The surface of the hepatic parenchyma was precoagulated with a 1-cm surgical margin using monopolar coagulation. Liver transection was performed under low (<5 mmHg) central venous pressure. Pringle's maneuver was used selectively. Hepatic transections were performed using different high energy devices according to surgeon's preference (bipolar coagulation, thermofusion, ultrasound section or ultrasonic surgical aspirator). Larger structures were controlled with endoclips and endoscopic linear stapler devices were used selectively for division of portal pedicles and hepatic veins or their branches. The resected liver specimen was placed in a plastic bag and extracted after finishing the colorectal procedure. It was retrieved either through a suprapubic, a prolonged 12mm port site or a short midline incision.

Laparoscopic colorectal surgery was performed according to standard oncologic procedures.

Open resection

A long midline incision was routinely performed which was extended to right subcostal incision whenever needed to adequately expose the posterosuperior segments of the liver. Intraoperative ultrasonography was routinely performed to guide resection. Hepatic transection was performed under low central venous pressure and intermittent pedicle clamping was used only in case of bleeding. Abdominal drains for liver resection were selectively used.

Colorectal resection routinely involved proximal ligation of vessels (the inferior mesenteric artery for the left colon and rectum, and the ileocolic artery for the right colon) and partial or total mesorectal excision depending on the location of the rectal cancer. After right colon resection a reconstruction was a hand-sewn ileocolic anastomosis. For cancer located in the left colon and the rectum, reconstruction was a stapled colorectal anastomosis. A protective ileostomy was always performed for a low anastomosis. Abdominal drains were always used for rectal resections.

Follow up

Patients were followed at outpatient clinics at periodic intervals. Follow-up included physical examination, biochemical carcinoembryogenic antigen (CEA) test, thoracic X-ray or computed tomography (CT), and liver ultrasound, CT or magnetic resonance imaging (MRI) evaluation every 3 months for the first 2 years, and every 6 months thereafter.

Metastatic recurrence was diagnosed by CEA rise and CT or MRI. Positron emission tomography (PET) - CT scans were carried out in selected patients. In any uncertainty, histology was required.

Follow-up data were obtained from outpatient follow-up and from the National Cancer Register of Slovenia. Patient follow-up included details of dates of disease recurrence and death, site of recurrence, further therapy (e.g. systemic therapy, surgery), and cause of death. Recurrences were classified as hepatic, extrahepatic or combined. Recurrent disease was treated according to standard clinical practice and included surgery and/or chemotherapy whenever possible. The principles behind the selection criteria for resecting recurrent CRLM were the same as those for the initial hepatectomy.

Follow up was fully completed for all patients included in this study. All patients were followed up until their death or until March 2017.

Primary endpoints: variables selected for analysis of the perioperative and oncologic outcomes

Several routinely available clinical variables were analyzed and were divided in four groups:

- *Preoperative* clinical variables included baseline characteristics of patients, primary colorectal tumor and synchronous liver metastases. Herein any neoadjuvant therapy was included in the analysis;
- *Intraoperative* - simultaneous liver and colorectal surgery related variables;
- *Postoperative* oncological results after patohistology and clinical risk score (CRS);
- *Postoperative* outcome: patient's recovery, morbidity, mortality and incisional hernia rate.

Performance status was defined according to the American Society of Anesthesiologists (ASA).

Location of SCLM were defined as anterolateral (segments 2, 3, 4b, 5, 6) or posterosuperior (segments 1, 4a, 7, 8). The liver anatomy and resection terminology were based on the Brisbane classification.[31] Hepatic resections were considered major when at least three adjacent segments were removed and defined as minor if <3 liver segments were resected. Conversion to an open operation was defined as an abdominal incision larger than that needed for specimen retrieval. CRS (from 0 to 5) as defined by Fong was applied.[32] Briefly, patients with lower CRS tends to have a better prognosis. The histological surgical margin was defined as microscopically positive (<1 mm, R1) or negative (R0). R0 resection was defined as complete removal of the tumors with a clear microscopic margin and without residual tumors. Complication was defined as any deviation from the normal course of recovery with the need for pharmacological, surgical, radiological, or endoscopic intervention. Postoperative morbidity was classified according to the Clavien-Dindo classification.[33] Morbidity and mortality were defined as complications or death occurring within 90 days of surgery, or at any time during the postoperative hospital stay.

Secondary endpoint: survival analysis

Overall survival (OS) was defined as the interval between the date of first therapy (the date of first cycle of neoadjuvant therapy; if it was not applied then the date of simultaneous resection) and the date of death or the date of the last follow-up in surviving patients. Disease-free survival (DFS) was calculated from the date of first therapy (neoadjuvant therapy or simultaneous resection) to the date of intra- and/or extrahepatic recurrence or the date of the last follow-up in patients with no recurrence.

Statistical analysis

SigmaPlot 11.0 for Windows (Systat Software, Inc, CA) was used for statistical computations. Because of the inherent bias between patients undergoing laparoscopic and open surgery in terms of preoperative clinical characteristics, a 1:1 propensity score-matched analysis have been used to adjust for these differences.[34] In this setting, propensity score adjustment was performed on the factors known to influence the choice of the approach. These factors included ASA score, primary tumor location (colon or rectal cancer), size, location, distribution and number of liver metastases and extent of liver surgery.

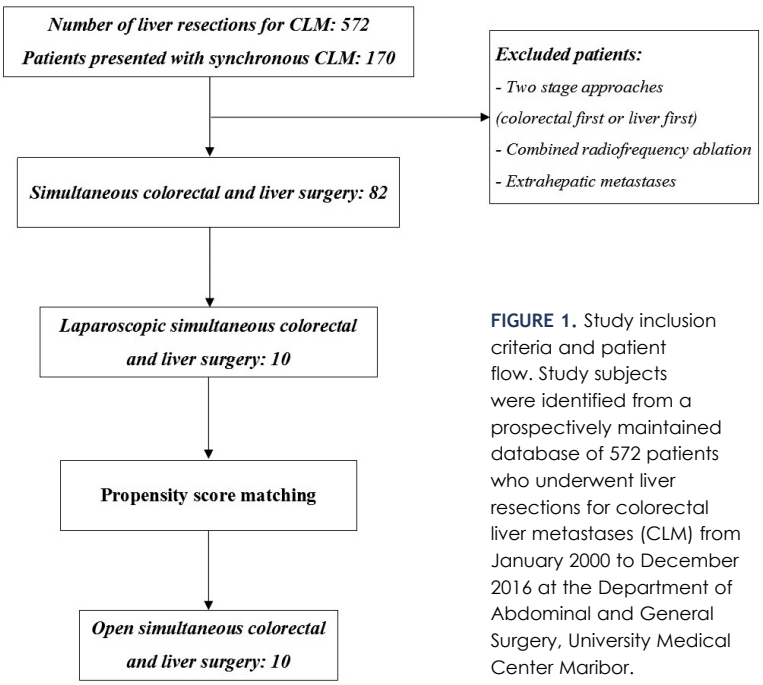

FIGURE 1. Study inclusion criteria and patient flow. Study subjects were identified from a prospectively maintained database of 572 patients who underwent liver resections for colorectal liver metastases (CLM) from January 2000 to December 2016 at the Department of Abdominal and General Surgery, University Medical Center Maribor.

Differences in the frequency distributions of preoperative, intraoperative and postoperative clinical variables in relation to open and laparoscopic surgery were tested using the chi-squared test for categorical variables (Pearson's or Fisher's exact test when appropriate, two-tailed in all instances). Continuous variables were analyzed using Student's t-test for independent samples or the Mann-Whitney U test if the criteria for a parametric testing were not met. The effects of open and laparoscopic surgery on overall and disease-free survival probabilities were estimated by using the Kaplan-Meier survival analysis and compared by using the log-rank test. A difference with a P value of < 0.05 was considered statistically significant.

Results

Study population and preoperative characteristics

Of the 572 patients identified who underwent liver resections for CLM during the study period, simultaneous resection of both the primary tumor and SCLM were performed in 82 patients. From these, 10 patients were submitted to simultaneous pure laparoscopic procedure. After propensity score matching, all these 10 patients operated laparoscopically (LAP) were compared with 10 patients

TABLE 1. Preoperative clinical characteristics of patients, primary colorectal tumor and synchronous colorectal liver metastases

Variable	Simultaneous Open (n = 10)	Simultaneous Laparoscopy (n = 10)	P
Patients			
Gender (male/female)	6/4	6/4	1.00
Age [mean ± SD (years)]	65.4 ± 8.1	62.2 ± 7.9	0.39
BMI [median (IQR) (kg/m2)]	24.0 (23.1–25.5)	26.9 (23.6–32.1)	0.34
ASA (I /II/III)	4/3/3	5/3/2	0.86
Preoperative chemotherapy (y/n)	3/7	7/3	0.18
Preoperative radiotherapy (y/n)	3/7	4/6	1.00
CEA at diagnosis [mean ± SD (ng/mL)]	15.2 ± 12.5	7.7 ± 7.7	0.12
Colorectal tumor			
Right colon/ left colon/ rectum	3/3/4	2/2/6	0.67
Colorectal liver metastases			
Number of lesions [median (IQR)]	1 (1–2)	1 (1–2)	0.68
Larger diameter [mean ± SD (cm)]	2.9 ± 1.5	2.0 ± 1.2	0.17
Laterality (unilateral /bilateral)	9/1	9/1	1.00
Proximity of major vessel [(hilar or hepatic confluence) (y/n)]	0/10	0/10	1.00
Location (anterolateral / posterosuperior)	8/2	9/1	1.00

ASA = American Society of Anesthesiologist physical status score; BMI = body mass index; CEA = carcinoembryonic antigen; SD = standard deviation

treated by traditional open surgery (OPEN). Study inclusion criteria and patient flow are shown in Figure 1. The diagnosis of primary colorectal cancer was confirmed preoperatively by histology in all patients of both groups. The diagnosis of SCLM was confirmed postoperatively by histology in both groups as well.

The two groups were well matched and comparable in terms of preoperative clinical characteristics of patients, primary colorectal tumor and SCLM. Results are shown in Table 1.

Intraoperative results

The patients from LAP and OPEN group were comparable in terms of intraoperative variables. Results are detailed in Table 2.

Since extent of liver resection was one of the terms of propensity score matching, only minor liver resections were performed in both groups. A portal triad clamping (Pringle's maneuver) was not routinely used and was applied selectively, only in the case of bleeding with no significant difference in both groups. All patients with rectal cancer had either stoma covering low anastomosis or terminal colostomy.

Postoperative short term outcomes: oncological results, clinical risk score, patient's recovery, morbidity and mortality

There were no differences between LAP and OPEN group in terms of oncological results and CRS. All patients were found to have a CRS within the range of 1–4; no patients had a CRS 0 or 5 (Table 3). Results of patient's recovery, morbidity and mortality are detailed in Table 4. No postoperative mortality occurred in either group. Fully description of morbidity and hospitalization of studied population are shown in Table 5.

Postoperative long term outcome: recurrence and survival

Of the 10 patients from OPEN group submitted to potentially curative simultaneous resection of primary colorectal cancer and SCLM four developed recurrent disease and, of these, all of them underwent repeat hepatic resection. Of the 10 patients from LAP two patients developed recurrence, which was both hepatic and extrahepatic and repeat resection was not feasible. Patterns and time

TABLE 2. Intraoperative - simultaneous liver and colorectal surgery related variables

Variable	Simultaneous Open (n = 10)	Simultaneous Laparoscopy (n = 10)	P
Totally pure laparoscopic	–	10	–
Conversion to laparotomy	–	0	–
Liver surgery			
Minor/major resection	10/0	10/0	1.00
Atypical/ segmentectomy/LLS	6/2/2	5/3/2	0.87
Pringle's maneuver (y/n)	2/8	3/7	1.00
Colorectal surgery			
Colon/rectal resection	6/4	5/5	1.00
Temporary stoma covering low anastomosis (y/n)	2*/8	3*/7	1.00
Terminal colostomy (Hartman or APE)	2/8	2/8	1.00
Operative time [mean ± SD (min)]	257 ± 66.8	261 ± 92.8	0.91
Blood loss			
Estimated [median (IQR) (mL)]	170 (70–230)	105 (30–180)	0.23
Hemoglobin drop** [median (IQR) (g/L)]	22.5 (9–28)	15.5 (9–17)	0.38
Transfusion required (y/n)	3/7	3/7	1.00

APE = abdominoperineal excision; LLS = left lateral sectionectomy; *in both groups one patient required ileostomy after anastomotic leak; **Hemoglobin drop = Hemoglobin preoperatively - Hemoglobin postoperatively (g/L)

of recurrences, redo surgical procedures and long-term outcomes are shown in Table 5.

The median follow-up for surviving patients in the OPEN and LAP was 78 (61–130) and 24 (1–63) months, respectively (P = 0.001). Among patients in OPEN OS/DFS was 100%/90% at 1 year, 90%/60% at 3 years, and 80%/60% at 5 years. Among patients in LAP OS/DFS was 100%/100% at 1 year, and 75%/57% at 3 years. Simultaneous laparoscopic resection of the primary tumor and associated SCLM was first performed in this center in May 2012, thus the median follow-up period was too short to calculate the 5-year survival expectations for LAP group. There were no statistically significant dif-

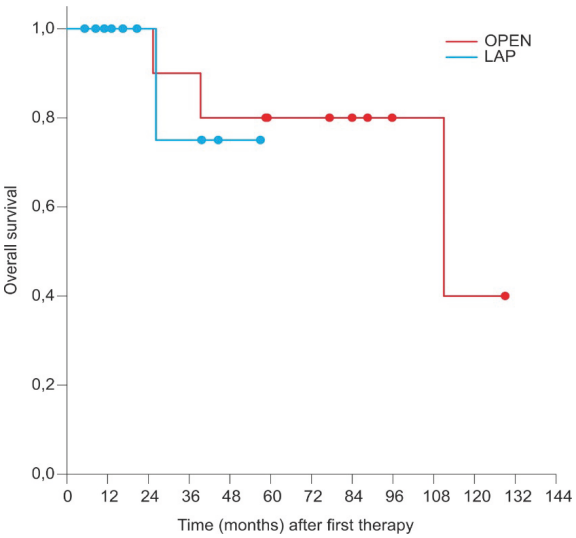

FIGURE 2. Kaplan-Meier estimates of overall survival between the simultaneous laparoscopy (blue line) and open surgery groups (red line).

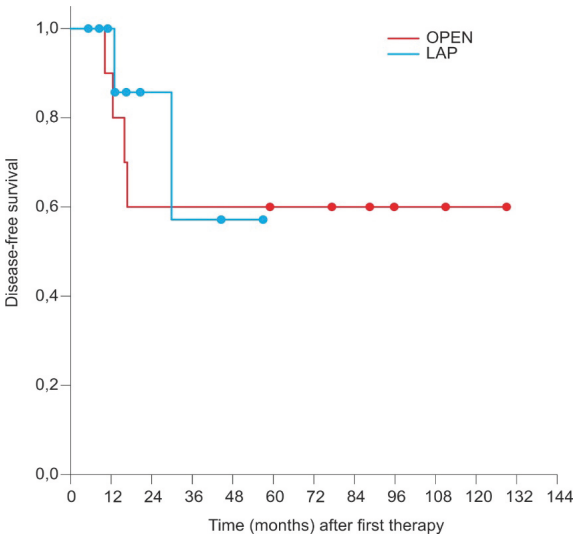

FIGURE 3. Kaplan-Meier estimates of disease-free survival between the simultaneous laparoscopy (blue line) and open surgery groups (red line).

TABLE 3. Postoperative oncological results after patohistology and clinical risk score

Variable	Simultaneous Open (n = 10)	Simultaneous Laparoscopy (n = 10)	P
Colorectal tumor			
T (T1/T2/T3/T4)	0/1/8/1	0/1/9/0	1.00
N (N0/N+)	2/8	2/8	1.00
Number of harvested lymph nodes (mean ± SD)	9.5 ± 6.2	13.7 ± 6.9	0.17
Well/moderately/poorly differentiated	4/5/1	4/6/0	1.00
Negative surgical margin			
Liver (y/n)	10/0	10/0	1.00
Colorectal (y/n)	10/0	10/0	1.00
Liver resection margin [median (IQR) (mm)]	2.5 (2–5)	5.0 (1.8–8)	0.38
CRS (1/2/3/4)	2/5/2/1	2/4/3/1	0.96

CRS = clinical risk score (no patients with CRS 0 or 5 in any of the group)

ferences between OPEN and LAP either in OS (P = 0.842) and DFS (P = 0.724), respectively. Kaplan-Meier estimates of OS and DFS between the LAP and OPEN group are shown in Figures 2 and 3.

Discussion

The optimal strategy for resectable SCLM has not been established yet. In selected cases, the simultaneous surgery approach gives the advantages to avoid two surgical procedures thus reducing risk for patients and provides for economic savings while keeping acceptable morbidity and adequate oncologic results.[6-8] However, open resection of both primary tumor and SCLM often requires an extensive incision, especially if the location of the liver metastasis is opposite to the primary tumor location. Using laparoscopic approach exposure can be improved thus avoiding extensive laparotomies.[20] Consequently, surgical stress and pain associated with large incisions can be reduced and patient's recovery enhanced. There is an ongoing effort to show the potential benefit of totally laparoscopic strategies for the radical treatment of stage IV colorectal cancer.[12-30,35]

The present study was designed to investigate the perioperative results, oncologic outcomes and survival of patients undergoing pure laparoscopic simultaneous resection of both the primary colorectal cancer and SCLM. During this study period, the choice of intervention was subject to selection bias since simultaneous laparoscopic liver procedures were reserved for the most ideal candidates. Moreover, the laparoscopic treatment of patients with an extraperitoneal rectal cancer remains clinically challenging compared to upper rectal or colon cancer. To minimize these biases, the LAP group was compared to OPEN group by propensity score matching on the factors known to influence the choice of the approach. Importantly, there were no differences in patient demographics, tumor characteristics, or the extent of the operation, so the present characteristics well identify the most ideal candidates to a combined laparoscopic liver and colorectal surgery. Patients selected for this approach were without severe comorbidities (ASA I–II in majority of cases), with a solitary (median number: 1), small (median diameter: 2 cm), unilateral SCLM, located in accessible anterolateral segments and were mostly resectable by atypical wedge resections or left lateral sectionectomy. Consequently, only minor liver resections were performed. These results are consistent with previous studies showing well selected patients and demonstrating a high rate of minor (89%) and nonanatomical resections (60%).[17-27,35] In this study colorectal cancer characteristics did not preclude the possibility to perform a laparoscopic surgery as well with majority of patients presenting a T3 primary tumor. There were no differences in N stage and importantly, the number of harvested lymph nodes was even higher in the LAP group. Half of the patients in the LAP group presented with rectal cancer. Surprisingly, previous studies have demonstrated that despite the high rate of rectal resections in some series, the number of the temporary ileostomies was low.[25,27,35] The results of the present study contradict this: all of the rectal cancer patients had either temporary ileostomy

TABLE 4. Postoperative outcome: patient's recovery, morbidity and mortality. No postoperative mortality occurred in either group. Adjuvant chemotherapy and incisional hernias

Variable	Simultaneous Open (n = 10)	Simultaneous Laparoscopy (n = 10)	P
ICU stay	0	0	–
HDU stay [median (IQR) (days)]	4 (2–6)	3 (2–5)	0.59
Solid food oral intake [median (IQR) (days)]	5.5 (4–6)	3 (3–4)	**0.006**
Stool passing [median (IQR) (days)]	4.5 (4–5)	4 (3–5)	0.46
Intravenous narcotics requirement [median (IQR) (days)]	6.5 (6–7)	4.5 (3–7)	0.08
Hospital stay [median (IQR) (days)]	11.5 (10–33)	8 (8–12)	**0.044**
Morbidity			
Overall (y/n)	5/5	3/7	0.65
Liver specific* (y/n)	2/8	0/10	0.47
CD < III (y/n)	2/8	2/8	1.00
CD IIIab (y/n)	3/7	1/9	0.58
CD > III (y/n)	0/10	0/10	1.00
Mortality (y/n)	0/10	0/10	1.00
Postoperative chemotherapy (y/n)	5/5	2/8	0.35
Incisional hernias (y/n)	3/7	0/10	0.21

HDU = high dependency unit; ICU = intensive care unit; *Liver specific complications included liver failure, bile leak, bile collection or liver hemorrhage; values in bold are significant at P < 0.05

covering low anastomosis or terminal colostomy. This finding might have been due to a high rate of preoperative radiotherapy, which highlights that most rectal resections were performed for cancer in the lower rectum. Moreover, according to some reports simultaneous resection generally is considered unsuitable for rectal cancer due to a high rate of anastomotic leakage.[36] Another possible explanation is a concern regarding prolonged vascular clamping which is responsible for transient portal hypertension with edema of the intestinal mucosa that might be leading to colorectal anastomotic failure.[21,35]

The feasibility of simultaneous laparoscopic operations was clearly demonstrated in the present study: no conversion to open surgery has been performed. This result reflects a findings of a recent review, where a conversion rate of only 0.7% has been reported.[35] Similarly, Tranchart *et al*. reported a low conversion rate of 7% in their large multicenter study.[30] It has been highlighted, that simultaneous resections executed by two different specialized teams allowing good results in terms of conversion rates and perioperative outcomes.[35] Of note, the present study was performed at high-volume tertiary referral center, where all procedures were performed by an expert surgical team, composed of experienced colorectal and hepatobiliary surgeons. Controversy still exist, which procedure should be carried out first and many authors reported colorectal resection was the first step of the simultaneous surgery.[15-16,20,22,29-30] Instead, in the present study liver resection precede colorectal surgery and the same strategy has been reported by others.[18-19,21,35] The underlying rationality is that the resection of liver metastases requires a low central venous pressure to minimize the blood loss and the preceding liver resection will not interfere with the subsequent fluid resuscitation in the process of colorectal resection. In addition, the choice of carrying out the liver resection as first step of treatment gives to the surgeon the opportunity to change surgical strategy from a simultaneous procedure to a "liver first" resection which has been showed to be another effective treatment of SCLM.[5] Moreover, liver metastases are the main determinant of patient prognosis and the present authors believe, that SCLM are leading the decision making process: if simultaneous strategies are not feasible, then the metastases should be managed first. However, no decisions were modified and all procedures were finished simultaneously.

In terms of intraoperative measurements of outcome, the median operating time of 261 min after LAP is comparable with the time reported by Jung *et al*.[25], and is shorter than the time reported by

TABLE 5. Morbidity details, hospital stay, patterns and time of recurrence, redo procedures and long-term outcome

Patients	Morbidity	Hospital stay (days)	Recurrence location (years after first surgery)	Redo	Survival (years)	Survival status (March 2017)
OPEN						
1	Wound infection (CD II)	12	1) Liver (2Y) 2) Liver (3Y)	1) Liver 2) /	3	DOD
2	Bile collection (CD IIIa)	36	Liver (1Y)	Liver	7	NED
3	nil	9	1) Liver (1Y) 2) Colon (3Y) 3) Peritoneal carcinosis (4Y)	1) Liver 2) Colon 3) /	4	DOD
4	Anastomotic leak (CD IIIb)	54	Liver (1Y)	Liver	5	NED
5	nil	10	no	/	11	NED
6	Pneumonia (CD II)	12	no	/	10	D - other
7	nil	11	no	/	8	NED
8	nil	9	no	/	8	NED
9	Bile collection (CD IIIa)	33	no	/	7	NED
10	nil	10	no	/	5	NED
LAP						
1	nil	8	no	/	5	NED
2	Anastomotic leak (CD IIIb)	42	Liver and peritoneal carcinosis (1Y)	/	2	DOD
3	nil	7	no	/	4	NED
4	nil	7	Liver and peritoneal carcinosis (3Y)	/	4	AWD
5	nil	8	no	/	2	NED
6	nil	12	no	/	2	NED
7	nil	8	no	/	1	NED
8	Pulmonary embolism (CD II)	9	no	/	1	NED
9	nil	8	no	/	<1	NED
10	Ictus cerebri (CD II)	21	no	/	<1	NED

AWD = alive with disease; CD = Clavien Dindo classification of complication severity; D - other = death without recurrence of disease; DOD = dead of disease; LAP = simultaneous laparoscopic surgery; OPEN = simultaneous open surgery; NED = no evidence of disease; Y = years

others, where it was more than 300 min.[13-16,19,22-24,30] Nevertheless, operative time was not different between OPEN and LAP group. This result is inconsistent with some previous studies showing that the duration of operation was significantly longer in the laparoscopic groups.[15,22,25] A possible explanation can be, that in contrast to present study, these reports included major liver resections as well, which are known to prolong operative time. However, several authors reported equivalent operative times for both groups.[16,23,30]

Intraoperative blood loss is a major concern especially in hepatic resection and perioperative transfusion has been associated with a poor prognosis.[37] The findings of decreased blood loss with the laparoscopic approach have been reported in several studies, explained in part by the laparoscopic magnification, and decreased venous oozing from the cut surface under pneumoperitoneum.[15-16,22-23] Results of present study contradicts this as laparoscopic approach did not allow diminishing blood loss and transfusion rate. Contrast to prior studies, in this analysis blood loss was not based only on estimation but it has been objectivized by measuring the volume of blood in the suction canister and precisely weighing the absorbed blood in the sponges. Moreover, the pre- and postoperative hemoglobin levels were demonstrated exactly as well. The reason for this was to exclude the possibility of differences in preoperative hemoglobin levels which can contribute to the difference in blood loss and transfusion rate between two groups since it is well known that patients with SCLM can develop anemia. Moreover, it has been suggested that the blood loss can be underestimated especially in the open surgery.[38] Despite analyzing additional objective variable in this study, there were no differences between groups. It should be

noted that outcome observed after open surgery was excellent as well (median estimated blood loss 170 ml). Similarly, several recent studies have suggested that there is no decreased blood loss and transfusion rate in the laparoscopic group.[19,25,30]

In respect to postoperative oncological results, a high CRS has been found to be an independent negative prognostic predictor in previous studies.[32,39] The impacts of CRS and colorectal tumor differentiation on survival analysis were eliminated, since the OPEN and LAP groups were comparable in that terms as well. The risk of inadequate oncologic resection is the major concern for the use of laparoscopic resection for malignancy. A positive surgical margin has been shown to predict worse DFS after resection.[40] Castaing *et al*. emphasized that the increase in R1 resections did not affect OS and suggest it might reflect complex anatomic locations of metastases adjacent to major vascular structures.[41] To avoid an inherent selection bias with more difficult cases potentially being relegated to open approach, it is important to point out that the two groups of the present study were perfectly matched in term of SCLM proximity to major vessels (hilar or hepatic confluence) as well; there were no tumors with such characteristics in any of groups. Importantly, complete R0 resections of both the primary and SCLM were achieved in all patients confirming the reports of others, which reported a high rate of R0 resections of 100% and 90% as well.[25,30] Surprisingly, the rate of R0 resections has been not reported by many authors.[14-16,22] The width of the surgical margin was not different between two groups and interestingly, the width was even larger in the LAP group. Moreover, a recent study failed to demonstrate that the width of negative margin correlated with recurrence or survival.[42] Importantly, in this study neither peritoneal carcinomatosis nor port site metastases after simultaneous resections of SCLM by laparoscopic means were found. These results suggest that laparoscopic procedure does not compromise oncologic principles.

The major findings in this study were lesser length of hospital stay and faster solid food oral intake for LAP group. The median hospital stay of 8 days in the LAP group is similar to or shorter than the time reported by others, where it has been in a range from 7.4 to 16 days. The benefit of decreased hospital stay was recognized in these analyses as well.[15-30] Interestingly, substantial geographical differences exist which depends on national health care systems. Takasu *et al*. confirmed the benefit of lesser length of hospital stay which were 16 days for the laparoscopy and 36 days for the open group.[23] However, Tranchart *et al.* found no differences in the length of stay between laparoscopic and open groups, and noted that simultaneous resections still appear as difficult procedures for surgeons, which could have influence their decisions concerning patient's hospital discharge.[30] Patients undergoing laparoscopic procedure resumed solid food oral intake earlier, however it has no impact on earlier stool passing in this study, thus the benefit of this parameter remains questionable. Similarly, several authors reported a shorter time to resume a bowel movement and starting an oral intake.[19,25]

In terms of other postoperative measurements of outcome none of the patients required intensive care unit stay and the high dependency unit stay was comparable between groups. Ferretti et al. reported a median one-day intensive care unit stay.[29] However, these relevant parameters were not reported in several previous analyses.[15-28,35]

Pain control is one of the potential advantage of laparoscopy and in this study, it was evaluated by intravenous narcotics requirement. Laparoscopy offered a benefit of less narcotic requirements, patients in the LAP group needed intravenous narcotics for 4.5 days compared with the OPEN group where these were necessary for 6.5 days. Notwithstanding, statistical significance was reached only marginally (P = 0.08). Hu *et al*. reported that patients having undergone laparoscopic resection had less severe postoperative pain, but it is not clear how they asses this parameter.[19] Surprisingly, in several other reports on this topic pain control was not investigated.[13-18,20-30] Some surgeons combined a laparoscopic colorectal resection with an open procedure for the liver, as reported by Hatwell *et al*.[20] However, this technique also left a large incision in the upper abdomen, and the advantage of laparoscopy was not realized fully.

The present study found that LAP and OPEN were not significantly different in terms of postoperative morbidity and mortality. Of note, no liver specific morbidity was observed in the LAP group. Nevertheless, some bile collections which occurred in the OPEN group were easily managed by percutaneous drainage. Importantly, there were no organ failures and postoperative deaths in two groups either. Similarly, no differences in morbidity and zero mortality were reported in several other analyses.[15-16,19,22-23] Polignano *et al*. reported that the surgical morbidity was mainly related to the colonic surgery.[18] Contrary, in the present series only one anastomotic leak occurred in OPEN and one in the LAP group, respectively. Jung *et al.* reported a

higher rate of minor complications in the open surgery group (superficial surgical site infections and adhesive ileus), which seem to be strongly related to the presence of the bigger wound.[25] However, the number of minor complications were equal in the present analysis. Interestingly, despite laparoscopy has the potential to reduce the incisional hernia rates, none of the studies on the present topic investigated this parameter which is responsible for long-term morbidity.[12-30,35] In the present study none of the LAP whereas three patients from the OPEN group developed incisional hernia, but the difference was not significant.

In the present study, neither the 3-year OS nor the DFS was found to be different for LAP compared with the OPEN group. Similarly, no differences were found between groups in terms of OS reported by others .[15-16,19,22-23,30] After long and adequate median follow-up of 78 months this analysis revealed excellent long-term results among patients in OPEN with 5-year OS/DFS of 80 and 60%, respectively. However, due to a shorter follow-up period, only mid-term results were available for the LAP group with 3-year OS of 75% and DFS of 57%, respectively. Similarly, in the current literature some of the authors reported the short- and mid-term results only and the 3-year OS rates ranged from 52 to 78%.[15,30] Unfortunately, data regarding recurrence were inconsistently reported in several case-matched series on this topic.[15-16,19,23,25]

The present study is a subject to a number of limitations. First and foremost, only a small cohort of patients from a single center were analyzed which were collected across a long interval of time. However, the majority of case-matched studies in the literature derived from a small single center series, which included from 7 to 24 patients.[15-16,19,22-23,25] Even in the largest multicenter analysis, which included 142 patients from 14 centers the average number of patients per hospital was ten.[29] It demonstrates clearly the limited indications of simultaneous laparoscopic procedures even in the most experienced centers worldwide. Second, given the retrospective nature of this study, selection bias may have been present. Although propensity score matching was performed to overcome potential bias and to make the two groups similar it is less effective than a prospective randomized trial. Notwithstanding, to conduct a randomized study on this topic is still an unresolved issue. Third, since laparoscopic simultaneous procedures started in 2012 the median follow-up data between groups differs and the excellent long-term survival results achieved with OPEN are still waiting to be proved by LAP. However, except for introduction of laparoscopy, the management of SCLM was homogeneous over the study period and the same surgical team made the treatment decisions and performed the procedures.

Indeed, the power of the present study is limited, but importantly the two surgical approaches brought about similar outcomes in terms of postoperative morbidity, mortality, survival and recurrence. Nevertheless, some surgeons may insist on traditional open approach and not to accept widespread changes in clinical practice given the lack of several investigated variables to support the superiority of laparoscopic approach. However, the results of a recently published studies investigating inflammatory markers are promising and have a potential to prove that the reduced inflammatory response by laparoscopy might have positive impact on oncogenesis.[43]

Conclusions

Based on limited evidence, LAP patients experienced some clinically relevant perioperative benefits without compromise of oncologic outcomes. In high-volume centers experienced in both laparoscopic colorectal and liver surgery, simultaneous minimally invasive approach is appropriate in well selected patients presenting with limited SCLM.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65:** 87-108. doi: 10.3322/caac.21262

2. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. *Br J Surg* 2006; **93:** 465-74. doi: 10.1002/bjs.5278

3. Adams RB, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. *HPB* 2013; **15:** 91-103. doi: 10.1111/j.1477-2574.2012.00557.x

4. Yoshidome H, Kimura F, Shimizu H, Ohtsuka M, Kato A, Yoshitomi H, et al. Interval period tumor progression: does delayed hepatectomy detect occult metastases in synchronous colorectal liver metastases? *J Gastrointest Surg* 2008; **12:** 1391-8. doi: 10.1007/s11605-008-0540-9

5. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg* 2006; **93:** 872-8. doi: 10.1002/bjs.5346

6. Fahy BN, Fischer CP. Synchronous resection of colorectal primary and hepatic metastasis. *J Gastrointest Oncol* 2012; **3:** 48-58. doi: 10.3978/j.issn.2078-6891.2012.004

7. Ejaz A, Semenov E, Spolverato G, Kim Y, Tanner D, Hundt J, et al. Synchronous primary colorectal and liver metastasis: impact of operative approach on clinical outcomes and hospital charges. *HPB* 2014; **16:** 1117-26. doi: 10.1111/hpb.12302

8. Muangkaew P, Cho JY, Han HS, Yoon YS, Choi Y, Jang JY, et al. Outcomes of simultaneous major liver resection and colorectal surgery for colorectal liver metastases. *J Gastrointest Surg* 2016; **20:** 554-63. doi: 10.1007/s11605-015-2979-9

9. Lacy AM, Delgado S, Castells A, Prins HA, Arroyo V, Ibarzabal A, et al. The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. *Ann Surg* 2008; **248:** 1-7. doi: 10.1097/SLA.0b013e31816a9d65

10. Park JS, Choi GS, Jun SH, Park SY, Kim HJ. Long-term outcomes after laparoscopic surgery versus open surgery for rectal cancer: a propensity score analysis. *Ann Surg Oncol* 2013; **20:** 2633-40. doi: 10.1245/s10434-013-2981-y

11. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg* 2015; **261:** 619-29. doi: 10.1097/SLA.0000000000001184

12. Leung KL, Lee JF, Yiu RY, Ng SS, Li JC. Simultaneous laparoscopic resection of rectal cancer and liver metastasis. *J Laparoendosc Adv Surg Tech A* 2006; **16:** 486-8. doi: 10.1089/lap.2006.16.486

13. Sasaki A, Nitta H, Otsuka K, Takahara T, Nishizuka S, Wakabayashi G. Ten-year experience of totally laparoscopic liver resection in a single institution. *Br J Surg* 2009; **96:** 274-9. doi: 10.1002/bjs.6472

14. Tranchart H, Diop PS, Lainas P, Pourcher G, Catherine L, Franco D, et al. Laparoscopic major hepatectomy can be safely performed with colorectal surgery for synchronous colorectal liver metastasis. *HPB* 2011; **13:** 46-50. doi: 10.1111/j.1477-2574.2010.00238.x

15. Huh JW, Koh YS, Kim HR, Cho CK, Kim YJ. Comparison of laparoscopic and open colorectal resections for patients undergoing simultaneous R0 resection for liver metastases. *Surg Endosc* 2011; **25:** 193-8. doi: 10.1007/s00464-010-1158-z

16. Chen KY, Xiang GA, Wang HN, Xiao FL. Simultaneous laparoscopic excision for rectal carcinoma and synchronous hepatic metastasis. *Chin Med J* 2011; **124:** 2990-2.

17. Hoekstra LT, Busch OR, Bemelman WA, van Gulik TM, Tanis PJ. Initial experiences of simultaneous laparoscopic resection of colorectal cancer and liver metastases. *HPB Surg* 2012; 893956. doi: 10.1155/2012/893956

18. Polignano FM, Quyn AJ, Sanjay P, Henderson NA, Tait IS. Totally laparoscopic strategies for the management of colorectal cancer with synchronous liver metastasis. *Surg Endosc* 2012; **26:** 2571-8. doi: 10.1007/s00464-012-2235-2

19. Hu MG, Ou-yang CG, Zhao GD, Xu DB, Liu R. Outcomes of open versus laparoscopic procedure for synchronous radical resection of liver metastatic colorectal cancer: a comparative study. *Surg Laparosc Endosc Percutan Tech* 2012; **22:** 364-9. doi: 10.1097/SLE.0b013e31825af6b2

20. Hatwell C, Bretagnol F, Farges O, Belghiti J, Panis Y. Laparoscopic resection of colorectal cancer facilitates simultaneous surgery of synchronous liver metastases. *Colorectal Dis* 2013; **15:** e21-8. doi: 10.1111/codi.12068

21. Spampinato MG, Mandalá L, Quarta G, Del Medico P, Baldazzi G. One-stage, totally laparoscopic major hepatectomy and colectomy for colorectal neoplasm with synchronous liver metastasis: safety, feasibility and short-term outcome. *Surgery* 2013; **153:** 861-5. doi: 10.1016/j.surg.2012.06.007

22. Lin Q, Ye Q, Zhu D, Wei Y, Ren L, Zheng P, et al. Comparison of minimally invasive and open colorectal resections for patients undergoing simultaneous R0 resection for liver metastases: a propensity score analysis. *Int J Colorectal Dis* 2015; **30:** 385-95. doi: 10.1007/s00384-014-2089-2

23. Takasu C, Shimada M, Sato H, Miyatani T, Imura S, Morine Y, et al. Benefits of simultaneous laparoscopic resection of primary colorectal cancer and liver metastases. *Asian J Endosc Surg* 2014; **7:** 31-7. doi: 10.1111/ases.12066

24. Ando K, Oki E, Ikeda T, Saeki H, Ida S, Kimura Y, et al. Simultaneous resection of colorectal cancer and liver metastases in the right lobe using pure laparoscopic surgery. *Surg Today* 2014; **44:** 1588-92. doi: 10.1007/s00595-013-0801-4

25. Jung KU, Kim HC, Cho YB, Kwon CH, Yun SH, Heo JS, et al. Outcomes of simultaneous laparoscopic colorectal and hepatic resection for patients with colorectal cancers: a comparative study. *J Laparoendosc Adv Surg Tech A* 2014; **24:** 229-35. doi: 10.1089/lap.2013.0475

26. Ida S, Oki E, Ando K, Kimura Y, Yamashita Y, Saeki H, et al. Pure laparoscopic right-sided hepatectomy in the semi-prone position for synchronous colorectal cancer with liver metastases. *Asian J Endosc Surg* 2014; **7:** 133-7. doi: 10.1111/ases.12098

27. Berti S, Francone E, Minuto M, Bonfante P, Sagnelli C, Bianchi C, et al. Synchronous totally laparoscopic management of colorectal cancer and resectable liver metastases: a single center experience. *Langenbecks Arch Surg* 2015; **400:** 495-503. doi: 10.1007/s00423-015-1281-3

28. Takorov I, Belev N, Lukanova T, Atanasov B, Dzharov G, Djurkov V, et al. Laparoscopic combined colorectal and liver resections for primary colorectal cancer with synchronous liver metastases. *Ann Hepatobiliary Pancreat Surg* 2016; **20:** 167-72. doi: 10.14701/ahbps.2016.20.4.167

29. Ferretti S, Tranchart H, Buell JF, Eretta C, Patriti A, Spampinato MG, et al. Laparoscopic simultaneous resection of colorectal primary tumor and liver metastases: results of a multicentric international study. *World J Surg* 2015; **39:** 2052-60. doi: 10.1007/s00268-015-3034-4

30. Tranchart H, Fuks D, Vigano L, Ferretti S, Paye F, Wakabayashi G, et al. Laparoscopic simultaneous resection of colorectal primary tumor and liver metastases: a propensity score matching analysis. *Surg Endosc* 2016; **30:** 1853-62. doi: 10.1007/s00464-015-4467-4

31. Strasberg SM, Belghiti J, Clavien PA, Gadzijev E, Garden JO, Lau WY, et al. The Brisbane 2000 Terminology of Liver Anatomy and Resections. *HPB* 2000; **2:** 333-9.

32. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230:** 309-18; discussion 318-21.

33. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205-13.

34. Austin PC. A comparison of 12 algorithms for matching on the propensity score. *Stat Med* 2014; **33:** 1057-69. doi: 10.1002/sim.6004

35. Garritano S, Selvaggi F, Spampinato MG. Simultaneous minimally invasive treatment of colorectal neoplasm with synchronous liver metastasis. *Biomed Res Int* 2016; 9328250. doi: 10.1155/2016/9328250

36. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005; **92:** 211-6. doi: 10.1002/bjs.4806

37. Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, Dematteo RP, et sl. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 2003; **237:** 860-9; discussion 869-70. doi: 10.1097/01.SLA.0000072371.95588.DA

38. Schiffman SC, Kim KH, Tsung A, Marsh JW, Geller DA. Laparoscopic versus open liver resection for metastatic colorectal cancer: a metaanalysis of 610 patients. *Surgery* 2015; **157:** 211-22. doi: 10.1016/j.surg.2014.08.036

39. Ivanecz A, Kavalar R, Palfy M, Pivec V, Sremec M, Horvat M, et al. Can we improve the clinical risk score? The prognostic value of p53, Ki-67 and thymidylate synthase in patients undergoing radical resection of colorectal liver metastases. *HPB* 2014; **16:** 235-42. doi: 10.1111/hpb.12089

40. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005; **241:** 715-22; discussion 722-4.

41. Castaing D, Vibert E, Ricca L, Azoulay D, Adam R, Gayet B. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. *Ann Surg* 2009; **250:** 849-55. doi: 10.1097/SLA.0b013e3181bcaf63

42. Postriganova N, Kazaryan AM, Røsok BI, Fretland ÅA, Barkhatov L, Edwin B. Margin status after laparoscopic resection of colorectal liver metastases: does a narrow resection margin have an influence on survival and local recurrence? *HPB* 2014; **16:** 822-9. doi: 10.1111/hpb.12204

43. Fretland AA, Sokolov A, Postriganova N, Kazaryan AM, Pischke SE, Nilsson PH, et al. Inflammatory response after laparoscopic versus open resection of colorectal liver metastases. *Medicine (Baltimore)* 2015; **94:** e1786. doi: 10.1097/MD.0000000000001786

research article

Impact factors for perioperative morbidity and mortality and repercussion of perioperative morbidity and long-term survival in pancreatic head resection

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Background. The focus of the present study was to reveal any impact factors for perioperative morbidity and mortality as well as repercussion of perioperative morbidity on long-term survival in pancreatic head resection.

Patients and methods. In a retrospective study, clinic-pathological factors of 240 patients after pancreatic head (PD) or total resection were analyzed for correlations with morbidity, 30- and 90-day mortality, and long-term survival. According to Clavien-Dindo classification, all complications with grade II and more were defined as overall complications (OAC). OAC, all surgical (ASC), general (AGC) and some specific types of complications like leaks from the pancreatoenteric anastomosis (PEA) or pancreatic fistula (PF, type A, B and C), leaks from other anastomoses (OL), bleeding (BC) and abscesses (AA) were studied for correlation with clinic-pathological factors.

Results. In the 9-year period, altogether 240 patients had pancreatic resection. The incidence of OAC was 37.1%, ASC 29.2% and AGC 15.8%. ASC presented themselves as PL, OL, BC and AA in 19% (of 208 PD), 5.8%, 5.8%, and 2.5% respectively. Age, ASA score, amylase on drains, and pancreatic fistulas B and C correlated significantly with different types of complications. Overall 30- and 90-day mortalities were 5 and 7.9% and decreased to 3.5 and 5% in P2.

Conclusions. High amylase on drains and higher mean age were independent indicators of morbidity, whereas PL and BC revealed as independent predictor for 30-day mortality, and physical status, OAC and PF C for 90-day mortality.

Key words: pancreatic resections; complications; impact factors

Introduction

Resection of the head of pancreas remains a significant challenge for many pancreaticobiliary surgeon. Recently, better perioperative care, surgical technique, and better patient's selection have undoubtedly led to better survival and have reduced the perioperative mortality. However, the high morbidity that accompanies these operations negates any positive long-term results in patients with otherwise poor prognosis that could have benefited from.

The complications associated with PD procedures are well described.[1,2] These are usually of higher grade than in comparable abdominal surgical procedures. Even more, they are usually associated with significant perioperative morbidity. Many attempts have been made to lower these complications.[1,3–7] Some authors have claimed that modifications of the surgical techniques, especially the formation of the pancreatojejunostomy, could have a positive impact on the postoperative course. Others have claimed that a better selection of patients would decrease the morbidity and mortal-

ity.[8–13] Since perioperative morbidity and mortality are important predictors for long-term survival of patients after PD's [14,15], we performed a retrospective study to determine factors associated with perioperative and specific surgical complications, general complications, and perioperative mortality. The identification of such negative prognostic factors could help to prevent complications or even mortality and could therefore have an impact on log-term survival after pancreatic surgery.

Factors like postoperative pancreatic fistula, age, and poor general condition have all been determined to have a negative impact on the postoperative course.[1,4,13,16,17] The drawbacks of some of these studies, however, are the small number of included patients, the inclusion of low-volume centers, and the short-term postoperative follow-up of the patients. In our study, we therefore evaluated which clinic-pathological factors significantly influence morbidity, mortality, and long-term results in a tertiary reference institution for pancreatic diseases, where about 50 pancreatic resections are performed annually. Preoperative workup, surgical procedures, and postoperative care are highly standardized. All these factors enabled us to perform a detailed study of factors influencing the perioperative course after pancreatic surgery.

Patients and methods

For the present retrospective study, the data of patients after pancreaticoduodenectomies (PD) and total pancreatectomies (TP) performed from January 1, 2008 to March 31, 2017 at the Department of Abdominal Surgery UMC Maribor were analyzed. Clinical and pathological data were prospectively stored in a computerized database. Data for the follow-up were obtained by our own outpatient follow-up and by the National cancer register of Slovenia. Complete follow-up was obtained up to June 1, 2017. We obtained informed consent from all patients and performed all procedures according to the guidelines of the Helsinki Declaration. The analysis includes patients having had PD and TP. There are no urgent resections included. The indications for the resection were malignant and premalignant lesions of the region sited in the head of pancreas, and chronic pancreatitis in few cases.

Preoperative workup

Patients' preoperative physical status was expressed by the American Society of Anesthesiology score (ASA).[18] Three ASA 4 patients from this period were not included in the study. Prior to the surgery, all patients were submitted to computer tomography (CT). Additional abdominal magnetic resonance imaging (MR) or endo-ultrasonography (EUS) with or without biopsy were done only in selected patients. Beside usual standard laboratory blood tests, tumor markers CEA and Ca 19-9 were also evaluated. Preoperative endoscopic biliary drainage (EBD) was done in patients with bilirubin value > 200 mmol/l or in subicteric patients when further preoperative workup was necessary.

Preoperative preparation

Intravenous antibiotic (1.5 g cefuroxime and 0.5 g metronidazole or 0.35 g gentamycin and 0.6 g clindamycin) and subcutaneous antithrombotic (4000 IE enoxaparin or 3800 nadroparin or 5000 IE dalteparine) prophylaxis were successively used in all patients 1 hour and 12 hours prior to operation. Urine catheter and nasogastric tube were usually inserted after induction of anesthesia.

Surgical technique

The usual operative approach was median or bilateral subcostal laparotomy. After confirming respectability (no distant dissemination, no tumor infiltration of the coeliac trunk, hepatic artery or superior mesenteric artery), the strategy was to perform a curable resection (R0) in malignant and premalignant lesions, and/or to relieve symptoms as in chronic pancreatitis. Usually pylorus-preserving PD, Whipple resection or TP (in patients with very soft texture of the pancreas unsuitable for anastomosis) were performed. In malignant disease, lymphadenectomy was done in hepatoduodenal ligament, around common hepatic artery, superior mesenteric artery (usually 180 to 270^0), and occasionally between vena cava and aorta. Resection borders on the bile duct and pancreas were checked for neoplastic infiltration by frozen section examination. If infiltration of the superior mesenteric or portal vein was suspected, "En-block" resection of the infiltrated vein was done to assure the curability of resection. Vascular reconstruction was done by direct continuous 6.0 monofilament non-absorbable suture; however, if more extended distance had to be bridged, vascular prosthesis was used. Anastomosis to pancreatic stump was exclusively performed by duct to mucosa end to side pancreaticoenteric anastomosis (PEA) using 5.0 monofilament non-absorbable

TABLE 1. Indications for pancreatic resection

Indication for pancreatic resection	P1 (n/ %)	P2 (n/ %)	All (n/ %)	p
Pancreatic adeno carcinoma	64	71	135	
	66.7%	50.0%	56.7%	
Neuroendocrine tumor of the pancreas	2	7	9	
	2.1%	4.9%	3.8%	
Main duct intraductal papillary mucinous neoplasm	0	3	3	
	0.0%	1.4%	0.8%	
Franz's tumor	1	0	1	
	1.0%	0.0%	0.4%	
Non-Hodgkin lymphoma of the pancreas	1	1	2	
	1.0%	0.7%	0.8%	
Adenocarcinoma of the distal bile duct	13	30	43	
	13.5%	20.8%	17.9%	
Adenocarcinoma of the papilla Vateri	12	18	30	
	12.5%	12.5%	12.5%	
Duodenal adenocarcinoma	2	6	8	
	2.1%	4.2%	3.3%	
Gastric cancer	0	2	2	
	0.0%	1.4%	0.8%	
Chronic pancreatitis	1	6	7	
	1.0%	4.2%	2.9%	

P1 (period 1) = from January 1, 2008 to December 31, 2012 (96 pts); P2 (period 2): from January 1, 2013 to March 31, 2017

sutures in two layers followed by single-layer bilioenteric anastomosis (BEA) with interrupted 5.0 absorbable polyfilament sutures. In selected patients (mostly with thin duct and/or soft texture of the pancreas), trans-anastomotic lost stent was used. The continuity of the gastrointestinal tract was further established by omega gastroenteric anastomosis (GEA) done with 3.0 absorbable monofilament sutures. In all patients, single-layer continuous entericenteric anastomosis (EEA) between afferent and efferent loop was done with 4.0 polyfilament absorbable suture. Two drains were placed in the right subhepatic region (one in space of resected head of the pancreas and one above bilioenteric anastomosis) and one in the Douglas region.

Postoperative care

Almost all patients were admitted in the high dependency unit except if admission to the intensive care unit was indicated. Patients started to receive fluid food on the first day. Gastric tube was removed after appearance of bowel movements or the first stools. Amylase was checked in the drained fluid on day 3 and thereafter when any clinical suspicion for anastomotic leaks was present. In selected patients (soft pancreas remnant) however, parenteral somatostatin (6 mg/24 h) was administrated for 6 to 10 days in the presence of clinical relevant amylase leak until the cessation of secretion on abdominal drains.

Definitions and statistical analyses

All complications (OAC) according to Clavien–Dindo classification grade II or more were considered as postoperative morbidity.[19]

All surgical (ASC), all general (AGC), and all surgical and general complications (SGC) were analyzed. In addition, special group of complications like leak from PEA (PL), leaks not from PEA (OL), abdominal abscess (AA) and abdominal or intestinal bleeding (BC) were identified.

Any postoperative mortality within 30 and 90 days was considered a probable consequence of

TABLE 2. Observed clinicopathological features in 240 operated patients

		P1 (n/%)	P2 (n/%)	All (n/%)	p
Gender (n = 240)	male	51	80	131	0.4
		53.1%	55.6%	54.6%	
	female	45	64	109	
		46.9%	44.4%	45.4%	
Age (n = 240)	Mean (years)	66.1 ± 9.9	65.98 ± 10.1	66.4	0.91
ASA (n = 240)	1	17	43	17	0.103
		17.7%	29.9%	17.7%	
	2	53	68	53	
		55.2%	47.2%	55.2%	
	3	26	33	26	
		27.1%	22.9%	27.1%	
Preoperative histology (n = 240)		4	32	36	0.0001
		4.2%	22.2%	15.0%	
Hospital stay (n = 222)	Mean (days)	21.2 ± 14.5	19 ± 11.6	19.8	0.138
Preoperative total bilirubin (n = 240)	Mean (mmol/l) (mmol/l)	67.6 ± 71.5	79.0 ± 85.5	74.7	0.028
Preoperative endoscopic biliary drainage (EBD) (n = 240)		34	51	85	0.554
		35.4%	35.4%	35.4%	
		P1 (n/%)	**P2** (n/%)	**All** (n/%)	**p**
Type of pancreatic resection (n = 240)	PD	92	115	207	0.0001
		95.8%	79.9%	86.3%	
	TP	4	29	33	
		4.2%	20.8%	14.2%	
Resection of VMS/VP (n=240)		12	28	40	0.17
		12.5%	19.4%	16.7%	
Type of vascular reconstruction (n=240)	Direct suture	10	14	24	0.043
		10.4%	9.7%	10.0%	
	Vascular graft	2	14	16	
		2.1%	9.7%	6.7%	
Overall complications (OAC) (n=240)		34	55	89	0.383
		35.4%	38.2%	37.1%	
30-day mortality (n=240)		7	5	12	0.152
		7.3%	3.5%	5.0%	
90-day mortality (n=240)		11	8	19	0.080
		11.5%	5.6%	7.9%	

ASA = American Society of Anesthesiologist Physical Status; VMS = mesenteric superior vein; VP = portal vein; P1 (period 1) = from January 1, 2008 to December 31, 2012 (96 pts); P2 (period 2): from January 1, 2013 to March 31, 2017

surgery and was declared as postoperative mortality (30- and 90-day mortality).

Receiver operating curve analysis for morbidity and mortality determined the threshold values of amylase secretion on abdominal drains. An area under curve (AUC) of > 0.75 was used to determine the value of significance. The ROC analysis was used to determine sensitivity and specificity of the determined amylase cut-off, which revealed to be more than 7 ukat/l. Sensitivity and specificity for prediction of pancreatic fistula type B or C (PF B or C) at cut-off 7 ng/ml were 100% and 85.4% re-

TABLE 3. Surgical complications in 240 operated patients

Type of all surgical complications (n = 240)	n	%	% 90-day mortality
No surgical complications	169	70.4	3
PF B or C	28	11.7	25
PF B or C and bleeding	8	3.3	62.5
Bleeding in the intestines	2	0.8	0
Intraabdominal bleeding – no PF	4	1.7	25
Bile leak	10	4.2	0
Leak from GEA	5	2.1	20
Dehiscence of laparotomy	3	1.3	0
Intraabdominal abscess	6	2.5	0
Ileus	1	0.4	0
Thrombosis of vascular graft	2	0.8	0
Volvulus coeci	1	0.4	0
Stenosis of coeliac trunk	1	0.4	0
Total	**240**	**100.0**	**7.9%**

GEA = gastroenteroanastomosis; PF B and C = pancreatic fistula type B and C

TABLE 4. General complications in 240 operated patients

Type of all general complications (n = 240)	n	%	% 90-day mortality
No general complications	202	84.2	5.0
Pneumonia	8	3.3	25
Cardiorespiratory decompensation	3	1.3	100
Heart failure	9	3.8	11.1
Pulmonary embolism	4	1.7	25
Different infections	10	4.2	10
Renal failure	1	.4	100
Brain stroke	1	.4	0
Miscellaneous	2	.8	0
Total	**240**	**100.0**	**7.9**

spectively. Consequently, any secretion of amylase rich fluid on drains more than 7 ukat/l was defined as elevated. Patients with high amylase on drains from PEA were declared to have (PF) and retrograde classified in three types of PF (A, B, C) respecting clinical picture, therapeutic consequences, and ISGPF PF recommendations.[20]

Two chronologically successive groups of patients (period 1 (P1): from January 1, 2008 to December 31, 2012 (96 pts); and period 2 (P2): from January 1, 2013 to March 31, 2017 (144 pts)) were compared for perioperative morbidity, and 30- and 90-day mortality.

Continuous data are expressed as mean ± standard deviation and categorical variables are given as percentages. Continuous variables were compared with Student's t-tests for parametric data and Mann-Whitney U tests for nonparametric data. Chi-square tests were used for comparisons of discrete variables.

All of the predictors that were significant on univariate analysis were included in the multivariate analysis. In the multivariate analysis, a binary logistic model was used. Survival analysis was performed with the Kaplan-Meier method. The differences between groups were compared with the log-rank test. P values < 0.05 were defined as the limit of significance. For statistical analysis, SPSS version 22 for Windows 7 (IBM Analytics, Armonk, NY) was used.

The aim of our study was to evaluate the incidence of morbidity and mortality, and to reveal any correlations with clinicopathological factors. In addition to morbidity and mortality, the impact of morbidity and mortality on survival was studied. The second aim was to reveal any differences between two chronologically successive groups (P1 and P2).

Results

Altogether 240 patients had pancreatic resection (male 131, female 109, mean age 66.04 years). The indications for resections and characteristics of the analyzed patients are presented in Tables 1 and 2.

The incidence of OAC was 37.1%. ASC occurred in 29.2% whereas AGC in 14.2%. ASC presented themselves as a leak from PEA (PL), non-PEA leak (OL), bleeding complications (BC) and abdominal abscesses (AA) in 19% (of 208 PD), 5.8%, 5.8% and 2.5% respectively. In case of OL, five were from GEA. Bleeding (BC) occurred in altogether 14 of 240 patients. Two patients had early intestinal bleeding and 12 occurred after 24 hours. Other rare surgical complications occurred in altogether 4.5% (Table 3). All general complications are described in Table 4.

Drained fluid was checked for amylase in 189 of 207 patients after PD. Elevated amylase more than 7 ukat/l on drains were found in 73 patients (38.6%). In 63 patients (33.3%), the high amylase on drains originated from PEA whereas in 10 patients amylase rich secretion evidently did not origin from PEA (6 bile leaks, 2 leaks from GEA, 1 ileus, 1 strangulation of the mobile cecum). The rate of PF A was 14.4%, PF B 9.6% and PF C 9.6%. Determination of PF in groups A, B and C did not correlate with means of amylase value in dis-

TABLE 5. Correlation of clinicopathological factors and perioperative morbidity and mortality in 240 operated patients

	N		OAC	P	ASC	P	BC	P	OL	P	AA	P	PL	P	AGC	P
Age (years)	240	No compl. Compl.	**64.6 ± 10** **68.4 ± 9.1**	**0.005**	65.3 ± 10.3 67.9 ± 9.1	0.051	66.2 ± 10 63.5 ± 12	0.452	66 ± 10 67.1 ± 8	0.665	65 73	0 056	65.7 ± 10 67.3 ± 8	0.256	**65.4 ± 10** **70.1 ± 9**	**0.007**
Age (<70 and >69)	240	<70 >69	28.6% 43.7F%	**0.011**	23.8% 33.3%	0.071	8.6% 3.7%	0.094	4.8% 6.7%	0.369	**0%** **100%**	**0.030**	16.3% 21.4%	0.234	**8.6%** **18.5%**	**0.021**
ASA 1.2 vs. 3	240	ASA 1+2 ASA 3	**32%** **52.5%**	**0.004**	**23.8%** **33.3%**	**0.042**	5.5% 6.8%	0.465	5.5% 6.8%	0.465		0.457	**16.1%** **29.5%**	**0.042**	**10.5%** **25.4%**	**0.006**
Total bilirubin (mmol/l)	240	No compl. Compl.	70.1 ± 74 82.9 ± 89	0.271	68.3 ± 73.6 89.5 ± 93.1	0.062	**71 ± 77** **134 ± 104**	**0.005**	74.4 ± 78 75.5 ± 108	0.969		0.231	68.1 ± 70 91.4 ± 99	0.195	**79 ± 82** **47.4 ± 61**	**0.033**
EBD (no/yes)	240	No EBD EBD	33.5% 43.5%	0.082	24.5% 37.6%	**0.024**	5.8% 5.9%	0.594	7.1% 3.5%	0.203		0.640	**12.8%** **30%**	**0.004**	11.6% 18.8%	0.092
PD/TP	240	PD TP	37.2% 36.4%	0.545	29.5% 27.3%	0.488	6.3% 3%	0.400	5.8% 6.1%	0.600	**1%** **12.1%**	**0.004**	-	-	13% 21.2%	0.126
Vasc. resect. (yes/no)	240	No vasc. Vasc. resect.	39.5% 27.5%	0.115	30.0% 25.0%	0.334	4.5% 12.5%	0.063	6% 5%	0.578		0.738	21.1% 7.7%	0.083	**16.5%** **2.5%**	**0.011**
Size of tumor (mm)	201	No compl. Compl.	**32.3 ± 19** **24.6 ± 12**	**0.001**	**31.7 ± 18.8** **23.7 ± 10.1**	**0.002**	29.5 ± 17 25 ± 10	0.187	29.4 ± 17 25.1 ± 13	0.320		0.069	**30.3 ± 18** **22.5 ± 9**	**0.001**	29.7 ± 17 25.7 ± 15	0.211
Type of tumor PAC/NPC	216	PAC NPC	**34.1%** **46.9%**	**0.042**	26.7% 37.0%	0.074	6.7% 4.9%	0.421	5.9% 7.4%	0.435		0.403	16.2% 25.7%	0.092	69.8 ± 183 83.5 ± 127	0.094
Amylase level (ukat/l)	187	No compl. Compl.	**21.3 ± 62.1** **150.6 ± 252**	**0.0001**	**24.0 ± 73** **179.9 ± 270**	**0.0001**	68.6 ± 175 128.1 ± 199	0.333	72.3 ± 180 62.5 ± 100	-0.773	**72.5 ± 177** **1.1 ± 1**	**0.0001**	**22.2 ± 70** **260 ± 310**	**0.0001**	69.8 ± 183 83.5 ± 127	0.640
Amylase (>7 ukat/l)	187	< 7 > 7	**20.2%** **69.8%**	**0.0001**	**11.4%** **61.6%**	**0.0001**	**3.5%** **12.7%**	**0.022**	**1.7%** **60.3%**	**0.0001**		0.529	**19.1%** **100%**	**0.0001**	35.6% 57.7%	0.033
PF C (yes/no)	187	No PF C PF C	**33.1%** **100%**	**0.0001**	**23.7%** **100%**	**0.0001**	**3%** **38.9%**	**0.0001**		0.318		0.818	**10.7%** **100%**	**0.0001**	**-**	0.464
PF B (yes/no)	187	No PF B PF B	**33.1%** **100%**	**0.0001**	**23.7%** **100%**	**0.0001**	6.5% 5.6%	0.676		0.318		0.818	10.7% 100%	**0.0001**	**-**	0.221
PF A (yes/no)	187	No PF A PF A	**42.5%** **22.2%**	**0.035**	**36.3%** **0**	**0.0001**		0.148		0.171		0.734	**24%** **100%**	**0.0001**	-	0.141
PF B or C	187	No PF B+C PF B+C	**25.2%.** 100%	**0.0001**	**14.6%** **100%**	**0.0001**	**2.6%** **22.2**	**0.0001**		0.088		0.655				
Period of the study	240	P1 P2	35.4% 38.2%	0.383	25.0% 31.9%	0.155	**2.1%** **8.3%**	**0.036**	5.2% 6.3%	0.485		0.230	16.9% 21.2%	0.292	17.7 11.8	0.137
Hospital stay (days)	240		**14.2 ± 4** **31.4 ± 16**	**0.0001**	**15.2 ± 6** **32.9 ± 17**	**0.0001**	**19.3 ± 13** **31.9 ± 8**	**0.003**	**18.1 ± 9** **44.9 ± 29**	**0.0001**	19.6 ± 13 29 ± 10	0.075	**17.8 ± 12** **30.7 ± 9**	**0.0001**	**18.4 ± 12** **30.9 ± 10**	**0.0001**

AA = intraabdominal abscess; ASC = all surgical complications; AGC = all general complications; BC = bleeding complications; comp. = complications, EBD = external biliary drainage; No compl. = no complications; NPC = non-pancreatic carcinoma; OAC = overall complications; OL = other anastomotic leak; PAC = pancreatic adenocarcinoma; PD = pancreaticoduodenectomy; PL = pancreatic leak anastomosis; PF C/ B/ A = pancreatic fistula type C/ B/ A; TP = total pancreatectomy; Vasc. resect. = vascular resection; No vasc. = no vascular resection

charged secretion on drains in ordinal fashion; it was rather the consequence of clinical factors and therapeutic measures.

One of the common consequences of complications was significantly prolonged hospital stay (OAC: 30.9 ± 16 vs. 14.2 ± 4.5 days; $p < 0.0001$). Overall 30- and 90-day mortality were 5% and 7.9%.

Correlation of clinicopathological factors and perioperative morbidity

Age and physical status

Patients with OAC and AGC were older, and their physical status according to ASA was worse. Physical status was worse also in a group of patients with PL (29.5% vs. 16.1%; $p = 0.042$). Regarding this, no correlations were found in other subsets of complications (AA, BC, and OL) (Table 5).

Preoperative bilirubin value and EBD. At our disposal were only bilirubin values from the period within a week before the PD, and the majority of patients was transferred to our institution with already placed EBD more than 1 week before the operation. This prevented us to make any conclusive analysis on this issue. Generally, patients with preoperative placed EBD had lower mean preoperative bilirubin values than those without EBD (57.4 ± 66 vs. 83.8 ± 86mmol/l; $p = 0.005$). Increased mean bilirubin level was noted in BC (134.7 ± 104 vs. 70.7 ± 71.6 mmol/l; $p = 0,005$). EBD was in 37.6% of our patients associated with the occurrence of ASC and in 30% with PL (ASC: 37.6% vs. 24.5%, $p = 0,024$, PL: 30% vs. 12.5%, $p = 0,004$), but there have been no correlations of EBD with other settings of complications (Table 5).

Type of resection and vascular resections

PD and TP were comparable regarding all clinicopathological factors except of AA which was more likely after TP (1% vs. 12.1%; p = 0.004). Resections of VMS/VP correlated only with AGC revealing even less complications if vascular resection has been done (2.5% vs. 16.5%; p = 0.011). This correlation was difficult to explain since patients with vascular resection were comparable regarding the age and physical status (mean age: 65.2 vs. 66.1 years; p = 0.556; ASA 3 vs. ASA 1 and 2: 22.2% vs. 25%; p = 0.456) (Table 5).

Type and size of the tumor

Data of tumor dimensions were available for 201 patients. There was a high correlation between tumor size and tumor type revealing NPCs to be smaller and PACs to be larger. In groups of OAC, ASC and PL, smaller size of tumor significantly predicted the onset of complications. Calculation revealed that patients with NPC were more prone for onset of OAC than those with PAC (Table 5).

Amylase on drains

Complications after PD were associated with amylase rates more than 7 ukat/l. The mean amylase value was increased only in OAC and ASC (OAC: 150.6 ± 252 vs. 21 ± 62; p < 0.0001, ASC: 179.9 ± 270 vs. 24 ± 73; p < 0.0001). Since PF A has never been noticed, it did not have any negative impact on any type of complications. There is an inverse correlation of mean amylase level and AA (1.1 ± vs. 72.5 ± 177 ukat/l; p < 0.0001) proving that abscesses did not originate from pancreatic leak. Smaller size of the tumor proved to be a predictor for the occurrence of PL (30.3 ± 18 vs. 22.5 ± 9; p = 0.001). Amylase rates more than 7 ukat/l and PF B were more often noted in NPCs (amylase < 7 ukat/l: 48.4% vs. 25.3%; p = 0.002, PF B: 17.2% vs. 6.3%; p = 0.029), but there was no correlation at the whole between PF C and type of tumor (Table 5).

Correlation of clinicopathological factors and perioperative mortality

Patients who suffered complications in terms of OAC, ASC, AGC, BC, PL and PF C were at a significant higher risk for postoperative mortality (OAC 30-day: 13.5% vs. 0%; p < 0.0001, OAC 90-day: 20% vs. 0.7%; p < 0.0001, ASC 30-day: 14.3% vs. 1.2%; p < 0.0001, ASC 90-day: 20% vs. 2.9%; p < 0.0001, AGC 30-day: 14.1% vs. 4.3%; p < 0.0001, AGC 90-day: 20% vs. 2.9%; p < 0.0001, BC 30-day: 35.7% Vs. 3.1%; p < 0.0001, BC 90-day: 34.3% vs. 7.2%; p < 0.0001, PL 30-day: 22.2% vs. 2%; p < 0.0001, PL 90-day: 33.3% vs. 3.2%; p < 0.0001, PF C 30-day: 33.3% vs. 2.9%; p < 0.0001, PF C 90-day: 50% vs. 4.7%; p < 0.0001). On the other hand, OL and AA did not impact the 30- and 90-day mortality.

Age did not correlate to 30- or 90-day mortality; however, ASA physical status did (30-day: 11.9% vs. 2.8%; p = 0.011, 90-day: 18.6% vs. 4.4%; p = 0,001).

Patients with amylase rich secretion more than 7 ukat/l were also at a higher risk to die within 30 or 90 days after operation (amylase > 7ukat/l 30-day: 14.3% vs. 1.7%; p = 0.002, amylase > 7ukat/l 90-day: 20.6% vs. 3.4%; p < 0.0001). However, mean value of amylase on drains was significantly higher in patients that died within 90 days compared to those who died in 30 days (90-day: 172 ± 231 vs. 59.1 ± 170ukat/l; p = 0.013). Tumor type or size of the tumor, mean preoperative total bilirubin, EBD, and PF A and B did not correlate with 30- and 90-day mortality.

Multivariate analysis

Predictors found to be significant for 30- and 90-day morbidity and mortality in the univariate analysis were included in the multivariate logistic regression analysis.

For OAC, higher mean age and drained amylase more than 7 ukat/l (age: CI 95%: 1.019-1.103; p = 0.004, amylase > 7ukat/l: 95% CI: 0.045-0.204; p < 0.0001) were predictive. For ASC, higher mean amylases and drained amylase more than 7 ukat/l (mean amylase: 95% CI: 1.000-1.007; p = 0.047, 95%, amylase > 7 ukat/l: CI: 0.070 – 0.427; p < 0.0001) were specific. Moreover, for AGC, physical status, mean age and mean level of total bilirubin preoperatively (ASA: 95% CI: 1.007 -1.121; p = 0.028, mean age: 95% CI: 1.042-6.715; p < 0.041, mean total bilirubin: 95% CI: 0.981-0.999; p < 0.027) revealed as independent predictors.

For 30-day mortality, PL and BC revealed as independent predictors (PL: 95% CI: 0.026-0,522; p = 0.005, BC: 95% CI: 0.024-0 537; p = 0.006). In case of 90-day mortality, physical status, OAC and PF C (ASA: 95% CI: 1.404 -16.514; p = 0.012, OAC: 95% CI: 1.622-117.599; p = 0.016, PF C: 2.030-28.244, p = 0.003) were noticed as predictive factors.

Survival analyses

Patients who had OAC, ASC, AA, OL or AGC have had comparable expectation for long-term survival to those without complications (OAC: 866 ± 139

vs. 760 ± 174 days, Log Rank: p = 0.242; ASC: 866 ± 134 vs. 901 ± 216 days, Log Rank: p = 0.234; AA: Log rank: p = 0,048, OL: 836 ± 123 vs. 1159 ± 673 days; Log rank: p = 0.760, AGC: 866 ± 135 vs. 760 ± 197 days, Log Rank: p = 0.431). Complications like PL in PD and BC in all resected patients seriously compromised the expected long-term survival (PL: 938 ± 67 vs. 499 ± 146 days; Log Rank: p = 0.010, BC: 901 ± 128 vs. 409 ± 457 days; Log Rank: p = 0.046). On the other hand, in patients who survived complications, the long-term survival was not impacted by any type of complications (Figures 1,2).

Differences between two chronologically successive groups

Two chronologically successive groups of patients were comparable on most clinicopathological factors except for preoperative gained histology, preoperative total bilirubin, and type of resection (Table 2). The indications for TP were: postoperative bleeding from the pseudo-aneurism of the proximal part of the common hepatic artery combined with leak of the PEA (1 patient); PAC and main duct IPMN (9 patients); diffuse main duct IPMN (1 patient); very soft pancreas (10 patients); positive resection margins (5 patients); tumor extending to the body of the pancreas (5 patients); and formerly removed left pancreas (2 patients) (Table 1). Five out of 10 patients with extremely soft pancreas had also vascular reconstructions with prosthetic interposition, and three already had insulin dependent diabetes. The overall (P1 and P2) 30- and 90-day mortality in our cohort were 5 and 7.9% respectively. In P2, the rates for 30- and 90-day mortality became lower, 3.5% and 5% respectively, but the statistical difference between P1 and P2 reveals only borderline statistical value (p = 0.08) (Table 2).

Discussion

Pancreatic resections present the only curative option for patients with malignant and premalignant diseases, and for relief of symptoms in selected group of patients with chronic pancreatitis. However, due to high morbidity and mortality, the treatment should not be worse than the disease.[21] Despite markedly progress on the field of pancreatic resections, morbidity remains quite high for decades whereas mortality rates gradually improved.[22–27] There was no exception in our study with OAC rate of 37.1%; ASC 29.2% and AGC 14.2% were AGC within the two observed periods. The 30-and 90-day mortality in our patients were 5% and 7.9% respectively. This result is well comparable to the reports of other authors. In many studies, postoperative mortality was defined traditionally as mortality within 30-days or during the initial hospitalization. This might had led to an underestimated postoperative morbidity and mortality rates. As shown by some Meta analyses, even in centers of Excellency, the 90-day mortality rate is double of the 30-day mortality rate and significantly differs concerning the hospital volume. One of the consequences of postoperative morbidity for patients who survive the complication was significantly prolonged hospitalization.[5,15,26,28] In our study, it was ranging between 30 and 44 days.

It has been often documented that higher age and low physical status can significantly affect the occurrence of postoperative complications.[12,13] In our study, higher mean age and higher ASA score impacted the incidence of OAC and AGC. ASA score alone impacted ASC and PL. Regarding our results, higher mean age was an independent predictor for OAC and AGC whereas ASA score was for AGC. On the other hand, specific complications like BC, AA and OL did not correlate with age or physical status. Age did not prove as an independent prognostic factor for any type of complications; however, ASA score did for 90-day mortality. Therefore, our results support the conclusion not to restrain patients from PD or TP only because of their age; however, caution is needed while selecting the patients for PD or TP.

There is an ongoing debate on whether jaundiced patients with obstructive lesion and higher bilirubin in the head of the pancreas should be drained or not.[29–34] Since only relevant laboratory data from the immediate preoperative period were at our disposal for the study, we can hardly profoundly discuss this issue. Based on our own data, however, we observed higher mean total bilirubin values in patients with BC and lower for the group with AGC. The results regarding EBD match with the results from others revealing higher incidence of ASC and PL in patients with EBD.[31,35-38] There was no correlation of mean total bilirubin or EBD with 30- and 90-day mortality.[32,39,40]

Our study confirms comparable results regarding the perioperative morbidity and mortality between PDs and TPs except for abdominal abscesses, which occurred more often in TP. This fact could speak for TP in selected cases of patients with pancreas remnant untenable for PEA, especially in elderly in less good general condition who do not

tolerate this kind of complications at all.[41–43] In patients with preexisting insulin dependent diabetes, this decision could even be easier. Relevant criteria for decision-making in this regard are still missing. Further analyses are needed for long-term quality of life, especially concerning insulin dependent diabetes.[44–46]

Resection of VMS or VP for infiltration was formerly regarded as a relative contraindication for the PD. However, nowadays it presents a standard treatment and was performed in 16.7% of our patients. In our study, neither type of pancreatic resection nor the incidence of VMS/VP resection influenced the occurrence of postoperative morbidity and mortality.[47–52]

The proportion of chronic pancreatitis in PACs and NPCs included in the reports can differ significantly, and if cases with predominantly hard pancreas remnant predominate, as in patients with chronic pancreatitis, the overall risk for postoperative morbidity and mortality rates could reveal at a lower rates. In our collective of patients, chronic pancreatitis and PAC contributed 2.9 and 56.7% of patients respectively, remaining more than 40% of patients with diseases where the pancreas remnant could be softer (Table 1).[9,53–55]

To our results, concerning only PACs and NPCs, OACs were more likely to occur in NPCs and in tumors of smaller size. Moreover, the majority of NPCs were also smaller than PACs. The size of tumor affects the onset of OAC, ASC and PL; however, neither 30- nor 90-day mortality were impacted by type or size of the tumor.[56–58]

Patients with amylase more than 7 ukat/l on drains and pancreatic fistula were retrospectively classified in three types of PF (A, B, C) respecting clinical picture, therapeutic consequences, and ISGPF PF recommendations.[20] Mean values of amylase in discharged secretion did not differ between PF A, B and C. There is consensus among all reports that PF negatively affected the postoperative course in patients after PD.[59,60] Our experience with PF was similar. In PD, the high mean amylase on drains or amylase more than 7 ukat/l predicted the onset of complications, especially if surgical complications were involved (OAC, ASC and PL). However, exception were AA where the mean amylases on drains were low proving that abscesses did not originate from pancreatic leak. PF A was not associated with any serious morbidity in postoperative course of our patients. Patients with OAC, ASC, AGC, BC, PL, PF C and high mean amylase or amylase more than 7 ukat/l are at a higher risk to die within 30 or 90 days. Although, most studies agree about the impact of PF on morbidity and mortality, there is less consensus for how to prevent the occurrence of PF. Most effort is focused on how to perform a save anastomosis in case of soft friable pancreas texture with a thin pancreatic duct.[5–7,10,61,62]

Both periods (P1 and P2) were comparable regarding almost all clinicopathological factors except for type of pancreatic resection and vascular reconstructions, and the count of performed TPs. There were more TPs in P2 as in P1 (20.8% vs. 4.2%). Both types of pancreatectomies were comparable regarding age, physical status, tumor markers, mean bilirubin value, morbidity and mortality. Logically, there were no PF in TP. In addition to other indications, TP was performed in 11 patients with pancreas remnant unsuitable for anastomosis. The indications for TP must be posed very responsible, even the inform consent must be done preoperatively in this issue.[24,41,43] The morbidity was stable within the whole study period, but 30- and 90-day mortality became twofold lower in P2 (3.5% and 5.7%), although without a significant correlation.

Most subtypes of complications did not compromise the long-term survival in our cohort of patients. The exceptions were PLs in PDs and BCs in PDs and TPs where the 5-year survival was significantly compromised. On the other hand, in patients who survived any of these complications the long-term survival was not impacted by any type of complications.[59,60,63,64]

In conclusion, the present study indicates that amylase rich secret on drains and higher mean age are independent indicator for OAC whereas. PL and BC proved as an independent predictor for 30-day mortality, and physical status, OAC and PF C for 90-day mortality. EBD, smaller size of tumor and NPC can provoke complications; however, there was no repercussion on postoperative mortality. Even though the decrease in 30- and 90-day mortality (3.5% and 5%) tightly missed the significance in our cohort of patients, the trends of better surgery in pancreatic resections in our institution seemed to be encouraging. Most subtypes of complications did not compromise the long-term survival in our cohort of patients. The exceptions were specific complications like PLs and BCs where the 5-year survival was significantly compromised. On the other hand, in patients who survived these complications, the long-term survival was not impaired by any type of complications. The worse scenario in pancreatic resection is an older patient in bad physical condition having low sized tumor

or NPC, amylase reach output on drains after resection, and eventually BC.

References

1. Ho C-K, Kleeff J, Friess H, Büchler MW. Complications of pancreatic surgery. *HPB (Oxford)* 2005; **7:** 99-108. doi:10.1080/13651820510028936
2. Kapoor VK. Complications of pancreato-duodenectomy. *Ceskoslovenske Chir Spolecnosti* 2016; **95:** 53-9.
3. Penumadu P, Barreto SG, Goel M, Shrikhande SV. Pancreatoduodenectomy - preventing complications. *Indian J Surg Oncol* 2015; **6:** 6-15. doi:10.1007/s13193-013-0286-z
4. Ren S, Liu P, Zhou N, Dong J, Liu R, Ji W. Complications after pancreaticoduodenectomy for pancreatic cancer: a retrospective study. *Int Surg* 2011; **96:** 220-7.
5. Assumpcao L, Cameron JL, Wolfgang CL, Edil B, Choti MA, Herman JM, et al. Incidence and management of chyle leaks following pancreatic resection: a high volume single-center institutional experience. *J Gastrointest Surg* 2008; **12:** 1915-23. doi:10.1007/s11605-008-0619-3
6. van Berge Henegouwen MI, De Wit LT, Van Gulik TM, Obertop H, Gouma DJ. Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: drainage versus resection of the pancreatic remnant. *J Am Coll Surg* 1997; **185:** 18-24
7. Vin Y, Sima CS, Getrajdman GI, Brown KT, Covey A, Brennan MF, et al. Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. *J Am Coll Surg* 2008; **207:** 490-8. doi:0.1016/j.jamcollsurg.2008.05.003
8. Sperti C, Pasquali C, Ferronato A, Pedrazzoli S. Median pancreatectomy for tumors of the neck and body of the pancreas. *J Am Coll Surg* 2000; **190:** 711-6.
9. Bourgouin S, Ewald J, Mancini J, Moutardier V, Delpero J-R, Le Treut Y-P. Predictive factors of severe complications for ampullary, bile duct and duodenal cancers following pancreaticoduodenectomy: Multivariate analysis of a 10-year multicentre retrospective series. *Surgeon* 2015; pii: S1479-666X(15)00118-3. doi:10.1016/j.surge.2015.11.003
10. Machado NO. Pancreatic fistula after pancreatectomy: definitions, risk factors, preventive measures, and management-review. *Int J Surg Oncol* 2012; **2012:** 602478. doi:10.1155/2012/602478
11. Hashimoto Y, Traverso LW. Pancreatic anastomotic failure rate after pancreaticoduodenectomy decreases with microsurgery. *J Am Coll Surg* 2010; **211:** 510-21. doi:10.1016/j.jamcollsurg.2010.06.018
12. Riall TS, Sheffield KM, Kuo Y-F, Townsend CM, Goodwin JS. Resection benefits older adults with locoregional pancreatic cancer despite greater short-term morbidity and mortality. *J Am Geriatr Soc* 2011; **59:** 647-54. doi:10.1111/j.1532-5415.2011.03353.x
13. Riall TS. What is the effect of age on pancreatic resection? *Adv Surg* 2009; **43:** 233-49.
14. Vollmer CM, Sanchez N, Gondek S, McAuliffe J, Kent TS, Christein JD, et al. A root-cause analysis of mortality following major pancreatectomy. *J Gastrointest Surg* 2012; **16:** 89-102. Discussion 102-3. doi:10.1007/s11605-011-1753-x
15. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226:** 248-257. Discussion 257-60.
16. Partelli S, Pecorelli N, Muffatti F, Belfiori G, Crippa S, Piazzai F, et al. Early postoperative prediction of clinically relevant pancreatic fistula after pancreaticoduodenectomy: usefulness of C-reactive protein. *HPB (Oxford)* 2017; **19:** 580-6. doi:10.1016/j.hpb.2017.03.001
17. Sperti C, Moletta L, Pozza G. Pancreatic resection in very elderly patients: A critical analysis of existing evidence. *World J Gastrointest Oncol* 2017; **9:** 30-6. doi:10.4251/wjgo.v9.i1.30
18. Crea N, Di Fabio F, Pata G, Nascimbeni R. APACHE II, POSSUM, and ASA scores and the risk of perioperative complications in patients with colorectal disease. *Ann Ital Chir* 2009; **80:** 177-81.
19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205-13.
20. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138:** 8-13. doi:10.1016/j.surg.2005.05.001
21. Rosenberg L. Treatment of pancreatic cancer. Promises and problems of tamoxifen, somatostatin analogs, and gemcitabine. *Int J Pancreatol* 1997; **22:** 81-93. doi:10.1007/BF02787465
22. Neoptolemos JP, Russell RC, Bramhall S, Theis B. Low mortality following resection for pancreatic and periampullary tumours in 1026 patients: UK survey of specialist pancreatic units. UK Pancreatic Cancer Group. *Br J Surg* 1997; **84:** 1370-6.
23. Dominguez-Comesaña E, Gonzalez-Rodriguez FJ, Ulla-Rocha JL, Lede-Fernandez A, Portela-Serra JL, Piñon-Cimadevila MÁ. Morbidity and mortality in pancreatic resection. *Cirugia Espanola* 2013; **91:** 651-8. doi:10.1016/j.ciresp.2012.12.004
24. Stauffer JA, Nguyen JH, Heckman MG, Grewal MS, Dougherty M, Gill KRS, et al. Patient outcomes after total pancreatectomy: a single centre contemporary experience. *HPB* 2009; **11:** 483-92. doi:10.1111/j.1477-2574.2009.00077.x
25. Riediger H, Adam U, Utzolino S, Neeff HP, Hopt UT, Makowiec F. Perioperative outcome after pancreatic head resection: a 10-year series of a specialized surgeon in a university hospital and a community hospital. *J Gastrointest Surg* 2014; **18:** 1434-40. doi:10.1007/s11605-014-2555-8
26. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 2015; **220:** 530-6. doi:10.1016/j.jamcollsurg.2014.12.031
27. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. *Ann Surg* 1993; **217:** 430-5.
28. Romano G, Agrusa A, Galia M, Di Buono G, Chianetta D, Sorce V, et al. Whipple's pancreaticoduodenectomy: Surgical technique and perioperative clinical outcomes in a single center. *Int J Surg* 2015; **21(Suppl 1):** S68-71. doi:10.1016/j.ijsu.2015.06.062
29. Álamo JM, Marín LM, Suarez G, Bernal C, Serrano J, Barrera L, et al. Improving outcomes in pancreatic cancer: Key points in perioperative management. *World J Gastroenterol* 2014; **20:** 14237-45. doi:10.3748/wjg.v20.i39.14237
30. Jinkins LJ, Parmar AD, Han Y, Duncan CB, Sheffield KM, Brown KM, et al. Current trends in preoperative biliary stenting in patients with pancreatic cancer. *Surgery* 2013; **154:** 179-89. doi:10.1016/j.surg.2013.03.016
31. Singal AK, Ross WA, Guturu P, Varadhachary GR, Javle M, Jaganmohan SR, et al. Self-expanding metal stents for biliary drainage in patients with resectable pancreatic cancer: single-center experience with 79 cases. *Dig Dis Sci* 2011; **56:** 3678-84. doi:10.1007/s10620-011-1815-7
32. Sahora K, Morales-Oyarvide V, Ferrone C, Fong ZV, Warshaw AL, Lillemoe KD, et al. Preoperative biliary drainage does not increase major complications in pancreaticoduodenectomy: a large single center experience from the Massachusetts General Hospital. *J Hepato-Biliary-Pancreat Sci* 2016; **23:** 181-7. doi:10.1002/jhbp.322
33. Pisters PW, Hudec WA, Hess KR, Lee JE, Vauthey JN, Lahoti S, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001; **234:** 47-55.
34. Scheufele F, Schorn S, Demir IE, Sargut M, Tieftrunk E, Calavrezos L, et al. Preoperative biliary stenting versus operation first in jaundiced patients due to malignant lesions in the pancreatic head: A meta-analysis of current literature. *Surgery* 2017; **161:** 939-50. doi:10.1016/j.surg.2016.11.001
35. Cavell LK, Allen PJ, Vinoya C, Eaton AA, Gonen M, Gerdes H, et al. Biliary self-expandable metal stents do not adversely affect pancreaticoduodenectomy. *Am J Gastroenterol* 2013; **108:** 1168-73. doi:10.1038/ajg.2013.93
36. Tsuboi T, Sasaki T, Serikawa M, Ishii Y, Mouri T, Shimizu A, et al. Preoperative biliary drainage in cases of borderline resectable pancreatic cancer treated with neoadjuvant chemotherapy and surgery. *Gastroenterol Res Pract* 2016; **2016:** 7968201.

37. Xiong J-J, Nunes QM, Huang W, Pathak S, Wei A-L, Tan C-L, et al. Preoperative biliary drainage in patients with hilar cholangiocarcinoma undergoing major hepatectomy. *World J Gastroenterol* 2013; **19:** 8731-9. doi:10.3748/wjg.v19.i46.8731

38. Kishi Y, Shimada K, Nara S, Esaki M, Kosuge T. The type of preoperative biliary drainage predicts short-term outcome after major hepatectomy. *Langenbecks Arch Surg* 2016; **401:** 503-11. doi:10.1007/s00423-016-1427-y

39. Coates JM, Beal SH, Russo JE, Vanderveen KA, Chen SL, Bold RJ, et al. Negligible effect of selective preoperative biliary drainage on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy. *Arch Surg Chic Ill 1960* 2009; **144:** 841-7. doi:10.1001/archsurg.2009.152

40. Ferrero A, Lo Tesoriere R, Viganò L, Caggiano L, Sgotto E, Capussotti L. Preoperative biliary drainage increases infectious complications after hepatectomy for proximal bile duct tumor obstruction. *World J Surg* 2009; **33:** 318-25. doi:10.1007/s00268-008-9830-3

41. Del Chiaro M, Rangelova E, Segersvärd R, Arnelo U. Are there still indications for total pancreatectomy? *Updat Surg* 2016; **68:** 257-63. doi:10.1007/s13304-016-0388-6

42. Müller MW, Friess H, Kleeff J, Dahmen R, Wagner M, Hinz U, et al. Is there still a role for total pancreatectomy? *Ann Surg* 2007; **246:** 966-75. doi:10.1097/SLA.0b013e31815c2ca3

43. Billings BJ, Christein JD, Harmsen WS, Harrington JR, Chari ST, Que FG, et al. Quality-of-life after total pancreatectomy: is it really that bad on long-term follow-up? *J Gastrointest Surg* 2005; **9:** 1059-66. doi:10.1016/j.gassur.2005.05.014

44. White MA, Agle SC, Fuhr HM, Mehaffey JH, Waibel BH, Zervos EE. Impact of pancreatic cancer and subsequent resection on glycemic control in diabetic and nondiabetic patients. *Am Surg* 2011; **77:** 1032-7.

45. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, et al. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. *J Am Coll Surg* 2010; **210:** 463-73. doi:10.1016/j.jamcollsurg.2009.12.029

46. Malleo G, Mazzarella F, Malpaga A, Marchegiani G, Salvia R, Bassi C, et al. Diabetes mellitus does not impact on clinically relevant pancreatic fistula after partial pancreatic resection for ductal adenocarcinoma. *Surgery* 2013; **153:** 641-50. doi:10.1016/j.surg.2012.10.015

47. Marsoner K, Langeder R, Csengeri D, Sodeck G, Mischinger HJ, Kornprat P. Portal vein resection in advanced pancreatic adenocarcinoma: is it worth the risk? *Wien Klin Wochenschr* 2016; **128:** 566-72. doi:10.1007/s00508-016-1024-7

48. Hoshimoto S, Hishinuma S, Shirakawa H, Tomikawa M, Ozawa I, Wakamatsu S, et al. Reassessment of the clinical significance of portal-superior mesenteric vein invasion in borderline resectable pancreatic cancer. *Eur J Surg Oncol* 2017; **43:** 1068-75. doi:10.1016/j.jamcollsurg.2010.06.018

49. Riediger H, Makowiec F, Fischer E, Adam U, Hopt UT. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. *J Gastrointest Surg* 2006; **10:** 1106-15. doi:10.1016/j.gassur.2006.04.002

50. Kulemann B, Hoeppner J, Wittel U, Glatz T, Keck T, Wellner UF, et al. Perioperative and long-term outcome after standard pancreaticoduodenectomy, additional portal vein and multivisceral resection for pancreatic head cancer. *J Gastrointest Surg* 2015; **19:** 438-44. doi:10.1007/s11605-014-2725-8

51. Cheung TT, Poon RTP, Chok KSH, Chan ACY, Tsang SHY, Dai WC, et al. Pancreaticoduodenectomy with vascular reconstruction for adenocarcinoma of the pancreas with borderline resectability. *World J Gastroenterol* 2014; **20:** 17448-55. doi:10.3748/wjg.v20.i46.17448

52. Flis V, Potrc S, Kobilica N, Ivanecz A. Pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head with venous resection. *Radiol Oncol* 2016; **50:** 321-8. doi:10.1515/raon-2015-0017

53. Park JR, Li F, Oza VM, Sklaw BC, Cronley KM, Wellner M, et al. High-grade pancreatic intraepithelial lesions: prevalence and implications in pancreatic neoplasia. *Hepatobiliary Pancreat Dis Int* 2017; **16:** 202-8.

54. Hwang IK, Kim H, Lee YS, Kim J, Cho JY, Yoon Y-S, et al. Presence of pancreatic intraepithelial neoplasia-3 in a background of chronic pancreatitis in pancreatic cancer patients. *Cancer Sci* 2015; **106:** 1408-13. doi:10.1111/cas.12744

55. Thorat A, Huang W-H, Yeh T-S, Jan Y-Y, Hwang T-L. Pancreatic ductal adenocarcinoma presenting with acute and chronic pancreatitis as initial presentation: is prognosis better? A comparison study. *Hepatogastroenterology* 2014; **61:** 2110-6.

56. Ahmad Z, Din NU, Minhas K, Moeen S, Ahmed A. Epidemiologic data, tumor size, histologic tumor type and grade, pathologic staging and follow up in cancers of the ampullary region and head of pancreas in 311 Whipple resection specimens of pakistani patients. *Asian Pac J Cancer Prev* 2015; **16:** 7541-6.

57. Perysinakis I, Avlonitis S, Georgiadou D, Tsipras H, Margaris I. Five-year actual survival after pancreatoduodenectomy for pancreatic head cancer. *ANZ J Surg* 2015; **85:** 183-6. doi:10.1111/ans.12422

58. Petermann D, Demartines N, Schäfer M. Is tumour size an underestimated feature in the current TNM system for malignancies of the pancreatic head? *HPB* 2013; **15:** 872-81. doi:10.1111/hpb.12052

59. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance, and management. *Am J Surg* 1994; **168:** 295-8.

60. Seetharam P, Rodrigues GS. Postoperative pancreatic fistula: A surgeon's nightmare! An insight with a detailed literature review. *JOP J Pancreas* 2015; **16:** 115-24.

61. Suzuki Y, Fujino Y, Tanioka Y, Ajiki T, Hiraoka K, Takada M, et al. Factors influencing hepaticojejunostomy leak following pancreaticoduodenal resection; importance of anastomotic leak test. *Hepatogastroenterology* 2003; **50:** 254-7.

62. Conzo G, Gambardella C, Tartaglia E, Sciascia V, Mauriello C, Napolitano S, et al. Pancreatic fistula following pancreatoduodenectomy. Evaluation of different surgical approaches in the management of pancreatic stump. Literature review. *Int J Surg* 2015; **21(Suppl 1):** S4-9. doi:10.1016/j.ijsu.2015.04.088

63. Balachandran P, Sikora SS, Raghavendra Rao RV, Kumar A, Saxena R, Kapoor VK. Haemorrhagic complications of pancreaticoduodenectomy. *ANZ J Surg* 2004; **74:** 945-50. doi:10.1111/j.1445-1433.2004.03212.x

64. Rumstadt B, Schwab M, Korth P, Samman M, Trede M. Hemorrhage after pancreatoduodenectomy. *Ann Surg* 1998; **227:** 236-41.

research article

Outcomes of the surgical treatment for adenocarcinoma of the cardia – single institution experience

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Background. Adenocarcinomas at the cardia are biologically aggressive tumors with poor long-term survival following curative resection. For resectable adenocarcinoma of the cardia, mostly esophagus extended total gastrectomy or esophagus extended proximal gastric resection is performed; however, the surgical approach, transhiatal or transthoracic, is still under discussion. Postoperative morbidity, mortality and long-term survival were analyzed to evaluate the potential differences in clinically relevant outcomes.

Patients and methods. Of altogether 844 gastrectomies performed between January 2000 and December 2016, 166 were done for the adenocarcinoma of the gastric cardia, which we analyzed with using the Cox proportional hazards model.

Results. 136 were esophagus extended total gastrectomy and 125 esophagus extended proximal gastric resection. A D2 lymphadenectomy was performed in 88.2%, splenectomy in 47.2%, and multivisceral resections in 12.4% of patients. R0 resection rate was 95.7%. The mean proximal resection margin on the esophagus was 42.45 mm. It was less than 21 mm in 9 patients. Overall morbidity regarding Clavien-Dindo classification (> 1) was altogether 28.6%. 15.5% were noted as surgical and 21.1% as medical complications. The 30-day mortality was 2.2%. The 5-year survival for R0 resections was 33.4%. Multivisceral resection, depth of tumor infiltration, nodal stage, and curability of the resection were identified as independent prognostic factors.

Conclusions. Transhiatal approach for resection of adenocarcinoma of the cardia is a safe procedure for patients with Siewert II and III regarding the postoperative morbidity and mortality; moreover, long-term survival is comparable to transthoracic approach. The complications associated with thoracoabdominal approach can therefore be avoided with no impact on the rate of local recurrence.

Key words: proximal gastric cancer; transhiatal resection; complications; survival

Introduction

The incidence of gastric cancer sited in the proximal third and esophago-gastric junction (EGJ) was rising worldwide; however, in Europe this tendency seems to be stabilizing.[1] Adenocarcinomas of the cardia (ACC) are the most frequent type within these tumors. They are typically diagnosed at an advanced stage of disease progression.[2-5] As a result, they are difficult to treat and the patient prognosis is poor even after curative surgical resection comparing to those sited in distal two thirds of stomach. The extension of gastrectomy in the mediastinum makes the resection of ACC more demanding and burdened by higher postoperative morbidity. Consequently, the long-term survival rate after surgical resection has been reported to be lower, ranging from 16% to 40%.[6-9]

The Siewert's classification (S I–III), founded almost 20 years ago, still presents an important ba-

sis for decision-making in clinical praxis for EGJ tumors; however, its implication regarding strict decision for thoraco-abdominal or transhiatal approach for ACC SI and SII is still under discussions.[8,10] Different reports of meta-analyses reveal contradictory conclusions and randomized control studies are lacking. In the western world, presently the only clear recommendation stays for SIII tumors to be approached transhiatal, whereas in the eastern world also SII tumors are mostly resected transhiatal.[9-14] The tumor free segment of the esophagus to be achieved is 5 cm and the infiltration of the esophagus should not exceed 2 cm.[15]

Extent of organ resection and lymphadenectomy are the next issue of discussion without any clear evidence based on the randomized control studies; however, most ACC of S I and II are surgically managed by distal esophagectomy with proximal gastrectomy, while distal esophagectomy with total gastrectomy is often applied in S III tumors.[7] In clinical practice, the exact origin of EGJ tumors can sometimes be hard to define, which complicates the choice between distal esophagectomy with total gastrectomy and esophagectomy with proximal gastrectomy.[16]

Regarding the extent and region of lymphadenectomy needed for ACC, huge nation-wide Japanese study analyzing the records of 2807 patients having had R0 resection of EGJ carcinoma was able to confirm that the incidence of lymph node metastases correlates highly with T stage and site of the tumor. In stomach, predominant cancer (2 cm below EGJ) lymph node metastases in the middle and upper mediastinum were seldom detected even in T3/4 tumors (< 6% in T4), whereas in esophagus predominant tumors (2 cm above EGJ) metastases to the lymph nodes were detected more often (> 30% in T4).[17]

Randomized control studies have demonstrated the preoperative therapy with chemoradiotherapy or chemotherapy alone improves survival outcome for patients in stages more than T1 and/or more than N0 in which R0 resection was possible. Evidence suggests, but does not confirm, that radiation-containing regimens are more beneficial.[16,18-20]

The aim of the present study was to reveal perioperative morbidity and mortality as well as long-term survival in proximal gastric adenocarcinoma resected exclusively with transhiatal approach. We also searched for correlations of clinicopathological factors with morbidity, mortality and long-term survival.

Patients and methods

The medical records of 844 consecutive patients who had gastric resection for adenocarcinoma of the stomach from January 1, 2000 through December 31, 2016 at the Department of Abdominal Surgery at Surgical clinic UMC Maribor, Slovenia were retrospectively reviewed. Patients resected for gastric stump tumors and those in which entire stomach was affected were excluded from the study. 161 patients with ACC and transhiatal resected were considered for the analyses. The level of the location on the gastric cardia was determined concerning the Siewert's classification.[8,10]

Patients' preoperative physical status was expressed by the American Society of Anesthesiology score (ASA).[21]

After the diagnosis of ACC was initially confirmed by endoscopy and biopsy, computed tomography (CT) of thorax and abdomen was done to rule out dissemination of the disease and to assess the locoregional stage to gain the clinical stage as well as to judge whether the tumor would be resectable with transhiatal approach.

As all other oncological patients, they were presented to the oncological board for treatment planning. Until 2010, adjuvant radio-chemo therapy was indicated in stages pT2 and higher and/or pN+; however, since 2010, all amenable patients in stage higher than cT2 and higher and/or cN+ were submitted for neoadjuvant oncological treatment.

If there were no contraindications regarding general status, radical resection in terms distal esophagectomy with total gastrectomy or esophagectomy with proximal gastrectomy was done with strategy to provide 6–7 cm in vivo distance from the upper aspect of the tumor. The distal esophagectomy with total gastrectomy was preferred; however, in some patients with poorer general status or if the mesentery was to short, esophagectomy with proximal gastrectomy was done. A ring of hiatal part of the diaphragm was regularly excised en-block with the resected specimen. If there were no contraindications regarding general status, a D2 lymphadenectomy (stations 1, 2, 3, 4sa, 4sb, 5, 6, 7, 8a, 9, 11p, 11d) was performed including distal mediastinal lymph nodes (station 110, 111).[22] The spleen was usually preserved, unless there was macroscopic infiltration, lymph node No. 10 was clearly enlarged, or the tumor extended toward the grater curvature and was adhered to the stomach wall.[23] Additional resections of infiltrated neighbor organs were done to assure R0 resection.

TABLE 1. Clinicopathological characteristics of the patients resected for adenocarcinomas of the cardia (ACC)

Gender (n=161)	**Male**	120	74.5%	
	Female	41	25.5%	
Age *(Mean, 95% CI)* (n = 161)		64. 6 ± 10.1	Lower: 62.90	Upper: 66.31
American Society of Anesthesiology score (ASA) (n = 161)	**1**	53	32.9%	
	2	83	51.6%	
	3	25	15.5%	
Type of resection (n=161)	**Distal esophagectomy and total gastrectomy**	136	84.5%	
	Distal esophagectomy and proximal gastrectomy	25	15.5%	
Extend of lymphadenectomy (n = 161)	**D1**	19	11.8%	
	D2	142	88.2%	
Metastatic lymph nodes *(mean, 95% CI)* (n = 161)		6.11 ± 7.7	Lower: 4.91	Upper: 7.32
All harvested lymph nodes *(mean, 95% CI)* (n = 161)		23.20 ± 11.7	21.37	25.03
Splenectomy (n = 161)		76	47.2%	
Additional oncological resections		20	12.4%	
R0 resection		154	95.7%	
Proximal resection margin in mm *(mean, 95% CI)* (n = 142)		42.45 ± 20.7	Lower: 39.0	Upper: 45.80
Proximal resection margin < 20 mm (in fixed specimen + 0,9cm stapler ring) (n = 142)		9	5.6%	
Diameter of the tumor in mm *(mean, 95% CI)* (n = 161)		63.16 ± 23.1	Lower: 58.18	Upper: 68.15
Any type of oncological treatment completed		56	34.8%	

At operation, definite site of the tumor and Siewert type were determined.

Intravenous antibiotic (1.5 g cefuroxime and 0.5 g metronidazole or 0.35 g gentamycin and 0.6 g clindamycin) and subcutaneous antithrombotic (4000 IE enoxaparin or 3800 nadroparin or 5000 IE dalteparine) prophylaxis were successively used in all patients 1 hour and 12 hours prior to operation. Urine catheter and nasogastric tube were usually inserted after induction of anesthesia.

Almost all patients were admitted in the high dependency unit except if admission to the intensive care unit was indicated. Patients started to receive fluid food on the third day. To confirm and also to stimulate the peristaltic movements 50 ml of hypertonic contrast (Gastrografin) is routinely administrated on the third or fourth day after operation. Gastric tube was removed after appearance of bowel movements or the first stools.

Resected specimens were examined according to standard pathophysiologic procedure and classified according to Lauren, WHO, TNM and UICC classification as well as according to differentiation of tumor cells (gradus).[24-26] Before fixation of the specimen, the proximal tumor free distance on the specimen has been measured by the pathologists. Additional 9 mm of stapler cylinder (circular stapler 25 mm) were added to the distance measured by the pathologists.

Any complication occurring postoperatively within 90 days was considered as surgery related and noted according to Clavien-Dindo classification.[27] Additionally, surgical and medical complications were listed separately. Postoperative deaths within 30 and 90 days were considered as probable consequence of surgery and were declared as postoperative mortality (30- and 90-day mortality).

For patients surviving longer than 90 days after operation, recurrence of the disease was determined by image procedures (CT, PET CT), cytological analyses of abdominal and pleural effusions as well as by autopsy reports.

Clinical and pathological data were prospectively stored in a computerized database. Data from the follow-up were obtained by our own outpatient follow-up and by the National cancer register of Slovenia. Complete follow-up was obtained as of June 1, 2017.

We obtained informed consent from all patients and performed all procedures according to the guidelines of the Helsinki Declaration.

Clinicopathological factors involved in correlation analyses were: gender, age, ASA, type of resection, extent of lymphadenectomy, additional

oncological resections, length of the proximal tumor free segment of esophagus, (mean and group < 2.1 cm), TNM classification, Lauren classification, perineural invasion, any completed oncological treatment, perioperative morbidity and mortality as well as long term survival.

For the calculation of long-term survival, only patients who survived 90 days after operation were included.

Continuous data are expressed as mean ± standard deviation and categorical variables are given as percentages. Continuous variables were compared with Student's t-tests for parametric data and Mann-Whitney U tests for nonparametric data. Chi-square tests were used for comparisons of discrete variables. Survival analysis was performed with the Kaplan-Meier method. The differences between groups were compared with the log-rank test. All of the predictors that were significant on univariate analysis were included in the multivariate analysis (Cox regression model). P values < 0.05 were defined as the limit of significance. For statistical analysis, SPSS version 22 for Windows 7 (IBM Analytics, Armonk, NY) was used.

TABLE 2. Type of additional oncological resections (n = 161)

	n	%
Left pancreatectomy	9	5.6
Liver resection	1	0.6
Local peritonectomy	6	3.7
Segmental resection of the jejunum	1	0.6
Resection of left suprarenal gland	2	1.2
Segmental colon resection	1	0.6
Total	**20**	

TABLE 3. Pathological classifications: depth of tumor infiltration (T), lymph node metastases (N), Lauren type, perinevral (n = 161)

		n	%
T0		1	0.6
T1		20	12.4
T2		21	13.0
T3		87	54.0
T4a		22	13.7
T4b		10	6.2
N0		48	29.8
N1		21	13.0
N2		41	25.5
N3a		33	15.6
N3b		18	11.2
Lauren type	Intestinal	97	67.8
	Diffuse	26	18.2
	mixed	20	14.0
Presence of perineural invasion		82	54.2

Results

Of altogether 844 patients resected for gastric adenocarcinoma, 161 (120 males, 41 females, mean age 64.6 ± 10.9 years) had resection for adenocarcinoma of the gastric cardia.

Demographic data of all patients are given in Table 1. There were 136 distal esophagectomies with total gastrectomies and 125 distal esophagectomies with proximal gastrectomies. The former was more often done in older patients (esophagectomy with proximal gastrectomy *vs.* distal esophagectomy with total gastrectomy: 72.52 ± 8.5 *vs.* 63.15 ± 10.7 years; p < 0.0001) and in some cases for technical reasons (short mesentery of the Roux loop). Distal esophagectomy with total gastrectomy was found to correlate with higher N stages (N > 0: 73.5% *vs.* 52.0%; p = 0.03); however, there was no difference regarding T stage.

Tumors were classified regarding the Siewert classification (6 type I, 29 type II, 126 type III). In all 6 patients with S I type ACC, a distal esophagectomy with total gastrectomy was done; in S II type, 25 (86.2%) patients had distal esophagectomy with total gastrectomy and 4 (13.8%) esophagectomy with proximal gastrectomy; whereas in S III type, 105 (83.3%) patients had distal esophagectomy with total gastrectomy and 21 (16.7%) esophagectomy with proximal gastrectomy. Regarding this, there were no significant correlations.

A D2 lymphadenectomy was performed in 88.2% (Table 1). In comparison to D1 lymphadenectomy, a significantly higher number of lymph nodes was harvested in D2 lymphadenectomy (mean, 24.07 ± 11.5 *vs.* 16.31 ± 11.3; p = 0.01). It was less extensive in esophagectomy with proximal gastrectomy than in distal esophagectomy with total gastrectomy by declarative way (D2 in esophagectomy with proximal gastrectomy *vs.* D2 in distal esophagectomy with total gastrectomy: 68.0% *vs.* 91.9%; p = 0.003) as well as regarding the mean count of all harvested lymph nodes (esophagectomy with proximal gastrectomy *vs.* distal esophagectomy with total gastrectomy: 17.60 ± 10.48 *vs.* 24.18 ± 11.65; p = 0.027).

Splenectomy was part of a resection in 47.2% patients, more often significant in distal esophagecto-

TABLE 4. List of surgical **(A)** and general complications **(B)** occurring within 90 days after resection (n = 161)

A

	n	%
No complications	136	84.5
Intraabdominal abscess	6	3.7
Intraabdominal bleeding (within 48h)	4	2.5
Acute gangrenous cholecystitis	2	1.2
Leak from the esophagojejuno anastomosis	3	1.9
Enteric fistula	1	0.6
Disruption of laparotomy	1	0.6
Ileus	2	2.5
Ischemic colitis	1	0.6
Pancreatitis	4	2.5
Late rupture of pseudoaneurysm of splenic a.	1	0.6
Total complications	25	15.5

B

	n	%
No complications	127	78.9
Heard failure	9	5.5
Bronchopneumonia	11	6.8
Pneumo/ fluidothorax	3	1.9
Pulmonary embolia	2	1.2
Brain stroke	3	1.9
Febrile state of unknown origin	5	3.1
Decompensation of liver cirrhosis	1	0.6
Total complications	33	21.1

my with total gastrectomy than in esophagectomy with proximal gastrectomy (50.7% *vs.* 28.0%; p = 0.029), in higher T (T > 2 stages: 55.1% *vs*. 33.3%; p= 0.027) and N stages (N > 0 stages: 52.2% *vs*. 35.4%; p = 0.037).

To achieve an R0 resection, additional organs resections were needed in 20 patients (12.4%) (Table 2). Multivisceral resections were typically more often done in higher T (16.0% *vs*. 2.4%; p = 0.014) and N stage (15.9% *vs*. 4.2%; p = 0.029).

R0 resection rate was 95.7%. The mean proximal resection margin on the esophagus was 42.45 mm. It was less than 21 mm in 9 patients (6 in Siewert III, 3 in Siewert II, 0 in Siewert I); however, only one of those patients had R1 resection because of tumor infiltration in proximal resection margin. In remaining 8 patients, the resection was declared as R2 resections because of nonresectable liver metastases (3 patients), metastasis in the mesentery (1patient), retroperitoneal spread (1 patient) and peritoneal carcinosis (1 patient).

Pathological features regarding TNM classification, Lauren classification and perineural infiltration of the tumors are given in Table 3.

According to the Clavien-Dindo classification (> 1) in altogether 28.6% of patient's complications occurred within 90 days in the postoperative course. 15.5% were noted as surgical and 21.1% were medical complications. The list of surgical and general complications is presented in Tables 4A and 4B. In 7.5% of patients, surgical and medical complications overlapped. Off all clinicopathological characteristics, only shorter mean proximal tumor free margin correlated significantly with onset of surgical complications (34.35 mm ± 21.2 *vs:* 43.78 mm ± 9.8; p = 0.024), whereas there were no significant correlations with medical complications.

Twenty-six (16.1%) patients needed reoperation, 7 (4.3%) were treated by percutaneous or endoscopic intervention (no general anesthesia); however, the rest of 13 patients could be treated conservatively.

Four (2.2%) patients died within 30 days from operation; however, additional 8 (7.5%) patients died within 90 days from operation. Both mortalities were significantly increased in surgical (30-day mortality: 12.5% *vs*. 0.7%; p = 0.011, 90-day mortality: 29.2% *vs*. 3.6%; p < 0.0001) and medical complications (30-day mortality: 9.1% *vs*. 0.8%; p = 0.027, 90-day mortality: 18.2% *vs*. 4.7%; p = 0.018) or if surgical treatment was indicated for complications (30-day mortality: surgical treatment *vs.* intervention *vs.* conservative *vs*. no treatment = 15.4% *vs.* 0% *vs.* 7.7% *vs.* 0%; p = 0.02, 90-day mortality: surgical treatment *vs.* intervention *vs.* conservative *vs.* no treatment = 38.5% *vs*. 0% *vs.* 11.5% *vs*. 0%, p < 0.0001).

In 54 (36.2%) of 149 patients (no 90-day mortality) recurrence of the disease could be confirmed. The patterns regarding the region (supradiaphragmatic, infradiaphragmatic) and type of recurrence are given in Table 5. No clinicopathological factor (type of resection, extent of the lymphadenectomy, splenectomy, T stage, N stage, Siewert type, Lauren classification, gradus of the tumor, length of tumor free resection margin) revealed any correlation to recurrence except if additional resection was needed to assure R0 resection (p = 0.011)

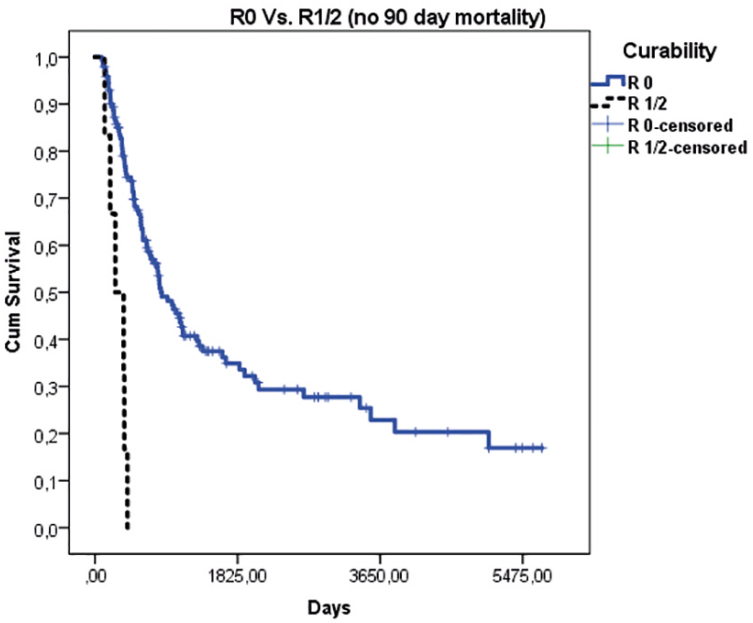

FIGURE 1. Long-term survival after resection for adenocarcinoma of the cardia in regard to curability of the resection (R0 vs. R1/2) (n = 149, median survival in days: 846 ± 118 vs. 260 ± 107; HR = 0,223, Log Rank: p < 0001).

revealing higher incidence of intraabdominal than mediastinal and systemic recurrence.

Overall 5-year survival was 33.4%. Any long-term survival could only be expected if resection was R0 (n = 149, median survival for R0 *vs.* R1/2 in days: 846 ± 118 *vs.* 260 ± 107; HR = 0.223, Log Rank: p < 0.0001) (Figure 1). Patients who survived surgical or medical complications in the postoperative course, irrelevant of its treatment modality, could expect comparable long-term survival to those without any complications (surgical complications: p = 0.317, medical complications: p = 0.986, type of treatment of complications: p = 0.888). In univariate analysis (Log Rank) for long-term survival splenectomy (yes *vs.* no), multivisceral resection (yes *vs.* no), gradus of the tumor (G 1–3), perineural invasion (yes *vs.* no), T stage (T < 3 *vs.* T >2), N stage (N0 *vs.* N > 0) and curability of the procedure (R0 *vs.* R1/2) proved as significant factors for long-term survival (Table 6).

The multivariate survival analysis (Cox regression analysis) multivisceral resection, depth of tumor infiltration (T < 3 *vs.* T > 2), nodal stage (N 0 *vs.* N > 0), and curability of the resection (R) proved as independent prognostic factors for long-term survival (Table 7).

TABLE 5. Pattern of recurrence after resection of the cardia for adenocarcinoma (n = 149, 90-day mortality excluded)

	n	%
No recurrence	**95**	**63.8**
Infradiaphragmal local recurrence	24	16.1
Supradiaphragmal local recurrence	2	1.3
Liver metastases	8	5.4
Liver metastases and infradiaphragmal recurrence	8	5.4
Lung metastases	1	0.7
Lung metastases and infradiaphragmal recurrence	1	0.7
Lung metastases and supradiaphragmal recurrence	3	2.0
Liver and lung metastases	5	3.4
Dissemination – other (bones, neck)	2	1.3
Total	149	

Discussion

The question which procedure is the best for patients with ACC has sparked a debate raging for more than a decade, but the final verdict is still a matter of debate.[5-13] To promote an easier stratification of patients for surgery, Siewert and colleges have proposed a classification of EGJ cancer patients based on the tumor location in their benchmark paper.[8] There are many who share their opinion that the tumors arising in the distal esophagus (S I) behave like esophageal tumors and are best treated with thoraco-abdominal approach, whereas S III tumors are treated like gastric tumors with the transhiatal approach.[9,10,12,16,18,19,28] However, there is much less agreement regarding the extent of resection and approach in S II tumors.[5,7,29-31] At our institution, most of the patients with S II tumors, as well as those with S III tumors, were treated transhiatal with distal esophagectomy with total gastrectomy, esophagectomy with proximal gastrectomy being done only in short mesentery or if patients were in suboptimal general condition. To determine whether this approach is safe for patients with S II and S III, we performed a retrospective study where we analyzed the results of a 16-year period of trans-abdominally operated patients with ACC.

In ACC, the resection margin has to be extended on the thoracic part of the distal esophagus in order to obtain free resection margins. There are two ways to obtain such a margin. The surgeon can choose a thoraco-abdominal approach and easily access even the carinal part of the esophagus, exposing the patients to a potentially harmful thoracotomy. The other method is the transhiatal approach to the distal part of the esophagus with en-bloc excision of a cylinder of the diaphragm

TABLE 6. Correlation for long-term survival in univariate analysis (Log Rank) for different clinicopathological characteristics. (n = 149, 90-day mortality excluded)

		Median survival (days)	HR	95% CI		p
				Lower	Upper	
Splenectomy	**No** **Yes**	1004 ± 148 616 ± 168	1.502	0.998	2.260	0.049
Multivisceral resection	**No** **Yes**	929 ± 132 324 ± 158	3.045	1.709	5.425	< 0.0001
Gradus of the tumor	**1** **2** **3**	1377 ± 504 855 ± 180 613 ± 97	1.478	1.095	1.994	0.011
Perineural invasion	**No** **yes**	1308 ± 466 660 ± 65	2.118	1.377	3.260	0.001
T stage	**T1 and 2** **T3 and 4**	3839 ±* 611 ± 79	4,147	2.297	7.488	< 0.0001
N stage	**N0** **> N0**	1915 ± 424 540 ± 70	3.037	1.810	5.096	< 0.0001
Curability of the procedure (R)	**R 0** **R 1/2**	846 ± 118 260 ± 107	2.110	1.359	3.276	< 0.0001

* less than 50% of patients censored

which obviates the need to perform a thoracotomy; however, the access to the more proximal part of the esophagus is obscured due to technical limitations of the technique.[6-9]

A D2 lymphadenectomy comprising dissection of perigastric, suprapancreatic and the lower mediastinal lymph nodes was routinely done along with EETG (in 88%).[22] Spleen was usually preserved, unless there was macroscopic adherence of the tumor to the spleen, suspicious lymph nodes in station 10, the tumor extended toward the greater curvature and penetrated the muscularis layer of the stomach, or if the spleen was unintentionally injured at the resection. Many studies supported this approach for tumors types S II and S III.[17,23,32-34] Yamashita analyzed the pattern of lymph nodes involvement in patients of tumors extending in the region of the EGJ. They found that in gastric predominant EGJ tumors suprapancreatic lymph nodes had the highest metastases rate. The incidence of upper and middle mediastinal lymph node metastases were negligible and their dissection offered no survival benefit.[17] Furthermore, an interesting fact was that even in esophagus predominating EGJ tumors, the rate of upper and middle mediastinal tumors was less relevant in adenocarcinoma than in squamous cell carcinoma of the esophagus predominating EGJ tumors. Similar results were obtained by other authors.[32-34] Moreover, the most prevalent site of lymph node recurrence was abdominal para-aortic.[17] This fact matches with the results of our study regarding the site of the recurrence. The most frequent metastatic lymph nodes are the proximal gastric lymph nodes, nodes at the esophageal hiatus, lower mediastinum and suprapancreatic lymph nodes.[33] Regarding this results and regarding the patterns of recurrence, many authors share the opinion that an extensive mediastinal lymph node dissection is unnecessary.[17,32-34] It therefore seems reasonable that the mediastinal lymphadenectomy *via* thoraco-abdominal approach is not mandatory.

The concern about the sufficient proximal resection margin is reason why some institutions recommend a thoraco-abdominal approach. Some authors argue that a sufficient proximal margin can only be obtained with a thoracic approach.[32] The R0 resection rate at our institution where the transhiatal approach with excision of the hiatal part of the diaphragm is practiced for S II and S III patients was obtained in 95.7%. This rate compares favorably to other papers that report a R0 rate from 80% to 95%.[35-38] With the transhiatal approach, we obtained a mean proximal resection margin of 42.4 mm, which is similar to margins obtained by other authors with the thoraco-abdominal approach.[32,35-38]

TABLE 7. Multivariate analysis (Cox regression) for long-term survival after resection for adenocarcinoma of the cardia (n = 149, 90-day mortality excluded)

	B	HR	95,0% CI		p
			Lower	Upper	
Multivisceral resection	-0.716	0.489	0.273	0.876	0.016
T < 3 *vs.* **T > 2**	-1.065	0.345	0.181	0.655	0.001
N 0 *vs.* **N > 0**	-0.620	0.538	0.307	0.942	0.030
Curability of resection (R)	0.747	2.110	1.359	3.276	0.001

Duan reported a 38 mm margin with right thoraco-abdominal approach in their patients' population, which corresponds to the results obtained in our study.[32] Studies have demonstrated that in patients with type S II and S III only in a dismal number of patients the tumor invaded more than 25 mm beyond the proximal margin.[37,38] A proximal margin of 38 mm in these patients was associated with a survival benefit.[16] Hence most authors agree that a proximal margin of more than 2 cm is sufficient to obtain an R0 resection and prevent an esophageal recurrence in SII and SIII patients.[16,37,38] The resection margin obtained on our institution was longer than suggested by these authors, but what is even more, it is comparable to reports from papers evaluating the thoraco-abdominal approach.[32]

Since it is evident that with the thoraco-abdominal approach free proximal margins and adequate lymphadenectomy can be obtained, it is only feasible to choose a procedure that offers a potentially less invasive and less morbid approach to patients with SII and SIII tumors. Although we did not perform a comparison of transhiatal and thoraco-abdominal approach, we did, however, analyzed the perioperative morbidity and mortality of the transhiatal extended total gastrectomy in order to see whether the transhiatal approach would have a lover complication rate than reported by others for the thoraco-abdominal approach. The 90-day intrahospital morbidity was 28.6% in our patients' cohort. The transhiatal approach has been shown by many authors to carry significantly less morbidity compared to thoraco-abdominal approach.[12,37,39] The complication rates for the transhiatal approach were reported to be from 25% to 28% and were similar to those in our institution.[12,13,36,37,39] In a meta-analysis done by Wei *et al.*, a significantly higher morbidity of the thoraco-abdominal approach has been found and was attributed to pulmonary complications.[12] The rate of pulmonary complications was only 9.2% in our cohort compared to 28.2% reported by Blank *et al*.[13] However, the 30-days mortality was reported to be similar no matter what approach was chosen for EGJ cancer patients.[13,36,37] The reported mortality rates from 1.1 to 3.8% compare favorably to our hospital where the 30-day mortality was 2.2%.[12,13,36,37] We also found a significant association between general and surgical complications and 30-day mortality. This correlation between complications and 30-day mortality is an important fact to consider when planning an operation for patients with S II and S III tumors; surgeons should offer their patients a curative approach with a smaller probability of complications.

The overall 5-year survivals for S II and S III patients were reported to be from 16% to 58%.[6-9,13,33,35,39] Although the Eastern authors consistently reported 5-year survival rates above 40%, most of Western authors report survivals over 30%.[13,33] Many studies also confirmed that the overall 5-year survival did not depend on the surgical approach as long as R0 resection could be obtained.[13,33,35,37,39] The patients in our cohort had a 5-year OS of 33.4%. The independent predictors for long-term survival were T and N stage, multivisceral resection and microscopic free surgical margins. Although, it is difficult to compare our 5-year overall survival to other results published, since the stages, general condition of patients, perioperative treatment and tumor location differ between studies; however, these results show that the type of approach does not influence the long-term survival.[37] The proximal extension of the resection margin did therefore not improve the survival of S II and S III patients. Moreover, the rate of local recurrences in the thoracic cavity seems not to be affected by the type of approach. In most of our patients, an infradiaphragmatic recurrence in the form of peritoneal carcinosis (16.1%) followed by hematological dissemination was noted. Only a minor portion of parents had a recurrence in the thoracic cavity (3.3% of patients). No correlation was found between clinicopathological characteristics and the type of recurrence, which supports the statement that the type of resection does not influence on the survival as long as an R0 resection is performed.

It is difficult to draw definitive conclusions from our study since the best way to determine the superiority of an approach would be a prospective randomized controlled trial. Our study is biased by the retrospective nature of the study design. Moreover, patients from different treating periods were included. During that time, the perioperative neoadjuvant treatment has changed and became more efficient, and this might have had an impact on overall survival. Also, the development of interventional radiological techniques has enabled us to resolve many complications non-operatively that would have otherwise been treated with surgical procedures and increased the perioperative morbidity. And finally, because of the long study period, we did not take into account the impact of modern minimally invasive techniques that have emerged recently.

This study supports the conclusion that the transhiatal approach is a safe procedure for S II and S III patients and that the morbidity and mortality associated with the surgery are low. The compli-

cations associated with transthoracic approach can therefore be altogether avoided with no impact on the rate of local recurrence. Our results confirm that the resection of ACC with transhiatal approach provides comparable proximal resection margins to thoraco-abdominal approach. The number of thoracic recurrences is negligible with the transhiatal approach and the long-term survival is comparable to other institutions irrelevant on approach. Based on these results, we feel that the transhiatal EETG, or in selected patients EEPG, is the procedure of choice for patients with ACC of type S II and S III.

References

1. Dubecz A, Solymosi N, Stadlhuber RJ, Schweigert M, Stein HJ, Peters JH. Does the incidence of adenocarcinoma of the esophagus and gastric cardia continue to rise in the twenty-first century?-a SEER database analysis. *J Gastrointest Surg* 2013; Epub 2013/11/16. doi:10.1007/s11605-013-2345-8
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; **97:** 142-6. doi:10.1093/jnci/dji024
3. Kusano C, Gotoda T, Khor CJ, Katai H, Kato H, Taniguchi H, et al. Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center in Japan. *J Gastroenterol Hepatol* 2008; **23:** 1662-5. doi:10.1111/j.1440-1746.2008.05572.x
4. Blaser MJ, Saito D. Trends in reported adenocarcinomas of the oesophagus and gastric cardia in Japan. *Eur J Gastroenterol Hepatol* 2002; **14:** 107-13.
5. Yamashita K, Sakuramoto S, Nemoto M, Shibata T, Mieno H, Katada N, et al. Trend in gastric cancer: 35 years of surgical experience in Japan. *World J Gastroenterol* 2011; **17:** 3390-7. doi:10.3748/wjg.v17.i29.3390
6. Mariette C, Castel B, Toursel H, Fabre S, Balon JM, Triboulet JP. Surgical management of and long-term survival after adenocarcinoma of the cardia. *Br J Surg* 2002; **89:** 1156-63. doi:10.1046/j.1365-2168.2002.02185.x
7. Haverkamp L, Ruurda JP, van Leeuwen MS, Siersema PD, van Hillegersberg R. Systematic review of the surgical strategies of adenocarcinomas of the gastroesophageal junction. *Surg Oncol* 2014; **23:** 222-8. doi:10.1016/j.suronc.2014.10.004
8. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1998; **85:** 1457-9. doi:10.1046/j.1365-2168.1998.00940.x
9. Kauppila JH, Lagergren J. The surgical management of esophago-gastric junctional cancer. *Surg Oncol* 2016; **25:** 394-400. doi:10.1016/j.suronc.2016.09.004
10. Kulig P, Sierzega M, Pach R, Kolodziejczyk P, Kulig J, Group PGCS. Differences in prognosis of Siewert II and III oesophagogastric junction cancers are determined by the baseline tumour staging but not its anatomical location. *Eur J Surg Oncol* 2016; **42:** 1215-21. doi:10.1016/j.ejso.2016.04.061
11. Mine S, Sano T, Hiki N, Yamada K, Kosuga T, Nunobe S, et al. Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the oesophagogastric junction. *Br J Surg* 2013; **100:** 1050-4. doi:10.1002/bjs.9170
12. Wei MT, Zhang YC, Deng XB, Yang TH, He YZ, Wang ZQ. Transthoracic vs transhiatal surgery for cancer of the esophagogastric junction: a meta-analysis. *World J Gastroenterol* 2014; **20:** 10183-92. doi:10.3748/wjg.v20.i29.10183
13. Blank S, Schmidt T, Heger P, Strowitzki MJ, Sisic L, Heger U, et al. Surgical strategies in true adenocarcinoma of the esophagogastric junction (AEG II): thoracoabdominal or abdominal approach? *Gastric Cancer* 2017. Epub 2017/07/06. doi:10.1007/s10120-017-0746-1
14. Uzunoglu FG, Reeh M, Kutup A, Izbicki JR. Surgery of esophageal cancer. Langenbecks *Arch Surg* 2013; **398:** 189-93. doi:10.1007/s00423-013-1052-y
15. Al-Haddad S, Chang AC, De Hertogh G, Grin A, Langer R, Sagaert X, et al. Adenocarcinoma at the gastroesophageal junction. *Ann N Y Acad Sci* 2014; **1325:** 211-25. doi:10.1111/nyas.12535
16. Di Leo A, Zanoni A. Siewert III adenocarcinoma: treatment update. *Updates Surg* 2017. Epub 2017/03/16. doi:10.1007/s13304-017-0429-9
17. Yamashita H, Seto Y, Sano T, Makuuchi H, Ando N, Sasako M. Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. *Gastric Cancer* 2017; **20(Suppl 1):** 69-83. doi:10.1007/s10120-016-0663-8
18. Kleinberg L, Brock M, Gibson M. Management of locally advanced adenocarcinoma of the esophagus and gastroesophageal junction: Finally a consensus. *Curr Treat Options Oncol* 2015; **16:** 35. doi:10.1007/s11864-015-0352-6
19. Cohen DJ, Leichman L. Controversies in the treatment of local and locally advanced gastric and esophageal cancers. *J Clin Oncol* 2015; **33:** 1754-9. doi:10.1200/jco.2014.59.7765
20. Roder JD, Bottcher K, Busch R, Wittekind C, Hermanek P, Siewert JR. Classification of regional lymph node metastasis from gastric carcinoma. German Gastric Cancer Study Group. *Cancer* 1998; **82:** 621-31.
21. Doyle DJ, Garmon E. American Society of Anesthesiologists Classification (ASA Class). StatPearls. Treasure Island (FL): StatPearls PublishingStatPearls Publishing LLC.; 2017.
22. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer* 1998; **1:** 10-24. doi:10.1007/s101209800016
23. Goto H, Tokunaga M, Sugisawa N, Tanizawa Y, Bando E, Kawamura T, et al. Value of splenectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction. *Gastric Cancer* 2013; **16:** 590-5. doi:10.1007/s10120-012-0214-x
24. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt to a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64:** 31-49.
25. *TNM classification of malignant tumours*. Eighth edition. Brierley J, Gospodarowicz MK, Wittekind C, editors. Chichester, West Sussex: John Wiley & Sons, Inc; 2017.
26. Wittekind C. [Patology of gastric carcinoma: typing, grading and staging]. [German]. *Chir Gastroenterol* 1999; **15:** 216-22. doi:10.1159/000012560.
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205-13. doi:org/10.1097/01.sla.0000133083.54934.ae.
28. Fox MP, van Berkel V. Management of gastroesophageal junction tumors. *Surg Clin North Am* 2012; **92:** 1199-212. doi:10.1016/j.suc.2012.07.011
29. Mullen JT, Kwak EL, Hong TS. What's the best way to treat GE junction tumors? Approach like gastric cancer. *Ann Surg Oncol* 2016; **23:** 3780-5. doi:10.1245/s10434-016-5426-6
30. Rizk N. Gastroesophageal junction tumors. *Ann Surg Oncol* 2016; **23:** 3798-800. doi:10.1245/s10434-016-5427-5
31. Giacopuzzi S, Bencivenga M, Weindelmayer J, Verlato G, de Manzoni G. Western strategy for EGJ carcinoma. *Gastric Cancer* 2017; **20(Suppl 1):** 60-8. doi:10.1007/s10120-016-0685-2
32. Duan F, Cui S, Song C, Zhao X, Dai L, Shen Y. Esophageal squamous cell carcinoma and gastric cardia adenocarcinoma shared susceptibility locus in C20orf54: Evidence from published studies. *Sci Rep* 2015; **5:** 11961. doi:10.1038/srep11961
33. Hosoda K, Yamashita K, Moriya H, Mieno H, Watanabe M. Optimal treatment for Siewert type II and III adenocarcinoma of the esophagogastric junction: a retrospective cohort study with long-term follow-up. *World J Gastroenterol* 2017; **23:** 2723-30. doi:10.3748/wjg.v23.i15.2723
34. Lee IS, Ahn JY, Yook JH, Kim BS. Mediastinal lymph node dissection and distal esophagectomy is not essential in early esophagogastric junction adenocarcinoma. *World J Surg Oncol* 2017; **15:** 28. doi:10.1186/s12957-016-1088-x
35. Lochowski M, Lochowska B, Kozak J. Transthoracic versus transhiatal esophagectomy - influence on patient survival. *Prz Gastroenterol* 2017; **12:** 118-21. doi:10.5114/pg.2016.64609

36. Fontana MG, La Pinta M, Moneghini D, Villanacci V, Donato F, Rindi G, et al. Prognostic value of Goseki histological classification in adenocarcinoma of the cardia. *Br J Cancer* 2003; **88:** 401-5. doi:10.1038/sj.bjc.6600663

37. Kurokawa Y, Sasako M, Sano T, Yoshikawa T, Iwasaki Y, Nashimoto A, et al. Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. *Br J Surg* 2015; **102:** 341-8. doi:10.1002/bjs.9764

38. Mine S, Watanabe M. A commentary on "Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia". *Transl Gastroenterol Hepatol* 2016; **1:** 12. doi:10.21037/tgh.2016.03.08

39. Kim KT, Jeong O, Jung MR, Ryu SY, Park YK. Outcomes of abdominal total gastrectomy for type II and III gastroesophageal junction tumors: Single center's experience in Korea. *J Gastric Cancer* 2012; **12:** 36-42. doi:10.5230/jgc.2012.12.1.36

research article

The impact of outpatient clinical care on the survival and hospitalisation rate in patients with alcoholic liver cirrhosis

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Background. In the study, we aimed to determine whether regular outpatient controls in patients with alcoholic liver cirrhosis have an impact on their survival and hospitalisation rates.

Patients and methods. We included patients with liver cirrhosis and regular outpatient controls as a prospective study group and patients with liver cirrhosis who were admitted to hospital only in cases of complications as a retrospective control group. The study was conducted between 2006 and 2011.

Results. We included 98 patients in the study group and 101 patients in the control group. There were more outpatient controls in the study group than in the control group (5.54 examinations *vs.* 2.27 examinations, p = 0.000). Patients in the study group had 25 fewer hospitalisations (10.2%; p = 0.612). The median survival rate was 4.6 years in the study group and 2.9 years in the control group (p = 0.021). Patients with Child A classification had an average survival of one year longer in the study group (p = 0.035). No significant difference was found for Child B patients. Patients with Child C classification had longer survival by 1.6 years in the study group (p = 0.006). Alcohol consumption was lower in the study group than in the control group (p = 0.018).

Conclusions. We confirmed that patients with regular outpatient controls had lower alcohol consumption, a lower hospitalisation rate and significantly prolonged survival time. We confirmed the necessity for the establishment of regular outpatient controls in patients with alcoholic liver cirrhosis.

Key words: liver cirrhosis; survival rate; regular outpatient controls; Child-Pugh classification

Introduction

Liver cirrhosis is characterised by the destruction of liver structures and the formation of regenerative nodules. It is a morphologically uniform response to chronic and recurring liver damage, and it represents the final, irreversible stage of various chronic liver diseases. Patients with liver cirrhosis are prone to many complications, have significantly shorter survival times and require frequent medical care and hospitalisations.[1] Excess alcohol consumption is the most frequent cause of cirrhosis in Europe.[2]

Liver failure is most commonly caused by chronic alcohol consumption (60–70%) and can manifest as fatty liver disease, alcoholic hepatitis and alcoholic liver cirrhosis. Liver cirrhosis is responsible for 32 deaths per 100,000 population each year and is also the 8th leading cause of death in Slovenia.[3,4,5] Liver cirrhosis is an important public health concern and a significant cause of morbidity and mortality worldwide.[6]

Not all patients who consume large amounts of alcohol will develop liver cirrhosis; 80% of them develop liver steatosis, 10% to 35% develop alcoholic hepatitis and 10% develop liver cirrhosis.[7]

Liver cirrhosis can be diagnosed in different ways. Patients may seek medical help because of symptoms; diagnosis may be made incidentally through a routine blood test or check-up, and

sometimes a diagnosis is made randomly during surgery, life-threatening conditions (such as bleeding varices, spontaneous bacterial peritonitis, portosystemic encephalopathy), or at autopsy.

Patients and methods

The study included a group of patients with alcoholic liver cirrhosis and regular outpatient controls (study group) and a group of patients with alcoholic liver cirrhosis who were admitted to hospital only in cases of complications (control group). We observed both groups between 2006 and 2011.

We included 99 patients in the study group and 101 patients in the control group. All consecutive patients with liver cirrhosis hospitalised in the Department of Gastroenterology of Murska Sobota General Hospital in 2006 were included in the study group. After discharge, patients were systematically monitored 3 to 4 times during the first year and then every 6 to 12 months for up to 5 years.

The National Medical Ethics Committee approved the survey protocol (85/01/09). All patients gave their informed consent prior to participation. Patient records were anonymized and de-identified prior to analysis. The study was conducted in accordance with the requirements of the Declaration of Helsinki and agreed with all the provisions set forth in the International Conference of Harmonization and Good Clinical Practice Guidelines.

The control group encompassed patients, who were admitted to hospital in 2006 and treated in other departments of the hospital. After discharge, they were not under regular outpatient control. Data for the control group were collected retrospectively from the hospital informatics programme Birpis.

Patients in both groups were divided into classes according to the Child-Pugh classification. Based on this classification, we attempted to determine the frequency of hospitalisation and patients' survival. The diagnosis of alcoholic liver cirrhosis was based on data of alcohol consumption, heteroanamnesis, with Alcohol Use Disorders Identification Test (AUDIT) and CAGE questionnaires, laboratory tests, abdominal ultrasound and gastroscopy. Liver biopsy was not performed. We excluded the following other causes of liver cirrhosis: autoimmune hepatitis, primary biliary cholangitis, metabolic hepatitis (α-1-antitrypsin deficiency, hemochromatosis, Wilson's disease) and viral hepatitis infection.

Variables monitored in both patient groups were as follows: alcohol consumption, degree of hepatic failure, comorbidities, laboratory findings, pharmacological treatment, number of hospitalisations, survival according to the Child-Pugh classification and estimated median age at death according to the Child-Pugh classification.

Patients in the study group were educated about the importance of the abandonment of drinking alcohol, diet and adjusting diuretic therapy (monitoring of liquid input, diuresis and weight). We offered all of them alcoholism treatment. We asked family members to help them in the recovery process. We expected better cooperation, less alcohol consumption and better compliance in taking drugs in the study group. The goal of regular outpatient examinations was the timely prevention of complications of liver cirrhosis and the proper treatment of patients. Patients were educated, therapy was customised to each patient and additional diagnostic tests were performed if they were needed.

Statistical analysis

Numerical variables were presented as average values ± standard deviations (SDs). Categorical variables were presented as absolute numbers and percentages. Survival of patients was monitored until December 31, 2011.

We used chi-square statistics to assess the relationship between variables and the t-test to test the hypothesis of equality of arithmetic means of the variables in both groups. Levene's test was used to assess the equality of a variables calculated in both groups. Survival probability was calculated with the Kaplan-Meier method and compared with the Breslow test and log-rank test. The time variable was set as the time between the date of hospitalisation and the event (death) or until December 31, 2011. The results were presented as risk ratios (RRs) and corresponding 95% confidence intervals (CIs). Statistical analysis was performed using IBM SPSS Statistics 20.0. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristic

One hundred and ninety-nine patients were included in the study, including 98 patients in the study group and 101 patients in the control group. Most of the patients were male (80.6% in the study

group and 79.2% in the control group). The average age of participants in the study group and control group was 58.2 and 59.1 years, respectively (Table 1).

In the study group, 66.3% of patients were unemployed, 24.5% of patients were retired and only 9.2% of patients were employed.

All patients consumed alcohol. Males had higher rates than females for all measures of drinking in the past month: any alcohol use (57.5% *vs.* 45%), binge drinking (30.8% *vs*. 15.1%), and heavy alcohol use (10.5% *vs*. 3.3%), and males were twice as likely as females to have met the criteria for alcohol dependence or abuse in the past year (10.5% *vs*. 5.1%).

Degree of hepatic impairment: comparison of both groups

According to the Child-Pugh classification, there were significant differences between groups (chi-square = 7.975, sp = 1, p = 0.019). Patients in the study group were classified into a higher Child-Pugh classification class (Child C 44.9% of patients in study group *vs*. 26.7% of patients in control group; p = 0.000; Table 1).

We monitored the presence of oesophageal varices, portal gastropathy, ascites, peripheral oedema, gastrointestinal bleeding and other possible aetiologic factors for liver cirrhosis in both groups.

There were no differences in the degree of oesophageal varices between the groups.

More patients in the study group had portal gastropathy (32.7% *vs*. 22.8%; p = 0.106), ascites (62.2% *vs*. 54%; p = 0.339) and peripheral oedema (54.6% *vs*. 33.7%; p = 0.100).

Concomitant diseases and comparison in both groups

We compared the most common comorbidities, hepatitis and gastrointestinal bleeding in patients of both groups. Statistically significant differences between the groups were not found (Table 2). Most of the patients had diabetes, hypertension and renal failure. More patients were on insulin in the control group than in the study group (11.9% *vs*. 6.1%; p = 0.198).

We compared cardiovascular diseases (stroke, heart failure, arterial hypertension, atrial fibrillation), kidney diseases and diabetes in both groups (Table 3).

TABLE 1. Demographic characteristics of patients with liver cirrhosis in the study group and the control group

		Study group		Control group		Both groups	
		Number	%	Number	%	Number	%
Gender	Male	79	80.6%	80	79.2%	159	79.9%
	Female	19	19.4%	21	20.8%	40	20.1%
	Total	98		101		199	
Age (mean)		58.2		59.1		58.6	
Standard deviation		10.8		11.3		11.1	

TABLE 2. Child-Pugh stage and complications of liver cirrhosis in both groups

		Study group		Control group		Both groups	
		Number	%	Number	%	Number	%
Child-Pugh classification	A	33	33.7%	51	50.5%	84	42.2%
	B	21	21.4%	23	22.8%	44	22.1%
	C	44	44.9%	27	26.7%	71	35.7%
	Total	98		101		199	
Varices	Without	21	21.4%	18	17.8%	39	19.6%
	I. Grade	27	27.6%	14	13.9%	41	20.6%
	II. Grade	20	20.4%	17	16.8%	37	18.6%
	III. Grade	25	25.5%	22	21.8%	47	23.6%
	IV. Grade	2	2.0%	3	3.0%	5	2.5%
	Unknown	3	3.1%	27	26.7%	30	15.1%
	Total	98		101		199	
Portal gastropathy	Yes	63	64.3%	39	38.6%	102	51.3%
	No	32	32.7%	23	22.8%	55	27.6%
	Unknown	3	3.1%	39	38.6%	42	21.1%
	Total	98		101		199	
Ascites	Yes	37	37.8%	46	46.0%	83	41.9%
	No	61	62.2%	54	54.0%	115	58.1%
	Total	98		100		198	
Peripheral oedema	No	45	46.4%	67	66.3%	112	56.6%
	Yes	52	53.6%	34	33.7%	86	43.4%
	Total	97		101		198	

Hospitalisation and outpatient examination rate in both groups

We compared the number of hospitalisations and outpatient examinations in both groups over 5 years. The hospitalisation rate caused by complications of liver cirrhosis (worsening of liver cirrhosis, worsening of renal function, alcoholic hepatitis, infection , gastrointestinal bleeding, hepatic encephalopathy) were measured in both groups.

TABLE 3. Concomitant diseases in both groups

		Study group		Control group		Total		p
		Nb.	%	Nb.	%	Nb.	%	
Stroke	Yes	96	98.0%	99	98.0%	195	98.0%	
	No	2	2.0%	2	2.0%	4	2.0%	0.84
	Total	98		101		199		
Atrial fibrillation	No	86	87.8%	90	89.1%	176	88.4%	
	Yes	12	12.2%	11	10.9%	23	11.6%	0.78
	Total	98		101		199		
Arterial hypertension	No	70	71.4%	86	85.1%	156	78.4%	
	Yes	28	28.6%	15	14.9%	43	21.6%	0.21
	Total	98		101		199		
Heart failure	No	87	88.8%	88	87.1%	175	87.9%	
	Yes	11	11.2%	13	12.9%	24	12.1%	0.17
	Total	98		101		199		
Diabetes	No	77	78.6%	78	77.2%	155	77.9%	
	Yes	21	21.4%	23	22.8%	44	22.1%	0.77
	Total	98		101		199		
Renal failure	No	74	75.5%	73	72.3%	147	73.9%	
	Yes	24	24.5%	28	27.7%	52	26.1%	0.34
	Total	98		101		199		

TABLE 4. The number of hospitalizations and outpatient examinations in study and control groups over 5 years

	Study group	Control group	p value
Total number of outpatient examinations over 5 years	543	229	0.00
Average number of outpatient examinations in 5 years (per patient)	5.54	2.27	
Total number of hospitalizations over 5 years	184	209	0.612
Average number of hospitalizations in 5 years (per patient)	1.88	2.07	

More outpatient controls were used in the study group than in the control group (5.54 examinations *vs*. 2.27 examinations, p = 0.000).

There were 10.2% of patients in the study group and 12.9% of patients in the control group admitted to hospital due to gastrointestinal bleeding (p = 0.083).

Over 5 years there were fewer hospitalisations in the study group than in the control group (1.88 hospitalisations *vs*. 2.07). Patients in the study group had 25 fewer hospitalisations (10.2%, p = 0.612) and 214 more outpatient examinations (23.7%, p = 0.000) than patients in the control group (Table 4).

Pharmacological treatment

The average number of medications that were taken was 2.7 ± 1.5 in the study group and 2.4 ± 1.4 in the control group. In the study group, furosemide was prescribed at a statistically higher percentage (59.2% *vs*. 41.6%, p = 0.047) and in higher doses than in the control group.

Spironolactone was prescribed at a higher percentage in the study group (55.1% *vs*. 46.5%; p = 0.279). More patients were treated with beta-blockers in the study group, but the difference was not statistically significant (p = 0.279). There were no other differences between uses of medications in both groups. We observed that laxatives were prescribed in less than one third of all patients in both groups.

Patient's survival in the study and control groups

Cumulative survival is a probability of survival. At the beginning of the hospitalisation (point 0), the probability of survival for all patients was the same (equals 1). Patients in the control group had decreased survival rates compared to the study group patients in the first year after hospitalisation. The median survival rate was 4.66 years in the study group and 2.9 years in the control group (p = 0.021).

We compared how many patients died at home and how many died in the hospital. In the study group, 39 (78%) patients died in the hospital and 49 (75.4%) patients in the control group died in the hospital (p = 0.001). All other patients died at home. We have analysed the causes of death of all 88 patients (in both groups) who died in the hospital. Data were collected from the hospital information system Birpis.

All patients died because of a complication or multiple complications of liver cirrhosis (hepatic encephalopathy, spontaneous bacterial peritonitis, other infections, gastrointestinal bleeding, hepatorenal syndrome, alcoholic hepatitis, heart failure). Patients who died in accidents were excluded from the study (Table 5).

We compared the distribution of patients' survival in both groups with the log-rank and Breslow tests. Survival probability at each time point during the observation interval was higher for the study group, irrespective of the number of cases that had been exposed to the risk (p = 0.021).

In general, the likelihood of survival depends on the degree of liver failure, which is defined by the Child-Pugh classification. Patients in the Child A stage had an average survival of one year longer (p = 0.035) in the study group compared to patients in the control group. Patients with Child B stage in the study group had 0.6 years of longer survival than patients in the control group, but the difference between groups was not statistically significant. Patients with Child C classification had longer survival by 1.6 years in the study group than patients in the control group (p = 0.006). Irrespective of the degree of severity of the disease (Child-Pugh classification), patients in the study group had a longer survival in the observed period (Table 6).

We monitored the average age at the time of death and found no difference between both groups. The average age at death of all patients independent of the Child-Pugh classification was 62.3 years.

Patients in both groups with Child A classification had on average 4.6 years longer survival than patients with Child C classification (p = 0.06). We tested the distribution of age at death in all Child-Pugh stages in both groups using the Breslow test. The difference between both groups was not statistically significant.

Alcohol consumption-comparison of both groups

We monitored the consumption of alcohol in both groups (Table 7). Data were collected with anamnesis, heteroanamnesis and from the hospital information system Birpis. We also monitored laboratory tests. The data were less reliable in patients who lived alone (39.8%). Consumption of alcohol was lower in the study group than in the control group. The difference between the groups was statistically significant (p = 0.018).

We collected data about alcohol addiction treatment at Ormož Psychiatric Hospital for all patients. In the study group seventeen patients were treated, and in the control group 15 patients were treated at the psychiatric hospital (p = 0.158).

TABLE 5. Comparison of all patients who died in the hospital because of a complication or multiple complications of liver cirrhosis (one patient may have more than one complication)

	Study group (n)	Control group (n)	p
Hepatic encephalopathy	12	13	0.320
Spontaneous bacterial peritonitis	5	5	
Hepatorenal syndrome	12	14	0.158
Bleeding	4	4	
Infections	14	13	0.320
Heart failure	3	8	0.025
Alcoholic hepatitis	4	6	0.158
Total number of patient deaths	39	49	

TABLE 6. Five-year survival of patients according to the Child-Pugh classification

CHILD	Group	All	Number of deaths	Survivors		p value
				Number	Percent	
A	Study	32	13	19	59.4%	0.035
	Control	51	29	22	43.1%	
	Both	83	42	41	49.4%	
B	Study	21	11	10	47.6%	0.083
	Control	23	14	9	39.1%	
	Both	44	25	19	43.2%	
C	Study	43	25	18	41.9%	0.006
	Control	27	22	5	18.5%	
	Both	70	47	23	32.9%	
	Total	**197**	**114**	**83**	**42.1%**	

TABLE 7. Alcohol consumption and treatment in the Ormož Psychiatric Hospital for both groups

	Study group %	Control group %	p value
No alcohol consumption	56.12	35.64	0.000
Alcohol consumption	43.88	64.36	0.018
Ormož Psychiatry	14.85	15.30	0.158

Discussion

Studies have shown a relationship between diabetes and the occurrence of liver cirrhosis. Sixty percent of patients with liver cirrhosis have intolerance to glucose, and approximately 20% of patients have diabetes.[8,9] In our study, 21.4% of patients in the study group and 22.8% of patients in the control group had diabetes. This result is comparable with the results of other studies. Diabetes most often occurs due to a decreased secretion of insulin.[10]

Arterial hypertension is rare in patients with hepatic impairment. Studies have shown that arterial hypertension is present in 3–7% of the patients. Blood pressure often reduces to normal upon the occurrence of liver cirrhosis. [11,12,13,14,15] Arterial hy-

pertension was more common in both groups as indicated in the literature. Heart failure was present in 12.1% of patients.

Renal failure represents a frequent and serious complication of advanced liver cirrhosis.[16] The prevalence of hepatorenal syndrome in patients affected by liver cirrhosis with ascites is equal to 18% after 1 year, increasing to 39% at 5 years. Hepatorenal syndrome occurs almost exclusively in patients with ascites.[17]

At the time of death, 12 patients (30.8%) in the study group and 14 patients (29.6%) in the control group had hepatorenal syndrome (NS). Hepatorenal syndrome was common and was a poor prognostic indicator in both groups.

We compared the number of hospitalisations and outpatient examinations of both groups. Patients in the study group had 25 fewer hospitalisations (10.2%) and 214 outpatient examinations more (237%) than patients in the control group. The difference in outpatient examinations was statistically significantly higher in the study group ($p = 0.000$). The difference in hospitalisation was lower in the study group (10.2%), but did not reach statistical significance ($p = 0.612$). Our study confirmed that patients who had undergone an increased number of outpatient examinations had fewer complications of liver cirrhosis.

We monitored pharmacological treatment and compared both groups. More medications were prescribed in the study group than in the control group. The diuretic of choice in liver cirrhosis is spironolactone. A combination treatment with furosemide might be necessary in patients who do not respond to spironolactone alone.[18] If necessary, the spironolactone dose is increased stepwise up to 400 mg/d and the furosemide dose is increased up to 160 mg/d.[19,20,21] In the study group, furosemide was prescribed at a statistically higher percentage and in higher doses than in the control group. Spironolactone was prescribed at a higher percentage in the study group, but the difference was not statistically significant. Furosemide and spironolactone were prescribed in combination in the majority of patients. Higher doses of diuretic therapy in the study group can be explained by the higher Child-Pugh classification class. All patients in the study group were hospitalised at the Department of Gastroenterology, where higher doses of diuretic therapy were prescribed.

At each time point during the observation interval, the probability of survival was higher in the study group than in the control group. Patients in the study group had longer expected survival; however, they were classified into a higher Child-Pugh classification class and had more severe hepatic failure.

We achieved decreased alcohol consumption in the study group, which may be one reason for improvement in the survival rate.

Some trials have shown that lower alcohol consumption or abstinence may improve survival in patients with alcoholic liver disease. Heavy drinkers and abstainers have higher mortality rates than moderate drinkers.[22] Thirty-four studies on men and women shows that higher doses of alcohol were associated with increased mortality.[23] While there is no question regarding the benefit of abstinence, motivating patients to follow this treatment regimen, monitoring their compliance and preventing relapse remain major obstacles to the treatment of alcoholic liver disease. Pharmacotherapy in combination with psychosocial interventions can aid patients in maintaining abstinence from alcohol.[23] The same conclusions were reached in our study. In the study group, patients had longer survival than patients in the control group. This was attributed to decreasing alcohol consumption, increased number of outpatient examinations, pharmacotherapy, better compliance and early detection of complications.

Survival data for patients with liver cirrhosis varied in different studies. When clinical signs of decompensation are present, prognosis is poor. Sixty percent of patients who stop drinking survive for 5 years. According to the literature, patients with liver cirrhosis survive 5 years in 15 to 42% of cases. Patients with portosystemic encephalopathy survive 1 year in 36% of cases.[24,25,26,27,28]

Abstinence from alcohol leads to the resolution of alcoholic fatty liver disease (benign steatosis), and abstinence improves survival in alcoholic cirrhotic patients, even those with decompensated liver function. Furthermore, reducing alcohol consumption, but not completely stopping it, has been shown to improve survival in patients with alcoholic liver disease.[29]

In the study group, consumption of alcohol was lower than in the control group, and the difference between the groups was statistically significant. Our study confirmed that abstinence remains the basis of the cure and improves overall survival. Survival of patients in our study is comparable to the rates reported by other published studies. Results for survival in the study group are comparable with the best results of published studies.[30,31]

A prospective study on the treatment of patients with liver cirrhosis was published in 2013

in Clinical Gastroenterology and Hepatology by Wigg *et al*. The primary outcome was the number of days spent in a hospital bed for liver-related reasons. Sixty consecutive patients with cirrhosis and complications (ascites, variceal bleeding, portosystemic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, protein malnutrition, alcoholic hepatitis, sepsis and hepatocellular carcinoma) from chronic liver failure were assigned randomly to groups given intervention (n = 40) or usual care (n = 20), from 2009 to 2010.

Support was provided through the following: enhanced patient education during contact with the nurses concerning diet, medications, and need for investigation. Patients in the intervention group had a 30% higher rate of attendance at outpatient care (incidence rate ratio, 1.3; 95% confidence interval, 1.1–1.5; P = 0.004) and significant increase in quality of care. There was no difference in hospitalisations between both groups (18.8 *vs*. 11.0 the day per person/year). The authors found no difference in the number of admissions due to liver cirrhosis, the number of admissions due to other causes or the median length of hospitalisation and survival. The population in this study was composed predominantly of patients with decompensated Child–Pugh class C (48%) or B (33%) liver disease with an associated very poor predicted 2-year survival (25% and 60%, respectively). They concluded that larger trials with longer follow-up periods are needed.[32]

We include more patients than Wigg *et al*. and implemented a longer follow-up period. The survival of patients in our study was longer. This could be partly attributed to more frequent systematic outpatient visits, reduced alcohol consumption and better medical treatment.

Weaknesses of our study

The diagnosis of alcoholic liver failure in the control group was made retrospectively on the basis of discharge diagnoses, data for history of alcohol consumption, laboratory tests, clinical status and abdominal ultrasound findings. Child-Pugh class was determined based on the collected data. The results of the control group were gathered from hospital discharges and the computer system Birpis.

In the control group, we used only discharge data from the hospital and did not follow any change of treatment in the course of research. Data about alcohol consumption may differ from actual consumption, because patients often conceal the truth about alcohol consumption. There may be also a difference between the groups due to the random selection of data.

Conclusions

Our study confirmed that patients who were treated in outpatient clinics for liver cirrhosis were hospitalised less frequently and had a significantly longer survival. To date, there have been no other studies with five-year follow-up of such a large patient sample. Our data suggested that patients who were monitored for liver cirrhosis in the outpatient clinic were better treated than other patients. Such management significantly improves survival, reduces hospitalisation rates and decreases alcohol consumption. Our results speak for the need for regular outpatient controls in patients with alcohol liver cirrhosis.

References

1. Hug BL, Lipsitz SR, Seger DL, Karson AS, Wright SC, Bates DW. Mortality and drug exposure in a 5-year cohort of patients with chronic liver disease. *Swiss Med Wkly* 2009; **139:** 737-46.
2. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol* 2013; **59:** 160-8. doi: 10.1016/j.jhep.2013.03.007
3. *[Internal medicine].* [Slovenian]. Third edition. Kocijančič A, Mrevlje F, Štajer D, editors. Ljubljana: Literra picta; 2005. p. 592-619.
4. *[Internal medicine].* [Slovenian]. Košnik M, Mrevlje F, Štajer D, Koželj M, Černelč P. Editors. Ljubljana: Literra picta; 2011; 663. p. 669-72.
5. Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al. Harrison´s principles of internal medicine Volume II. New York: McGraw-Hill Medical; 2008. p. 233, 1969-78, 1982-3.
6. Magdaleno F, Blajszczak CC, Nieto N. Key events participating in the pathogenesis of alcoholic liver disease. *Biomolecules* 2017; **9:** 1-14. doi: 10.3390/blom7010009
7. Grant BF, Dufour MC, Harford TC. Epidemiology of alcoholic liver disease. *Sem Liver Disease* 1988; **8:** 12-25.
8. Petrides AS: Liver disease and diabetes mellitus. *Diabet Rev* 1994; **2:** 2-18.
9. Asbert M, Gines A, Gines P, Jiménez W, Clària J, Saló J, et al. Circulating levels of endothelin in cirrhosis. *Gastroenterology* 1993; **104:** 1485-91.
10. Baig NA, Herrine SK, Rubin R. Liver disease and diabetes mellitus. *Clin Lab Med* 2001; **21:** 193-207.
11. Gentilini P, Romanelli RG, Laffi G, Barletta G, Del Bene R, Messeri G, et al. Cardiovascular and renal function in normotensive and hypertensive patients with compensated cirrhosis: effects of posture. *J Hepatol* 1999; **30:** 632-8.
12. Spatt SD, Rosenblatt P. The incidence of hypertension in portal cirrhosis: a study of 80 necropsied cases of portal cirrhosis. *Ann Int Med* 1949; **31:** 479-83.
13. Loyke HF. The relationship of cirrhosis of the liver to hypertension: a study of 504 cases of cirrhosis of the liver. *Am J Med Sci* 1955; **230:** 627-32.
14. Veglio F, Pinna G, Melchio R, Rabbia F, Panarelli M, Schiavone D, et al. Hormonal aspects of the relation of liver cirrhosis to essential hypertension. *Clin Exp Hypertens* A 1992; **14:** 889-903.

15. Raaschou F. Blood pressure and heart weight in chronic hepatitis. Does the liver play a role in the development of essential hypertension? *Nord Med* 1949; **46:** 1791-95.

16. Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361:** 1279-90. doi: 10.1056/NEJMra0809139

17. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology* 1993; **105:** 229-36.

18. Biecker E. Diagnosis and therapy of ascites in liver cirrhosis. *World J Gastroenterol* 2011; **17:** 1237-48. doi: 10.3748/wjg.v17.i10.1237

19. Bernardi M, Servadei D, Trevisani F, Rusticali AG, Gasbarrini G. Importance of plasma aldosterone concentration on the natriuretic effect of spironolactone in patients with liver cirrhosis and ascites. *Digestion* 1985; **31:** 189-93.

20. Pérez-Ayuso RM, Arroyo V, Planas R, Gaya J, Bory F, Rimola A, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-aldosterone system. *Gastroenterology* 1983; **84:** 961-8.

21. Gatta A, Angeli P, Caregaro L, Menon F, Sacerdoti D, Merkel C. A pathophysiological interpretation of unresponsiveness to spironolactone in a stepped-care approach to the diuretic treatment of ascites in nonazotemic cirrhotic patients. *Hepatology* 1991; **14:** 231-36.

22. Power C, Rodgers B, Hope S. U-shaped relation for alcohol consumption and health in early adulthood and implications for mortality. *Lancet* 1998, **352:** 877.

23. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med* 2006; **166:** 2437. doi: 10.1001/archinte.166.22.2437

24. Edmondson HA: Pathology of alcoholism. *Am J Clin Pathol* 1980; **74:** 725-42,

25. Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010; **51:** 1675-82. doi: 10.1002/hep.23500

26. Galambos JT. Alcoholic hepatitis: Its therapy and prognosis. *Prog Liver Dis* 1972; **4:** 567-88.

27. Pares A, Caballeria J, Bruguera M. Histological course of alcoholic hepatitis: Influence of abstinence, sex and extent of hepatic damage. *J Hepatol* 1986; **2:** 33-42.

28. Morgan, MY. The prognosis and outcome of alcoholic liver disease. *Alcohol Suppl* 1994; **2:** 335-43.

29. Frazier TH, Stocker AM, Kershner NA, Marsano LS, McClain CJ. Treatment of alcoholic liver disease. *Therap Adv Gastroenterol* 2011; **4:** 63-81. doi: 10.1177/1756283X10378925

30. O'Shea RS, Dasarathy S, and McCullough AJ. Alcoholic liver disease. *Am J Gastroenterol* 2010; **105:** 14-32; doi: 10.1038/ajg.2009.593

31. Bruha R, Dvorak K, Petrtyl J. Alcoholic liver disease. *World J Hepatol* 2012; **4:** 81-90. doi: 10.4254/wjh.v4.i3.81

32. Wigg AJ, McCormick R, Wundke R, Woodman RJ. Efficacy of a chronic disease management model for patients with chronic liver failure. *Clin Gastroenterol Hepatol* 2013; **11:** 850-8. doi: 10.1016/j.cgh.2013.01.0154

research article

Nutrition of patients with severe neurologic impairment

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Background. Commercial enteral formulas are generally recommended for gastrostomy feeding in patients with severe neurologic impairment. However, pureed food diets are still widely used and even gaining popularity among certain groups. We tried to compare the effectiveness of gastrostomy feeding for treatment of severe malnutrition with either enteral formulas or pureed feeds.

Patients and methods. A 6-month nutritional intervention was made with 37 malnourished children, adolescents and young adults (2–26 years old) with severe neurologic impairment (Gross Motor Function Classification system [GMFCS] grade V). The individual needs were calculated. Participants were fed by gastrostomy with either enteral formulas (n = 17) or pureed food (n = 20). Measurements to assess nutritional status were made at the beginning and at the end of intervention.

Results. The Z scores for weight-for-age and for the body-mass index increased more in enteral formula than in pureed food group (2.07 *vs.* 0.70, p = 0.0012; and 3.75 *vs.* 0.63, p = 0.0014, respectively). Fat mass index increased more in enteral formula than in pureed food group (1.12 kg/m^2 *vs.* 0.38 kg/m^2; p = 0.0012). Patients in the enteral formula group showed increase in lean body mass expressed as fat-free mass index (0.70 kg/m^2), while those in pureed food group did not (-0.06 kg/m^2) (p = 0.0487).

Conclusions. The results suggest that even professionally planned pureed food diet is less effective than commercial enteral formula for nutritional rehabilitation of malnourished patients with severe neurologic impairment. However, larger and if possible randomised clinical studies should be made to confirm our findings.

Key words: malnutrition; severe neurologic impairment; gastrostomy; enteral formula; pureed food

Introduction

Patients with neurologic impairment often suffer from feeding difficulties and limitations. Severity of feeding problems usually correlates with functional degree of neurologic impairment. Dysphagia and frequent food aspirations, gastroesophageal reflux, dysmotility of gastrointestinal tract, slow gastric emptying and digestion very often appear in patients with severe impairment.[1-5] Consequently, malnutrition is common problem in this group of patients. According to published studies, at least 40% of patients with severe neurologic impairment are malnourished, however, some studies estimated that the rate of malnourished patients is even above 90%.[4,6-8] Therefore, it is essential that malnutrition in these patients is recognized as soon as possible and appropriately treated to prevent the risk of bad outcomes.[6]

Built and body composition as well as energy and nutritional needs of these patients are importantly altered by the nature of their illness, so there is no consistent recommendation for the assessment of their nutritional status.[8,9] To prevent

or/and treat malnutrition, it is very important to estimate energy needs and adequacy of energy and nutrient intake. In case there is suspicion that patient has feeding difficulties, they should be reviewed and evaluated by team of experts.[10,11] If mild feeding problems are recognized, rehabilitation therapy and teaching of right feeding techniques by experts is recommended.[12,13] In patients with swallowing problems, liquid or pureed foods can be used. In patients with chocking problems during eating liquid foods, thickening agents can be added. When appropriate nutritional intake is not achieved by natural food, medium chain fatty acids (MCT oil), sugar polymers or hypercaloric enteral formulas can be added to increase energy density of food.[11]

In patients with severe feeding problems, that cannot eat sufficient amount of food through mouth, placement of feeding gastrostomy tube is necessary.[14] Additional indications for gastrostomy feeding are frequent aspirations during feeding and an excessive amount of time spent to feed the patient during the day. Numerous studies demonstrated important improvements in nutritional status of patients with severe neurologic impairment after the placement of gastrostomy tube.[15-19]

Enteral formulas with all macro and micro nutrients that suffice for long term exclusive use are recommended for gastrostomy feeding of neurologic patients[19], but pureed food diets are still very popular and widely used by parents due to beliefs such food is more natural and healthy.[20] Several researches studying composition of pureed gastrostomy feedings prepared at home or at hospital showed that they were less reliable in providing energy and nutrients, and could be contaminated by pathogenic microorganisms.[21-23] On the other hand, recent cross-sectional study of tube-fed adult patients receiving home enteral nutrition revealed that over 50% of patients were consuming homemade pureed food occasionally or regularly, despite they had been prescribed commercially available formulas.[24] Moreover, 46% of the patients reported that pureed food comprised more than 50% of their daily enteral feedings, most of them using their own recipes or recipes obtained from the internet. In the aforementioned study, patients reported fewer overall symptoms while using pureed feeds compared with a commercial enteral formula. A recently published review concerning special issues in tube-fed children found very little evidence regarding the appropriateness of home-prepared pureed food for gastrostomy feeding in children. It was emphasized that patients on pureed food should be under the supervision of health professionals, who could ensure that the diet was providing the proper nutrients profile. In addition, they pointed out that controlled trials were needed to evaluate the effectiveness of pureed tube feedings.[25]

In the face of these facts, whether pureed food accurately planned by skilled clinical dietitian, who takes into account all a patient's need for energy, macro- and micronutrients, ensures adequate nutritional support for patients with severe neurological impairment, appears an important issue. We therefore performed a prospective study to compare the effect of two different types of gastrostomy feeding, either enteral formula or pureed food, on the nutritional status of severely undernourished neurologically impaired children, adolescents and young adults.

Patients and methods

This study was conducted as a part of a PhD research project. It was a study made on young patients with severe neurologic impairment and feeding difficulties that were identified as moderately or severely malnourished in the outpatient Clinic for Enteral Nutrition of the University Children's Hospital Ljubljana, Slovenia, between the years 2013 and 2016. Patients received intervention during a 6-month period.

Forty-five young patients aged between 2 and 26 years with severe neurologic impairment (Gross Motor Function Classification system [GMFCS] grade V) were identified with moderate or severe malnutrition and included in the study. Their nutritional status was evaluated by Z scores of weight-for-age, with definition of moderate malnutrition as Z score below -2 and severe malnutrition with Z score below -3 according to WHO standards.[26] All included patients were fed by gastrostomy with at least of 80% of their food daily intake. Patients with progressive neurologic diseases or genetic syndromes were excluded. We also excluded patients that require special diets, such as ketogenic diet. Protocol of the study was approved by the Slovenian National Committee for Medical Ethics (KME n. 170/05/14), and written consent was obtained from parents/legal guardians.

Nutritional intervention

We calculated energy and macronutrient requirements for all included patients with D-A-CH refer-

ence values for typically developing children.[27] We used energy needs per body weight for children, adolescents or adults of the same age with addition of 30% for catch up' growth of severely malnourished patients.[28] Target energy intake was achieved within 2 weeks, with gradual increase from 100 to 130% of recommended daily energy intake to prevent the risk of refeeding syndrome.

Patients were divided into 2 groups, the first receiving exclusively enteral formula and the second receiving carefully planned pureed food diet with maximum of 20% of energy intake provided by food supplements or formula, when it was necessary to meet their requirements. As majority of parents/caregivers did not agree with randomisation, but demanded that their child was included in one or another group, the study was performed as open labelled comparative interventional study. Diet plans for pureed food group were carefully prepared by the team of clinical dietitians to meet requirements for energy, macro and micronutrient intake. An intake of about 2 g of protein per kg of body weight was used to cover increased needs during nutritional rehabilitation.[28] For the formula-fed group we used relatively high-energy density formula (1.5 kcal/ml) with added fibre, as majority of the patients were having poor tolerance for feeding volumes. Patients under the age of 12 years were fed with NutriniDrink Multi Fibre, while patients over the age of 12 with NutriDrink Multi Fibre (manufactered by Nutricia, Netherlands). The daily intake of enteral formula was determined based on previously calculated energy requirements. Parents/caregivers of both groups received personal nutritional counselling and instruction from the clinical dietitian.

Nutritional status assessment

We measured body weight with an electronic scale (Seca, Germany), length of ulna with sliding calliper (Holtain, UK), and skinfold thicknesses with skinfold calliper (Harpenden, UK) on patients' left-hand side or less affected side (in case of asymmetrical impairment) at the time of inclusion and again after 6 months of intervention.

Patients' body height was estimated with the equations using ulna length from Gauld *et al*.[29]

$$H = 4.605U + 1.308A + 28.003 \quad \text{for boys}$$
$$H = 4.459U + 1.315A + 31.485 \quad \text{for girls}$$

where H is height (cm), A is age (years), and U is ulna length (cm).

Body weight and estimated body height were used to obtain Z-scores for weight-for-age, height-for-age and BMI-for-age by using calculator based on 2006 WHO child growth standards.[26] Detected Z scores were used for the estimation of nutritional status before and after intervention, because we wanted to assess differences in the grade of nutrition according to normal population considering age, sex as well as starting grade of malnutrition.

Percentage of body fat was calculated from skinfold thickness data by using Slaughter's equations[30] modified by Gurka *et al*. for patients with cerebral palsy.[31] We calculated body fat mass (FM) and lean body mass (fat free mass) (LM) from percentage of body fat and body weight. Fat mass and lean body mass were then normalised for height (H) by calculating fat mass index (FMI) and fat-free mass index (FFMI) (both in kg/m^2):

$$FMI = FM / H^2$$
$$FFMI = FFM / H^2$$

Statistical methods

The differences between the pureed food group and enteral formula group at baseline were tested with t-test, Welch t-test or Mann-Whitney test as appropriate for the continuous variables (the normality assumption and the assumption of homoscedasticity, *i.e.* equal variances, were verified with the Shapiro-Wilk test and Bartlett test, respectively) and Chi-square test or Fisher exact test for categorical variables.

The differences between the groups in time were tested with linear mixed effects models including subject as a random effect using maximum likelihood method for parameter estimation. Group and time interaction was included in all the models, and its significance was verified with the likelihood ratio test. Contrast analysis was used to explore the interaction effect; note that since the contrasts were not orthogonal the p-values were adjusted with Holm's method to appropriately control the type I error.

A p-value of less than 0.05 was considered as statistically significant. The analysis was performed with R language for statistical computing (R version 3.0.0).[32]

Results

From the 45 included patients, 37 have completed the 6-month interventional study. In four cases

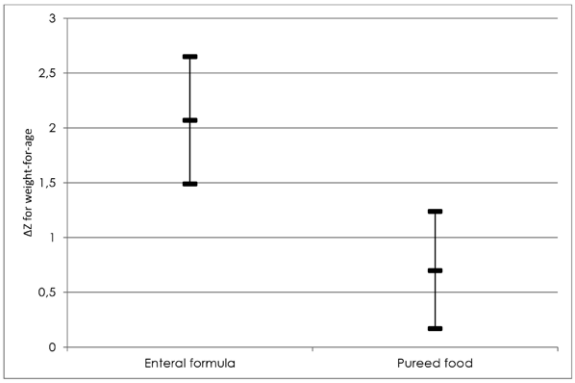

FIGURE 1. Changes of Z scores for weight-for-age after 6-month nutritional intervention expressed as mean values with 95% confidence interval.

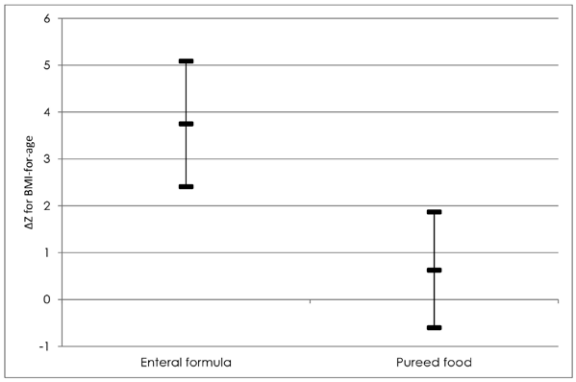

FIGURE 2. Changes of Z scores for BMI-for-age after 6-month nutritional intervention expressed as mean values with 95% confidence interval.

parents didn't follow the instructions and switched the feeding regime (three from formula and one from pureed group), three decided to abandon the regime due to personal reasons and one of the patients died few months after the inclusion. There were 17 patients in enteral formula and 20 in pureed food group who completed the interventional study.

As the patients in enteral formula were significantly older (13.7 ± 4.7 years *vs*. 9.4 ± 6.6 years), we applied multivariate models that adjusted to age difference.

Weight gain and growth

Patients in both groups improved in their weight-for-age Z scores significantly, in enteral formula group for 2.07 (95% CI: 1.49 - 2.65, p = 0.0000) and in pureed food group for 0.7 (95% CI: 0.17 - 1.24, p = 0.0114) as shown in Figure 1. Both groups also improved in body height, for 0.32 (95 % CI: 0.02-0.61, p = 0.0365) in enteral formula and for 0.51 (95% CI: 0.24-0.79, p=0.0005) in pureed food group. Much like weight-for-age Z-scores, BMI-for-age Z-scores increased for 3.75 (95% CI: 2.41 - 5.09, p = 0.0000) in enteral formula group and for 0.63 (95% CI: -0.60 - 1.87, p = 0.3045) in the pureed food group as shown in Figure 2. Z score for BMI-for-age changed significantly in enteral formula group, but not in pureed food group. Both weight-for-age and BMI-for-age Z scores increased significantly more in enteral formula than in pureed food group (p = 0.0012 and p = 0.0014, respectively).

Changes in body composition

The percentage of fat increased in both groups of patients, for 6.5% (95% CI: 4.5%– 8.4%, p = 0.0000) in enteral formula group and for 2.6% (95% CI: 0.8% - 4.5%, p = 0.0065) in pureed food group. The

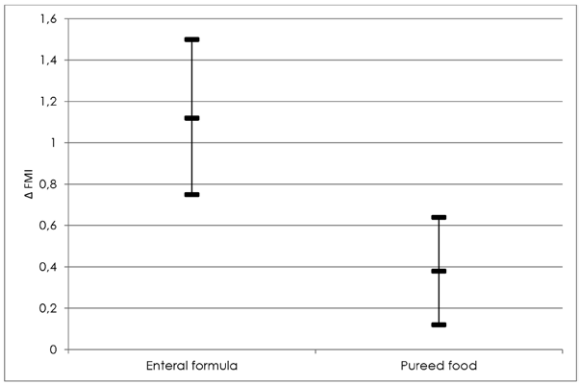

FIGURE 3. Changes in fat mass indexes (FMI) after 6-month nutritional intervention expressed as mean values with 95% confidence interval.

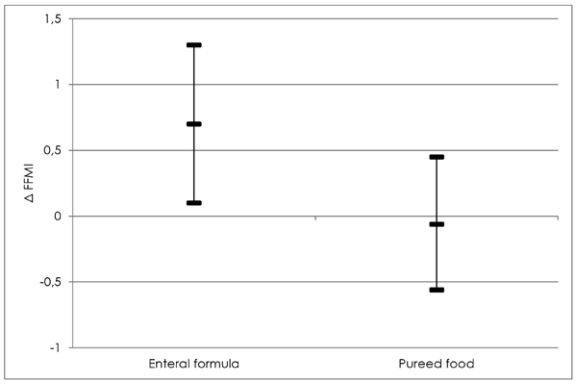

FIGURE 4. Changes in fat-free mass indexes (FFMI) after 6-month nutritional intervention expressed as mean values with 95% confidence interval.

increase of % of body fat was significantly higher in the formula group (p = 0.0051). After we converted % of body fat into body fat mass and lean body mass, we found out increases of both in majority of patients. When normalisation for height was applied with the use of FMI and FFMI, we found significantly higher increase of fat body mass indexes in the enteral formula group than pureed food group (for 1.12 kg/m^2; 95% CI: 0.75-1.50; and for 0.38 kg/m^2; 95% CI: 0.12-0.64; respectively; p = 0.0012) as presented in Figure 3. According to FFMI, we only found improvement in lean body mass in enteral formula group (for 0.70 kg/m^2, 95% CI: 0.1-1.3) while there was no significant change in pureed food group (-0.06 kg/m^2, 95% CI: -0.56-0.45) (p = 0.0487) which is demonstrated in Figure 4.

Discussion

To the best of our knowledge, this is the first prospective controlled study that objectively compared efficacy of gastrostomy feeding with professionally designed home-prepared pureed food diet and with commercially available enteral formula for treatment of malnutrition in patients with severe neurological impairment.

Although prescribed energy and nutrient intake were similar for both groups, there was significantly better improvement of both body weight and body composition in the enteral formula group. What is most important, results showed that patients in that group even gained lean body mass, which is extremely difficult to achieve in patients with severe limitations in movement.

Better effectiveness of enteral formula can be explained in different ways. It seems probable that the actual food intake in pureed food group was less than what we had recommended based on calculations of the patient's daily needs. The preparation of fresh food in the quantity and composition corresponding to accurate instructions of a clinical dietitian is a challenging task for parents/carers in comparison to the provision of the recommended daily volume of enteral formulas. We suspect that parents gradually started to improvise, both in the selection of foods and in the amounts (*i.e.* no more weighting). Even with the same volume of feeding, the daily intake may substantially alter due to a change in the selection of foods and/or their amount (especially the amount of oil or MCT).

Another reason for better effectiveness of enteral formula might also be in slow gastric emptying and gastroesophageal reflux, which are common in patients with severe neurologic impairment.[33] These patients tolerate poorly large volumes of food. As the energy density of enteral formula (1.5 kcal/ml) is higher than average energy density of pureed food, volumes of pureed food needed to cover energy and nutrient intake were higher. Although parents did not report increase in vomiting or regurgitation, volumes of food prescribed in the intervention were bigger than the ones they were used to before the study for most of the patients.

Furthermore, there is also a chance that biologic availability and utilization of nutrients from enteral formula was significantly better than from pureed food. There were some observational studies in malnourished people in developing countries and animal-model studies that show that both gut and pancreatic structure and function are affected in cases of severe malnutrition.[34-36] Therefore, digestion and absorption of some of the nutrients could be impaired in our patients. However, enteral formulas used in the study were polymeric enteral formulas based on milk protein. Although manufacturer claimed that their composition of macro and micro nutrient is in ideal proportion and in form with good absorption, there is not much evidence that macronutrients from polymeric formulas are really absorbed better than from natural foods.

Unfortunately, our study had some limitations. The first one is relatively small number of included patients, because the criteria that we used were very strict. Secondly, the randomisation into two groups was not possible due to strict demand of majority of parents for their child to be placed in the group they preferred. That is why the pureed food group patients were significantly younger and therefore less malnourished at the inclusion. It has been well documented that level of malnutrition usually increases with age in patients with severe neurologic impairment.[7] Although we used multivariate models that take into account the difference in age, more severe undernutrition at the starting point of the study in formula-fed group might affect the results. Metabolic rate of more malnourished patients is lower than the one of less malnourished, because of relatively smaller fat-free body mass, which is the strongest predictor of resting energy expenditure, and adaptation to a chronically low energy intake.[37] Therefore, with the same energy input, less energy is spend for coverage of basal metabolism and more can be used for growth of body tissues.

Despite aforementioned limitations, the results of this study suggest, that even professionally

planned diet using pureed food with highly motivated parents/caregivers, who have personally decided to feed their children with home-prepared food, is less effective or at least less reliable in nutritional rehabilitation of malnourished patients with neurologic impairment in comparison to the commercial enteral formula. However, larger and randomised clinical studies comparing efficacy of both feeding regimes should be made in the future to confirm our findings.

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References

1. Kuperminc MN, Gottrand F, Samson-Fang J, Arvedson J, Bell K, Craig GM, et al. Nutritional management of children with cerebral palsy: a practical guide. *Eur J Clin Nutr* 2013; **67:** 21-3. doi: 10.1038/ejcn.2013.227
2. Sullivan, PB, Lambert B, Rose M, Ford-Adams M, Johnson A, Griffiths P. Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. *Dev Med Child Neurol* 2000; **42:** 674-80. doi: 10.1111/j.1469-8749.2000.tb00678.x
3. Trier E, Thomas AG. Feeding the disabled child. *Nutrition* 1998; **14:** 801-5. doi: 10.1016/S0899-9007(98)00088-4
4. Penagini F, Mameli C, Fabiano V, Brunetti D, Dilillo D, Zuccotti GV. Dietary intakes and nutritional issues in neurologically impaired children. *Nutrients* 2015; **7:** 9400-59. doi: 10.3390/nu7115469
5. Shapiro BK, Green P, Krick J, Allen D, Capute AJ. Growth of severely impaired children: neurological versus nutritional factors. *Dev Med Child Neurol* 1986; **28:** 729-33. doi: 10.1111/j.1469-8749.1986.tb03924.x
6. Fung EB, Samson-Fang L, Stallings VA, Conaway M, Liptak G, Henderson RC, et al. Feeding dysfunction is associated with poor growth and health status in children with cerebral palsy. *J Am Diet Assoc* 2002; **102:** 361-73.
7. Sullivan PB, Juszczak E, Lambert BR, Rose M, Ford-Adams ME, Johnson A. Impact of feeding problems on nutritional intake and growth: Oxford Feeding Study II. *Dev Med Child Neurol* 2002; **44:** 46-67. doi: 10.1111/j.1469-8749.2002.tb00307.x
8. Samson-Fang L, Bell KL. Assessment of growth and nutrition in children with cerebral palsy. *Eur J Clin Nutr* 2013; **67:** 5-8. doi: 10.1038/ejcn.2013.223
9. Marchand V, Motil KJ; NASPGHAN Committee on Nutrition. Nutrition support for neurologically impaired children: a clinical report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2006; **43:** 123-35. doi: 10.1097/01.mpg.0000228124.93841.ea
10. Waterman ET, Koltai PJ, Downey JC, Cacace AT. Swallowing disorders in a population of children with cerebral palsy. *Int J Pediatr Otorhinolaryngol* 1992; **24:** 63-71. doi: 10.1016/0165-5876(92)90067-Y
11. Benfer KA, Weir KA, Bell KL, Ware RS, Davies PS, Boyd RN. Clinical signs suggestive of pharyngeal dysphagia in preschool children with cerebral palsy. *Res Dev Disabil* 2015; **38:** 192-201. doi: 10.1016/j.ridd.2014.12.021
12. Morgan AT, Dodrill P, Ward EC. Interventions for oropharyngeal dysphagia in children with neurological impairment. *Cochrane Database Syst Rev* 2012; **10:** CD009456. doi: 10.1002/14651858.CD009456.pub2
13. Hirata GC, Santos RS. Rehabilitation of oropharyngeal dysphagia in children with cerebral palsy: A systematic review of the speech therapy approach. *Int Arch Otorhinolaryngol* 2012; **16:** 396-9. doi: 10.7162/S1809-97772012000300016
14. Martinez-Costa C, Borraz S, Benlloch C, Sanchiz V, Brines J. Early decision of gastrostomy tube insertion in children with severe developmental disability: a current dilemma. *J Hum Nutr Diet* 2011; **24:** 115-21. doi: 10.1111/j.1365-277X.2010.01146.x
15. Sullivan PB, Juszczak E, Bachlet AME, Lambert B, Vernon-Roberts A, Grant HW, et al. Gastrostomy tube feeding in children with cerebral palsy: a prospective, longitudinal study. *Dev Med Child Neurol* 2005; **47:** 77-85. doi: 10.1017/S0012162205000162
16. Brant CQ, Stanich P, Ferrari AP Jr. Improvement of children's nutritional status after enteral feeding by PEG: an interim report. *Gastrointest Endosc* 1999; **50:** 183-8.
17. Corwin DS, Isaacs JS, Georgeson KE, Bartolucci AA, Cloud HH, Craig CB. Weight and length increases in children after gastrostomy placement. *J Am Diet Assoc* 1996; **96:** 874-9. doi: 10.1016/S0002-8223(96)00239-8
18. Dahlseng MO, Finbråten A-K, Júlíusson PB, Skranes J, Andersen G, Vik T. Feeding problems, growth and nutritional status in children with cerebral palsy. *Acta Paediatr* 2012; **101:** 92–98. doi: 10.1111/j.1651-2227.2011.02412.x
19. Braegger C, Decsi T, Dias JA, Hartman C, Kolacek S, Koletzko B, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. *J Pediatr Gastroenterol Nutr* 2010; **51:** 110-22. doi: 10.1097/MPG.0b013e3181d336d2
20. Escuro AA. Blenderized tube feeding: suggested guidelines to clinicians. *Pract Gastroenterol* 2014; **138:** 58-66.
21. Sullivan MM, Sorreda-Esguerra P, Platon MB, Castro CG, Chou NR, Shott S, et al. Nutritional analysis of blenderized enteral diets in the Philippines. *Asia Pac J Clin Nutr* 2004; **13:** 385-90.
22. Jalali M, Sabzghbaee MM, Badri SS, Soltani HA, Maracy MR. Bacterial contamination of hospital-prepared tube feeding formulas in Isfahan, Iran. *J Res Med Sci* 2009; **14:** 149-56.
23. Borghi R, Araujo TD, Viera RIA, de Souza TT, Waitzberg DL. ILSI task force on enteral nutrition: estimated composition and costs of blenderized diets. *Nutr Hosp* 2013; **28:** 2033-8. doi: 10.3305/nutr hosp.v28in06.6759
24. Hurt RT, Edakkanambeth Varayil J, Epp LM, Pattinson AK, Lammert LM, Lintz JE, et al. Blenderized tube feeding use in adult home enteral nutrition patients: A cross-sectional study. *Nutr Clin Pract* 2015; **30:** 824-9. doi: 10.1177/0884533615591602
25. Edwards S, Davis AM, Bruce A, Mousa H, Lyman B, Cocjin J, et al. Caring for tube-fed children: A review of management, tube weaning, and emotional considerations. J Parenter Enteral *Nutr* 2016; **40:** 616-22. doi: 10.1177/0148607115577449
26. WHO AnthroPlus for personal computers Manual: for assessing growth of the world's children and adolescents. Geneva: WHO; 2009. Available at http://www.who.int/growthref/tools/en/
27. Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährungsforschung, Schweizerische Vereinigung für Ernährung. [Reference levels for nutrient intake]. [German]. Neustadt: Neuer Umschau Buchverlag; 2008.
28. Bell KL, Samson-Fang L. Nutritional management of children with cerebral palsy. *Eur J Clin Nutr* 2013; **67:** 13-6. doi: 10.1038/ejcn.2013.225
29. Gauld LM1, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. *Dev Med Child Neurol* 2004; **46:** 475-80. doi: 10.1111/j.1469-8749.2004.tb00508.x
30. Slaughter MH, Lohman TG, Boileau RA, Horswill CA, Stillman RJ, Van Loan MD, Bemben DA. Skinfold equations for estimation of body fatness in children and youth. *Hum Biol* 1988; **60:** 709-23.
31. Gurka MJ, Kuperminc MN, Busby MG, Bennis JA, Grossberg RI, Houlihan CM, et al. Assessment and correction of skinfold thickness equations in estimating body fat in children with cerebral palsy. *Dev Med Child Neurol* 2010; **52:** 35-41. doi: 10.1111/j.1469-8749.2009.03474.x
32. R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2009. ISBN 3-900051-07-0. Available at http://www.R-project.org

33. Sullivan PB. Gastrointestinal disorders in children with neurodevelopmental disabilities. *Dev Disabil Res Rev* 2008; **14:** 128-36. doi: 10.1002/ddrr.18

34. Durie PR, Moore DJ, Forstner GG. Malnutrition and the exocrine pancreas. In: Walker-Smith JA, McNeish AS, editors. *Diarrhoea and malnutrition in childhood.* London: Butterworth & Co. Publishers Ltd; 1986. p. 135-46.

35. Hamilton R. The effect of malnutrition on gut structure, function and healing after injury. In: Walker-Smith JA, McNeish AS, editors. *Diarrhoea and malnutrition in childhood.* London: Butterworth & Co. Publishers Ltd; 1986. p. 23-7.

36. Penny ME. Protein-energy malnutrition: patophisiology, clinical consequences, and treatment. In: Duggan C, Watkins JB, Walker WA, editors. *Nutrition in paediatrics*. Hamilton: BC Decker Inc; 2008. p. 127-41.

37. Arrowsmith FE, Allen JR, Gaskin K, Sommerville H, Birdsall J, Barzi F, O'Laughlin EV. Nutritional rehabilitation increases resting energy expenditure of malnourished children with severe cerebral palsy. *Dev Med Child Neurol* 2012; **54:** 170-5. doi: 10.1111/j.1469-8749.2011.04166.x

research article

MRI and ^{11}C acetate PET/CT for prediction of regional lymph node metastasis in newly diagnosed prostate cancer

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Background. The aim of the study was to examine the value of quantitative and qualitative MRI and ^{11}C acetate PET/CT parameters in predicting regional lymph node (LN) metastasis of newly diagnosed prostate cancer (PCa).

Patients and methods. Patients with intermediate (n = 6) and high risk (n = 47) PCa underwent 3T MRI (40 patients) and ^{11}C acetate PET/CT (53 patients) before extended pelvic LN dissection. For each patient the visually most suspicious LN was assessed for mean apparent diffusion coefficient (ADCmean), maximal standardized uptake value (SUVmax), size and shape and the primary tumour for T stage on MRI and ADCmean and SUVmax in the index lesion. The variables were analysed in simple and multiple logistic regression analysis.

Results. All variables, except ADCmean and SUVmax of the primary tumor, were independent predictors of LN metastasis. In multiple logistic regression analysis the best model was ADCmean in combintion with MRI T-stage where both were independent predictors of LN metastasis, this combination had an AUC of 0.81 which was higher than the AUC of 0.65 for LN ADCmean alone and the AUC of 0.69 for MRI T-stage alone.

Conclusions. Several quantitative and qualitative imaging parameters are predictive of regional LN metastasis in PCa. The combination of ADCmean in lymph nodes and T-stage on MRI was the best model in multiple logistic regression with increased predictive value compared to lymph node ADCmean and T-stage on MRI alone.

Key words: prostatic neoplasm; lymph nodes; lymph node excision; diffusion magnetic resonance imaging; positron-emission tomography

Introduction

Detection of regional lymph node (LN) metastases in prostate cancer (PCa) is of great importance, as it is a prognosticator of significantly decreased disease-specific survival rates and biochemical recurrence-free rates.[1] Further correct identification of patients with lymph node metastases, might have important implications regarding the addition of adjuvant therapy.

Extended pelvic lymph node dissection (ePLND) is gold standard for diagnosing LN involvement in patients at increased risk of LN metastases.[2] An extended approach is recommended since limited dissection of the obturator fossa misses 50% of metastases.[3] However ePLND is associated with high cost, hospitalization and possibly post-operative complications. Hence imaging may have a role to select patients suitable for lymph node dissection.

Conventional imaging methods such as CT and MRI have limited value in the evaluation of LN metastases in patients with prostate cancer. Both techniques depend on morphological criteria, mainly size and shape of lymph nodes, which is the likely explanation to the low sensitivity of conventional CT and MRI.[4-6]

As morphological criteria not are sufficient, functional imaging techniques have received increased attention in the scientific literature. Diffusion weighted (DWI) MRI has been studied by several researchers[7-12] as well as ^{11}C and ^{18}F Choline PET/CT.[13-16] There are a few publications on lymph node staging in PCa with the PET radiotracer ^{11}C acetate.[17,18] Acetate can be metabolized in different ways, the most important in PCa is the fatty acid synthase pathway (FAS), as this pathway is overexpressed in PCa.[19-21] The uptake of this tracer can be measured semi-quantitatively by the standardized uptake value (SUV).

DWI depicts the motion of water molecules within tissues, a process that is restricted in highly cellular tissues, for example malignant tumors. Apparent diffusion coefficient (ADC) value is a quantitative parameter of DWI.[22] A few studies have indicated that ADC measurements can differentiate malignant prostate lesions from benign prostatic tissue, however with a significant overlap.[23-25]

The aim of this study was to examine the value of quantitative and qualitative MRI and ^{11}C acetate PET/CT parameters in predicting regional lymph node metastasis of newly diagnosed prostate cancer of intermediate and high risk, with histopathology from ePLND as reference standard

Patients and methods

Patients

Between July 2010 and June 2013, 53 consecutive patients with intermediate- (n = 6) and high-risk (n = 47) prostate cancer according to D´Amico risk categories[26] were prospectively included. All patients underwent imaging within two weeks before ePLND, 40 had 3T MRI DWI and ^{11}C acetate PET/CT, the remaining 13 had ^{11}C acetate PET/CT only. Inclusion criteria were a negative bone scintigraphy and a risk of LN spread of >20% according to the Briganti nomogram.[27] Exclusion criteria were contraindication to laparascopy, contraindication to MRI examination (*e.g.*, pacemaker, magnetic implants) and hip replacement or previous hip or lower pelvis fractures. The study was approved by the regional ethics and radiation ethics committees. Informed consent was obtained in all patients before participation.

All patients in our study have been included in two previous studies[11,18] that focused on non-quantitative validation of MRI DWI and ^{11}C acetate PET/CT.

MRI and ^{11}C acetate PET/CT

Both examinations were performed within the same day.

Patients were measured with a 3 Tesla scanner (Achieva, Philips Medical Systems, Best, The Netherlands) using a two-channel whole body coil for excitation and a six-element phase-array coil for receiving. MRI from apex of the prostate to the aortic bifurcation was performed using T_1- (T1W) and T_2-weighted (T2W) turbo spin echo (TSE) sequences in axial plane. The main T1W acquisition parameters were as follows: Repetition time/Echo time (TR/TE), 670/10 ms; field of view (FOV) 260 x 260 mm^2; acquisition matrix 150 x 186; number of signal averages (NSA), 2. T2W TSE scans were acquired with TR/TE 7000/120 ms; FOV 260 x 260 mm^2; acquisition matrix 166 x 173; NSA, 2. Axial fat suppressed diffusion weighted imaging (DWI) was performed using the spin-echo single-shot echo-planar imaging (SE-EPI) technique (TR/TE, 2450/55 ms; FOV 220 x 280 mm^2; acquisition matrix 73 x 94; diffusion encoding gradients b = 0, 100, 200, 400, 500 s/mm^2; NSA, 3). The apparent diffusion coefficient (ADC) maps were obtained with mono-exponential fitting. Separate DWI imaging with single b value (1000 s/mm^2) was performed for qualitative diagnostics

Axial T1W (TR/TE, 500/8 ms) and T2W TSE (TR/TE, 3000/100 ms) images of the prostate gland and vesicles were obtained with FOV 160 × 160 and acquisition matrix 182 x 200 and 160 x 200, respectively. NSA = 3 for both acquisitions. Axial DWI/ADC SE-EPI scans used following parameters: TR/TE, 1800/55 ms; FOV, 220×220 mm^2; acquisition matrix 98 x 126; NSA, 4; diffusion encoding gradients b = 0, 100, 200, 400, 500 s/mm^2. The apparent diffusion coefficient (ADC) maps were obtained with mono-exponential fitting Separate DWI imaging with single b value (1000 s/mm^2) was performed for qualitative diagnostics.

^{11}C acetate was synthesized according to in-house good manufacturing practice (GMP) procedures. Patients were fasted for at least 4 hours prior to PET. Five MBq/kg body weight of ^{11}C acetate was injected intravenously in an antecubital vein 10 min prior to PET acquisition. PET/CT was per-

formed on a GE Discovery ST16 (GE Healthcare, Waukesha, ML) hybrid scanner. A venous phase contrast-enhanced low dose CT used both for morphologic analysis and for attenuation correction (140 kV, auto-mA 10-80 mA), and PET with 3 min per bed position, covering regions from the upper thighs to the neck, typically obtained in 6 bed positions. Total PET acquisition time was 18 min. Total effective dose of both PET and CT with this protocol was approx. 9 mSv. PET images were corrected for attenuation, dead-time, scatter and decay, and reconstructed to a 50 cm field of view in a 128 x 128 matrix using an iterative reconstruction algorithm with 2 iterations and 21 subsets as supplied by the manufacturer.

Surgical technique

A systematic laparoscopic extended lymph node dissection was performed first from the external and common iliac artery and vein from the ureter and to the deep circumflex vein, respecting the genitofemoral nerve, secondly from the obturator fossa, meaning the space between the external iliac vein down to the obturator nerve and lastly the internal iliac area from the obturator nerve down to internal iliac artery and to the deep pelvic floor. The specimen were separated in 3 fractions from each side and sent to the pathologist.

Histopathological evaluation

The specimens were fixed in 4% buffered formaldehyde. Lymph nodes smaller than 10 mm were embedded whole. Larger lymph nodes were dissected longitudinally through the hilum or cut serially at 3 mm intervals depending on the size. The specimens were dehydrated in alcohol for 21 hours. Thereafter embedded in paraffin and sectioned (4 μm) at two levels. Sections were stained with haematoxylin and eosin. For each patient the presence and the number of LN metastases were reported. Immunohistochemistry with pan-cytokeratin was used when necessary to confirm a minor metastasis.

MRI and ^{11}C acetate PET/CT analysis

A specialized radiologist (C.v.B) with more than ten years experience in nuclear medicine and oncological radiology, blinded to histopathology results and clinical information, analysed the images using Carestream Vue PACS with built in PET/CT as software (Carestream Health, Inc, Rochester, NY, USA). At least 6 months passed between the non quantitative analysis of this material, previous published[11,18] and the quantitative analysis in the present manuscript.

MRI and ^{11}C acetate PET/CT were reviewed side by side, the lymph node with the visually most suspicious findings with regard to diffusion restriction, PET activity, shape and size, were chosen from any of the the anatomical regions included in a ePLND, for each patient. Diffusion restriction and PET activity weighed heavily in the selection of the visually most suspicious LN, secondly LN shape and thirdly LN size. In case of normal LN findings, the largest LN was assessed. The chosen lymph nodes were assessed for the following features; SUVmax measured by placing a region of interest (ROI) encompassing the uptake, the maximum pixel value representing SUVmax, ADCmean measured by placing a ROI within the LN contour in the lymph nodes largest axial section, size was measured in the lymph nodes short axis and LN shape was registered as oval or round. MRI DWI was also analysed for primary tumour T stage; obvious extra-capsular extension was registered as MRI-T3a, obvious spread to seminal vesicles was registered as MRI-T3b, if non of this features were present the T stage was registered as ≤ MRI-T2. The index lesion, *i.e.* the largest lesion, in the primary tumour was also assessed, tumour-SUVmax and tumour-ADCmean were measured by the same method described for LNs above.

Statistics

Receiver operating curve (ROC) analysis of LN-ADCmean, LN-SUVmax, LN size, tumour-ADCmean and tumour-SUVmax was performed to determine optimal cut-off from which the variables were dichotomized. Variables were then analysed in simple logistic regression analysis to determine their significance. Different combinations of the significant variables in the simple analysis were then included in multiple logistic regression models but the number of observations in each variable did not allow us to use more than two variables at the same time. For each model the predicted values were compared with the observed values, area under the curve (AUC), sensitivity, specificity, positive and negative predictive value (PPV, NPV), accuracy, pseudo R^2 (Nagelkerke) and Hosmer-Lemeshow statistic were calculated to determine their classification performance. Multicollinearity between variables, was measured with Cramer´s V.

A p-value less than 0.05 was considered statistically significant. Statistical analysis was performed with Dell Inc. (2015). Dell Statistica (data analysis software system), version 13. software.dell.com.

Results

The patients´ clinical characteristics are outlined in Table 1. Of the 53 patients included in the study 26 (49%) had LN metastases at ePLND. Among the 40 patients that had 3T MRI DWI plus ^{11}C acetate PET/CT 50% had LN metastasis, patient characteristics for this subset of patients has previously been described.[11] The variables MRI-T-stage, LN-ADCmean and tumour-ADCmean had 40 observations, the remaining variables tumour-SUVmax, LN-SUVmax, LN-size and LN-shape had 53 observations. The smallest LN in the material was 3.8 mm, the median ROI size for ADC measurements in LN´s was 42 mm^2 with range 16–334 mm^2, the ROI size for ADC measurements in primary tumour was ≥ 80 mm^2 (Table 2).

The ROC analysis of Tumour-ADCmean and Tumour-SUVmax showed insufficient classification with AUC of 0.53 and 0.49 respectively. For LN-SUVmax, LN-ADCmean and LN-size the corresponding AUC were 0.69, 0.72 and 0.62 respectively, these variables were dichotomized using optimal thresholds calculated from the ROC curve and included in simple logistic regression along with MRI-T-stage and LN-shape (Table 3). ROC determined threshold values are presented in Table 3. All variables included in simple logistic regression analysis were significant predictors of LN metastasis and therefore included in multiple logistic regressions models in combination of two (Table 4). Ten combinations were calculated and in model one to three both variables appeared as independent predictors of LN metastasis: LN-ADCmean in combination with LN-SUVmax, LN-shape and MRI-T-stage, respectively, where the best combinations for prediction of LN metastasis (Table 4). Model three (LN-ADCmean and MRI-T-stage) was the model with highest AUC and pseudo R^2, 0.81 and 0.39 respectively, which was higher than the AUC of 0.65 and pseudo R^2 of 0.12 for LN-ADCmean alone and the AUC of 0.69 and pseudo R^2 of 0.17 for MRI-T-stage alone

In model one to three both variables were significant, multicollinearity between the predictors were weak, Cramers´V of 0.09, 0.15 and 0.16 respectively. This in combination with adequate goodness of fit show the validity of the models.

TABLE 1. Patient characteristics

Patient characteristics	
Patients, *n*	53
Age, median (range)	68 (55–76)
LN positive patients, *n*	26
PSA level ng/ml, mean (median, range)	24 (19, 3–112)
Biopsy Gleason score, *n* (%)	
6	5 (9.4)
7	39 (73.6)
8	5 (9.4)
9	4 (7.5)
D´Amico risk classification, *n* (%)	
Intermediate	6 (11.3)
High	47 (88.7)
Clincal T-stage, *n* (%)	
T1c	1 (1.9)
T2	11 (20.8)
T3	41 (77.4)
Risk of LN invasion*, *n*	
19–59%	27
≥ 60%	26

LN = lymph node; * Calculated according to Briganti nomogram (26)

TABLE 2. Investigational findings at MRI DWI and ^{11}C Acetate PET/CT

MRI DWI and ^{11}C Acetate PET/CT findings	
LN-ADCmean 10^{-6} mm^2 /s, mean (SD) range	917 (191) 582–1398
LN-SUVmax, mean (SD) range	1.8 (1.2) 0.7–5.9
LN size mm, mean (SD) range	6.6 (3.7) 3.8–28.3
Proportion of LNs with round shape, *n*	19
Proportion of LNs with oval shape, *n*	34
MRI T-stage, *n*	
< T3	25
T3a	14
T3b	14
LN ADC Roi size mm^2, median (range)	42 (16–334)
Tumor ADC Roi size mm^2	≥ 80

ADC = Apparent diffusion coefficient b0-b500; LN = lymph node; MRI T-stage: determined with MRI, only clear cut cases were reported as T3a and T3b; ROI = Region of interest; SUV = Standardized uptake value

Discussion

Our prospective study of predominantly high risk PCa patients undergoing ePLND for LN staging,

TABLE 3. MRI DWI and [11]C Acetate PET/CT variables dichotomized using ROC curve and analyzed with simple logistic regression

	N0 *n*	N1 *n*	OR	95%CI	p-value	Threshold	AUC	Pseudo R²*	Sensitivity/Specificity/PPV/NPV
LN-ADCmean 10^{-6} mm² /s	21	19	3.6	1.1-11.6	0.031	≤ 800	0.65	0.12	58/**73**/**76**/53
LN-SUVmax	28	25	5.4	1.6-18.7	0.008	≥ 1.6	0.68	0.18	72/68/52/83
LN-size mm	28	25	8.7	1.7–44.9	0.010	≥ 7.9	0.66	**0.20**	**83**/63/40/**93**
LN round shape	5	14	5.9	1.7-20.4	0.006		**0.69**	**0.20**	74/68/56/82
LN oval shape	23	11	ref	ref	ref	ref	ref	ref	ref
MRI-T-stage									
≤ T2	18	7	ref	ref	ref	ref	ref	ref	ref
T3a	7	7	2.00	0.4-10.5	0.412				
T3b	3	11	6.0	1.2-29.4	0.027		**0.69**	0.17	65/67/65/67

* Nagelkerke´s R²; ADC = Apparent Diffusion Coefficient b0-b500; AUC = Area Under the Curve; CI = Confidence Interval; LN: lymph node; MRI T-stage: determined with MRI, only clear cut cases were reported as T3a and T3b; N0 = No lymph node metastases at ePLND (extended lymph node resection); N1 = Verified lymph node metastases at ePLND; NPV = Negative Predictive Value; OR = Odds Ratio; PPV = Positive Predictive Value; SUV = Standardized uptake value; Treshold calculated with ROC analysis; Bold numbers indicate highest values

show that a quantitative and qualitative analysis of LN and primary tumor findings at MRI DWI and [11]C acetate PET/CT can provide a range of single and combined parameters to help radiologists evaluating the probability of regional LN metastases. LN-ADCmean, LN-SUVmax and LN-size were significant predictors of LN metastases as were lymph node with round shape and stage T3b at MRI, while Tumour-ADCmean and Tumour-SUVmax had insufficient classification properties. In multiple logistic regression analysis the best combination was LN-ADCmean and MRI-T-stage

TABLE 4. MRI DWI and [11]C Acetate PET/CT variables dichotomized with ROC curve and analyzed with multiple logistic regression

Model*	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
LN-ADCmean 10^{-6} mm² /s	3.7 (1.1–13.3), 0.040	4.1 (1.1–14.7), 0.032	8.4 (1.8–39.0), 0.007	2.7 (0.8–9.5), 0.110						
LN-SUVmax	5.6 (1.5–20.6), 0.010				2.7 (0.6–11.1), 0.179	4.7 (1.1–20.5), 0.040	2.3 (0.5–10.7), 0.30			
LN-shape		5.7 (1.5–21.2), 0.010			3.7 (0.9–15.0), 0.069			6.2 (1.4–27.2), 0.016	2.8 (0.5–14.7), 0.226	
MRI T-stage T3b[a] / ≤ T2			6.8 (1.1–41.6), 0.039			5.3 (1.0–28.6), 0.051		3.9 (0.7–22.0), 0.126		4.5 (0.8–25.2), 0.083
LN-size mm				7.5 (1.4–40.3), 0.018			4.8 (0.7–34.7), 0.116)		3.8 (0.4–31.6), 0.224	9.3 (1.4–61.1), 0.020
[c]Psedo R²	0.27	0.30	**0.39**	0.26	0.24	0.29	0.22	0.33	0.23	0.34
AUC	0.75	0.76	**0.81**	0.73	0.71	0.75	0.68	0.79	0.71	0.75
Sensitivity	72	74	67	**83**	63	65	68	74	74	74
Specificity	68	68	77	65	66	72	65	**83**	68	73
PPV	52	56	80	40	60	75	52	**85**	56	70
NPV	83	82	62	**93**	68	62	79	71	82	76
Cramers´V[b]	0.09	0.15	0.16	0.25	0.54	0.28	0.66	0.37	0.72	0.34
Accuracy	69	70	71	69	64	68	66	**78**	70	73

* Model one through ten: presented with OR (95%CI), p-value. [a] T3a is not presented in the table, this is because it is not significant in any of the ten models above. [b] Multicollinearity; [c] Nagel-kerke´s R²; AUC = Area Under the Curve; CI = Confidence Interval; LN = lymph node; MRI T-stage: only clear cut cases were reported as T3b, Apparent Diffusion Coefficient b0-b500, NPV = Negative Predictive Value; OR = Odds Ratio; PPV = Positive Predictive Value; SUV = Standardized uptake value; Bold numbers indicate highest values

(model three), this combination increased the predictive value compared to that of each parameter alone. To the best or our knowledge this is the first study investigating quantitative and qualitative predictors of regional LN metastases from MRI and ^{11}C acetate PET/CT, in patients with a risk of LN spread of >20% according to the Briganti nomogram[27] with histopathology as reference standard.

One article, which combines quantitative and qualitative analysis of 11C acetate PET/CT and MRI for diagnostic analysis or suspected prostate cancer, has previously been published.[28] However, in that study they included both patients with suspected and verified prostate cancer and analysed the combined imaging modalities to determine diagnostic accuracy for both local and distant staging, including only 15 patients with histopathological lymph node verification. Eleven of these 15 patients were found to have positive regional lymph nodes giving a sensitivity, specificity, and diagnostic accuracy for multiparametric MRI of 72.7%, 100%, and 95%, respectively, *i.e.* better than our results. They also found that multiparametric [11C]-acetate PET-MRI further improved the diagnostic accuracy for detection of regional lymph node metastases compared with MRI and PET alone. This is similar to our results that LN-ADCmean in combination with LN-SUVmax, LN-shape and MRI-T-stage, respectively, where the best combinations and significant predictors of LN metastasis.

A recent retrospective study by Park *et al.*[29] investigated 101 PCa patients, with normal sized lymph nodes, undergoing ePLND with MRI DWI at 3T. In simple logistic regression PSA, Gleason score, greatest percentage of biopsy core, percentage of positive cores, ADC of index lesion in prostate gland and MRI T stage were all independent predictors of regional LN metastasis. In multiple analyses only MRI T stage was significant. This finding is similar to our study since MRI-T-stage is a strong predictor in our material. A limitation of the study by Park *et al.* is that only 9 patients had LN metastasis, whereas 92 patients did not, this makes the logistic regression model unbalanced.

Another recent study by Batra *et al.*[30] investigated predictive factors for LN metastases in 100 patients undergoing ePLND. Variables examined in simple logistic regression analysis were PSA, Gleason score, clinical stage, D'Amico risk category and features of locally advanced disease on MRI (defined as extraprostatic extension, seminal vesicle invasion and enlarged pelvic lymph nodes). Clinical stage and features of locally advanced disease were predictive of LN metastases. In multiple logistic regression clinical stage only was predictive of LN metastases.

These results are not directly comparable to ours since all but 2 patients in the study by Batra *et al.* had clinically localized disease, whereas the majority of patients in our study (77.4%) had T3 disease. Further the definition of locally advanced disease included findings of enlarged pelvic lymph nodes, while in our study MRI-T-stage was defined by T stage on MRI. A disadvantage of the study by Batra *et al.* is that only 17% of the included patients had N1 disease.

Recently ^{68}Ga-PSMA PET/CT became apparent as a promising new tracer binding to the prostate specific membrane antigen (PSMA). A few studies have evaluated the diagnostic performance of this tracer, in lymph node staging at initial diagnosis of PCa, with ePLND as reference standard.[30-32] Sensitivity ranged from 61% to 82% and specificity from 84% to 95% in these studies. The sensitivity of ^{68}Ga-PSMA PET/CT is higher, but specificity is somewhat lower, compared to ^{11}C acetate PET/CT.[18]

The ADC value is largely dependent on the diffusion weighting factors (b values) used in the protocol, variability of the ADC value of up to 40% has been described with the use of different b values.[34] To a lesser degree, ADC values can differ between MRI systems.[35] This explains why cut-offs for ADC values cited in the literature vary greatly. For example in our study the lymph node ADCmean cut-off obtained with ROC curve analysis was 800 x 10^{-6} mm^2/s, based on the b values 0,100, 200, 400, 500. In another study the cut-off of the ADCmean value was 910 x 10^{-6} mm^2/s based on b values 500, 800, 1000 and 1500.[12] In three studies with the following b values 50, 300, 600, the reported pelvic lymph node ADC mean cut-off were 1430 x 10^{-6} mm^2/s, 1010 10^{-6} mm^2/s and 1300 10^{-6} mm^2/s respectively.[7,9,10] There is clearly a need for standardization of DWI acquisitions to enable comparisons of ADC values between reports.[36]

Up to 80% of regional LN metastases in PCa are located in normal sized lymph nodes[36], it is therefore unavoidable to measure ADC in normal sized lymph nodes when evaluating DWI in nodal staging of PCa. This is reflected by the ADC ROI size of pelvic lymph nodes in our study ranging from 16-334 mm^2 with median size of 42 mm^2. In a study by Thoeny *et al.*[38] investigating normal sized pelvic lymph nodes in bladder cancer and PCa, the ADC ROI size ranged from 2.8-40.7 mm^2. Obviously there is a risk of partial volume effect when measuring ADC in small lymph nodes. However, Eiber *et al.*[9] showed that measurements of the ADC value

are not substantially distorted by partial volume effects even in lymph nodes down to 6 mm.

The ROC curve analysis optimal cut-off for LN size short axis diameter was 7.9 mm in our study, this is similar to the cut-off of 8 mm for LN size that has been reported in two previous studies of pelvic nodes in PCa.[7,9] Regarding optimal cut-off for lymph node SUVmax in ^{11}C acetate PET/CT, there are no previous publications to compare with.

Interestingly, we could show that lymph nodes with round shape were predictive of metastases, which is confirming its position in general interpretation criteria of CT and MRI imaging in PCa. Regarding the multiple logistic regression analysis, one can argue that the combination of LN-shape and MRI-T-stage (model eight) had AUC and pseudo R^2 close to model three (LN-ADCmean and MRI-T-stage) and even higher accuracy 0.78 *vs*. 0.71 compared to model three. However only LN-shape in mode eight appeared as independent predictor. LN-ADCmean and LN-SUVmax were independent predictors in model one as were LN-ADCmean in combination with LN-shape in model two, however not reaching the results in model three.

It should be noted that all of the predictive factors in our study except LN-SUVmax can be obtained from non-contrast enhanced MRI, this is of relevance since ^{11}C acetate PET/CT is associated with high cost and limited availability. However the LN for measurement of ADC values was also chosen according to ^{11}C acetate PET/CT uptake, and this might bias the interpretation.

A limitation of this study is that the number of observations did not allow for more than two variables in multiple logistic regression analysis, which prevented us from exploring the true diagnostic performance of a large model with all predictors included. Another limitation is that the ADC measurements in lymph nodes smaller than 6 mm could be hampered by partial volume effect. Since it is very difficult to correlate single, specific lymph node histology to imaging, we chose to select the lymph node with the visually most suspicious findings from any of the anatomical regions included in the ePLND, for each patient.

Conclusions

In this prospective study we could show that a number of predictive factors for regional lymph node metastasis in patients with intermediate- and high-risk PCa could be retrieved from MRI and ^{11}C acetate PET/CT. SUVmax, ADCmean, size and shape of regional lymph nodes were all predictive of lymph node metastases as were T-stage on MRI. The combination of ADCmean in lymph nodes and T-stage on MRI was the best model in multiple logistic regression with increased predictive value compared to lymph node ADCmean and T-stage on MRI alone. The relatively low diagnostic accuracy in the present study, as well as in other previously published studies[10,32], show that there is at present a limited role of anatomical and functional imaging for lymph node staging in patients with prostate cancer. Future studies including more patients are needed to validate our findings.

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References

1. Cai T, Nesi G, Tinacci G, Giubilei G, Gavazzi A, Mondaini N, et al. Clinical importance of lymph node density in predicting outcome of prostate cancer patients. *J Surg Res* 2011; **167:** 267-72. doi: 10.1016/j.jss.2009.05.004
2. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 2014; **65:** 124-37. doi: 10.1016/j.eururo.2013.09.046
3. Heidenreich A, Varga Z, Von Knobloch R. Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. *J Urol* 2002; **167:** 1681-6.
4. Jager GJ, Barentsz JO, Oosterhof GO, Witjes JA, Ruijs SJ. Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR imaging with a three-dimensional TI-weighted magnetization-prepared-rapid gradient-echo sequence. *AJR Am J Roentgenol* 1996; **167:** 1503-7. doi: 10.2214/ajr.167.6.8956585
5. Wang L, Hricak H, Kattan MW, Schwartz LH, Eberhardt SC, Chen HN, et al. Combined endorectal and phased-array MRI in the prediction of pelvic lymph node metastasis in prostate cancer. *AJR Am J Roentgenol* 2006; **186:** 743-8. doi: 10/2214/AJR.04.1682
6. Borley N, Fabrin K, Sriprasad S, Mondaini N, Thompson P, Muir G, et al. Laparoscopic pelvic lymph node dissection allows significantly more accurate staging in "high-risk" prostate cancer compared to MRI or CT. *Scand J Urol Nephrol* 2003; **37:** 382-6. doi: 10.1080/00365590310006309
7. Beer AJ, Eiber M, Souvatzoglou M, Holzapfel K, Ganter C, Weirich G, et al. Restricted water diffusibility as measured by diffusion-weighted MR imaging and choline uptake in (11)C-choline PET/CT are correlated in pelvic lymph nodes in patients with prostate cancer. *Mol Imaging Biol* 2011; **13:** 352-61. doi: 10.1007/s11307-010-0337-6

8. Budiharto T, Joniau S, Lerut E, Van den Bergh L, Mottaghy F, Deroose CM, et al. Prospective evaluation of 11C-choline positron emission tomography/computed tomography and diffusion-weighted magnetic resonance imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases. *Eur Urol* 2011; **60:** 125-30. doi: 10.1016/j.eururo.2011.01.015.

9. Eiber M, Beer AJ, Holzapfel K, Tauber R, Ganter C, Weirich G, et al. Preliminary results for characterization of pelvic lymph nodes in patients with prostate cancer by diffusion-weighted MR-imaging. *Inves Radiol* 2010; **45:** 15-23. doi: 10.1097/RLI.0b013e3181bbdc2f

10. Vag T, Heck MM, Beer AJ, Souvatzoglou M,Weirich G,Holsapfel K, et al. Preoperative lymph node staging in patients with primary prostate cancer: comparison and correlation of quantitative imaging parameters in diffusion-weighted imaging and 11C-choline PET/CT. *Eur Radiology* 2014; **24:** 1821-6. doi: 10.1007/s00330-014-3240-8.

11. von Below C, Daouacher G, Wassberg C, Grzegorek R, Gestblom C, Sörensen J, et al. Validation of 3 T MRI including diffusion-weighted imaging for nodal staging of newly diagnosed intermediate- and high-risk prostate cancer. *Clin Radiol* 2016; **71:** 328-34. doi: 10.1016/j.crad.2015.12.001.

12. Vallini V, Ortori S, Boraschi P, Manassero F, Gabelloni M, Faggioni L, et al. Staging of pelvic lymph nodes in patients with prostate cancer: Usefulness of multiple b value SE-EPI diffusion-weighted imaging on a 3.0 T MR system. *Eur J Radiol Open* 2016; **3:** 16-21. doi: 10.1016/j.ejro.2015.11.004.

13. Beheshti M, Imamovic L, Broinger G, Vali R, Waldenberger P, Stoiber F, et al. 18F choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. *Radiology* 2010; **254:** 925-33. doi: 10.1148/radiol.09090413.

14. Heck MM, Souvatzoglou M, Retz M, Nawroth R, Kübler H, Maurer T, et al. Prospective comparison of computed tomography, diffusion-weighted magnetic resonance imaging and [11C]choline positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer patients. *Eur J Nucl Med Mol I* 2014; **41:** 694-701. doi: 10.1007/s00259-013-2634-1.

15. Contractor K, Challapalli A, Barwick T, Winkler M, Hellawell G, Hazell S, et al. Use of [11C]choline PET-CT as a noninvasive method for detecting pelvic lymph node status from prostate cancer and relationship with choline kinase expression. *Clin Cancer Res* 2011; **17:** 7673-83. doi: 10.1158/1078-0432.CCR-11-2048.

16. Poulsen MH, Bouchelouche K, Hoilund-Carlsen PF, Petersen H, Gerke O, Steffansen SI, et al. [18F]fluoromethylcholine (FCH) positron emission tomography/computed tomography (PET/CT) for lymph node staging of prostate cancer: a prospective study of 210 patients. *BJU Int* 2012; **110:** 1666-71. doi: 10.1111/j.1464-410X.2012.11150.x.

17. Haseebuddin M, Dehdashti F, Siegel BA, Liu J,Roth EB, Nepple KG, et al. 11C-acetate PET/CT before radical prostatectomy: nodal staging and treatment failure prediction. *J Nucl Med* 2013; **54:** 699-706. doi: 10.2967/jnumed.112.111153.

18. Daouacher G, von Below C, Gestblom C, Ahlström H, Grzegorek R, Wassberg C, et al. Laparoscopic extended pelvic lymph node (LN) dissection as validation of the performance of [C]-acetate positron emission tomography/computer tomography in the detection of LN metastasis in intermediate- and high-risk prostate cancer. *BJU Int* 2016; **118:** 77-83. doi: 10.1111/bju.13202.

19. Swinnen JV, Roskams T, Joniau S, Van Poppel H, Oyen R, Baert L, et al. Overexpression of fatty acid synthase is an early and common event in the development of prostate cancer. *Int J Cancer* 2002; **98:** 19-22.

20. Dhanasekaran SM, Barrette TR, Ghosh D, Shah R, Varambally S, Kurachi K, et al. Delineation of prognostic biomarkers in prostate cancer. *Nature* 2001; **412:** 822-6. doi: 10.1038/35090585

21. Vavere AL, Kridel SJ, Wheeler FB, Lewis JS. 1-11C-acetate as a PET radiopharmaceutical for imaging fatty acid synthase expression in prostate cancer. *J Nucl Med* 2008; **49:** 327-34. doi: 10.2967/jnumed.107.046672

22. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology* 1988; **168:** 497-505. doi: 10.1148/radiology.168.2.3393671

23. Sato C, Naganawa S, Nakamura T, Kumada H, Miura S, Takizawa O, et al. Differentiation of noncancerous tissue and cancer lesions by apparent diffusion coefficient values in transition and peripheral zones of the prostate. *J Magn Reson Imaging* 2005; **21:** 258-62. doi: 10.1002/jmri.20251

24. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, and Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. *J Magn Reson Imaging* 2007; **25:** 146-52. doi: 10.1161/01.ATV.0000251615.61858.33

25. Verma S, and Rajesh A. A clinically relevant approach to imaging prostate cancer: review. *AJR Am Journal Roentgenol* 2011; **196:** S1-10 Quiz S11-14. doi: 10.2214/AJR.09.7196

26. D'Amico AV, Schultz D, Loffredo M, Dugal R, Hurwitz M, Kaplan I, et al. Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for clinically localized prostate cancer. *JAMA* 2000; **284:** 1280-3.

27. Briganti A, Gallina A, Suardi N, Chun FK, Walz J, Heuer R, et al. A nomogram is more accurate than a regression tree in predicting lymph node invasion in prostate cancer. *BJU Int* 2008; **101:** 556-60. doi: 10.1111/j.1464-410X.2007.07321.x

28. Polanec SH, Andrzejewski P, Baltzer PAT, Helbich TH, Stiglbauer A, Georg D, et al. Multiparametric [11C]Acetate positron emission tomography-magnetic resonance imaging in the assessment and staging of prostate cancer. *PLoS One* 2017; **12:** e0180790. doi: 10.1371/journal.pone.0180790

29. Park SY, Oh YT, Jung DC, Cho NH, Choi YD, Rha KH. Prediction of micrometastasis (< 1 cm) to pelvic lymph nodes in prostate cancer: Role of preoperative MRI. *AJR Am J Rroentgenol* 2015; **205:** W328-34. doi: 10.2214/AJR.14.14138

30. Batra V, Gautam G, Jaipuria J, Suryavanshi M, Khera R, Ahlawat R. Predictive factors for lymph node positivity in patients undergoing extended pelvic lymphadenectomy during robot assisted radical prostatectomy. *Indian J Urol* 2015; **31:** 217-22. doi: 10.4103/0970-1591.156918

31. Herlemann A, Wenter V, Kretschmer A, Thierfelder KM, Bartenstein P, Faber C, et al. 68Ga-PSMA Positron emission tomography/computed tomography provides accurate staging of lymph node regions prior to lymph node dissection in patients with prostate cancer. *Eur Urol* 2016; **70:** 553-7. doi: 10.1016/j.eururo.2015.12.051

32. van Leeuwen PJ, Emmett L, Ho B, Delprado W, Ting F, Nguyen Q, et al. Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. *BJU Int* 2017; **119:** 209-15. doi: 10.1111/bju.13540

33. Uprimny C, Kroiss AS, Decristoforo C, Fritz J, von Guggenberg E, Kendler D, et al. 68Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. *Eur J Nucl Med Mol I* 2017; **44:** 941-9. doi: 10.1007/s00259-017-3631-6

34. Kallehauge JF, Tanderup K, Haack S, Nielsen T, Muren LP, Fokdal L, et al. Apparent Diffusion Coefficient (ADC) as a quantitative parameter in diffusion weighted MR imaging in gynecologic cancer: Dependence on b-values used. *Acta Oncol* 2010; **49:** 1017-22. doi: 10.3109/0284186X.2010.500305

35. Sasaki M, Yamada K, Watanabe Y, Matsui M, Ida M, Fujiwara S, et al. Variability in absolute apparent diffusion coefficient values across different platforms may be substantial: a multivendor, multi-institutional comparison study. *Radiology* 2008; **249:** 624-30. doi: 10.1148/radiol.2492071681

36. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia* 2009; **11:** 102-25.

37. Heesakkers RA, Hövels AM, Jager GJ, van den Bosch HC, Witjes JA, Raat HP, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. *Lancet Oncol* 2008; **9:** 850-6. doi: 10.1016/S1470-2045(08)70203-1

38. Thoeny HC, Froehlich JM, Triantafyllou M, Huesler J, Bains LJ, Vermathen P, et al. Metastases in normal-sized pelvic lymph nodes: detection with diffusion-weighted MR imaging. *Radiology* 2014; **273:** 125-35. doi: 10.1148/radiol.14132921

research article

Electrochemotherapy with bleomycin of different types of cutaneous tumours in a ferret (Mustela putorius furo)

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Background. Mast cell tumour, sebaceous gland adenoma, and less common squamous papilloma are skin tumours in ferrets (*Mustela putorius furo*), and early excisional surgery is usually the treatment of choice. The aim of our study was to investigate the effectiveness of electrochemotherapy (ECT), a new, minimally invasive non-surgical method, as first treatment option of different types of ferret skin tumours located on surgically difficult sites.

Materials and methods. A 5-year-old castrated male ferret with two cutaneous masses, presenting 4 months apart and a 7-year-old spayed female ferret with two cutaneous masses, that appeared simultaneously on two locations are presented. In the first patient, both masses were diagnosed as mast cell tumours, and in the second patient, squamous papilloma and sebaceous adenoma were diagnosed. One session of ECT with bleomycin injected intratumourally was applied in all tumours.

Results. Complete response (CR) of all tumours was obtained, without recurrence during observation period of 15 months after ECT for first tumour and 11 months after ECT of the tumour located on the right hock in first patient, and 8 months after treatment for the second patient.

Conclusions. In present study, ECT with bleomycin proved to be safe and effective against different cutaneous tumours in ferrets. Due of good results, low cost and relatively easy procedure, ECT could be the treatment of choice instead of surgery for the selected skin tumours in ferrets.

Key words: electrochemotherapy; bleomycin; cutaneous tumours, ferret

Introduction

Tumours are common health problem in domestic pet ferrets (*Mustela putorius furo*), most commonly affected are endocrine, integumentary and lymphatic system.[1] Mast cell tumours (MCTs) and sebaceous tumours (sebaceous epitelioma, sebaceous adenoma) are most prevalent tumours of the skin.[2]

Most frequently, MCTs appear on the extremities, following the trunk and head or neck. They are usually small (1–4 mm in diameter), round to plaque-like nodules with surface crusting.[3] In some cases, animals develop local pruritus, and overlying skin may be ulcerated due to self-trauma.[1] In ferrets, MCTs are considered clinically benign and they do not spread locally or metastasize.[1,3] However, there are some suggestions about visceral involvement and malignant behaviour of this tumours.[4]

Sebaceous adenomas are benign tumours, which involve only skin and may occur anywhere on the

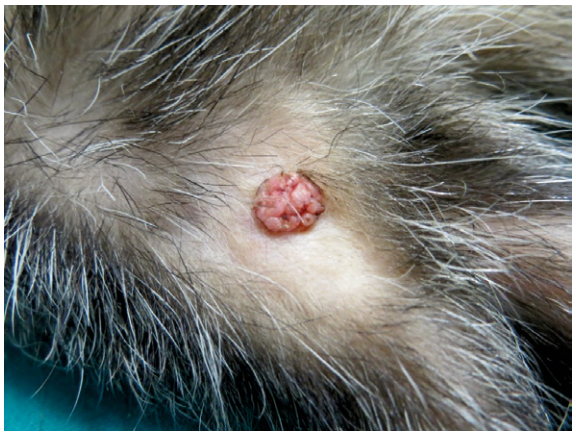

FIGURE 1. Macroscopic presentation of squamous papilloma (Tumour 4).

body. They are firm, warty and often multinodular, sometimes looking very similar to MCTs. They can be ulcerated, irritated and traumatised with local inflammation.[2,4]

Squamous papilloma is very rare skin tumour of ferrets with only one case noted in a study of 1,525 ferret neoplasia's collected in years 1990 to 2000.[5] Although there is some evidence that some squamous cell carcinomas (SCC) of the skin in ferrets can be associated with papillomavirus[6], possible viral aetiology of cutaneous squamous papilloma in ferrets was yet not investigated. Moreover, recent publications suggested that, squamous papilloma of skin and conjunctiva in dogs are not connected with papillomaviruses.[7]

Fine needle aspiration (FNA), incisional or excisional biopsy are recommended to confirm the diagnosis of any cutaneous tumour.[2] Early excisional surgery is the treatment of choice, and wide surgical margins are always advisable.[2,5] However, some tumours are large with invading surrounding tissue on unsuitable sites, which makes the closure of defect after surgery, and consequently preservation of function, difficult. ECT is a new anti-neoplastic therapy in veterinary medicine that combines administration of a chemotherapeutic agent, cisplatin or bleomycin, with electric pulses to the tumour.[8]

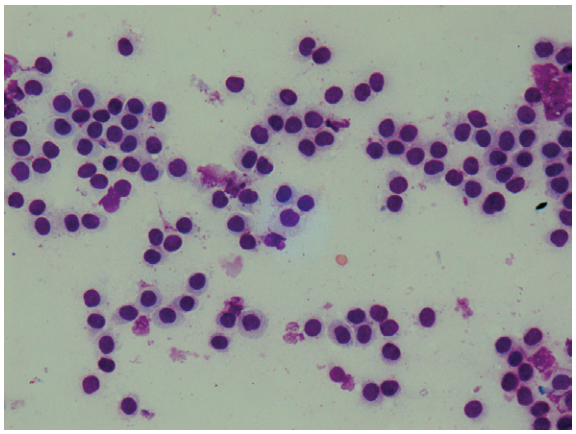

FIGURE 2. Cytological presentation of mast cell tumours (Tumour 2). Hemacolor, 400 x.

The aim of our study was to investigate the effectiveness of electrochemotherapy (ECT), as a new, minimally invasive non-surgical method, for treatment of different types of ferret skin tumours located on surgically difficult sites.

Materials and methods

Patients

First patient was a 5-year-old castrated male ferret with two cutaneous masses presented 4 months apart. First mass (0.8 cm x 0.8 cm x 0.5 cm) was located on the laterodorsal tail base (tumour 1), while the second one (1.2 cm x 1.0 cm 0.7 cm) was found on the lateral side of the right hock (tumour 2). The ferret had no major health issues since the initial presentation, and masses apparently did not produce any health problems or discomfort. Regular health checks and vaccinations were carried out every year.

Second patient was a 7-year-old spayed female ferret with two cutaneous masses that appeared simultaneously on two locations. First mass (0.7 cm x 0.7 cm x 0.5 cm) was located on the lateral side of the left hock (tumour 3) (Figure 1), while the location of the second mass (0.4 cm x 0.4 cm x 0.2 cm) was dorsolateral on the left chest region (tumour 4). Before the initial presentation, the ferret had a history of insulinoma managed with diet, corticosteroids and regular glucose measurements. On physical examination, both patients were alert, bright and responsive with body masses of 1700 g and 430 g respectively. Incisional biopsies of tumours 1, 3 and 4, and FNA of tumour 2 were obtained under general gaseous anaesthesia, and histopathology and cytology were done. Briefly, samples for histopathology were fixed in 10% buffered formaline and routinely embedded in paraffin. Four-μm-thick sections were stained with hematoxylin and eosin and examined microscopically. Cytological smears were stained with Hemacolor (Merck®, Darmstadt, Germany).

Histopathological examination of the tumour 1 presented as nonencapsulated, slightly infiltrative

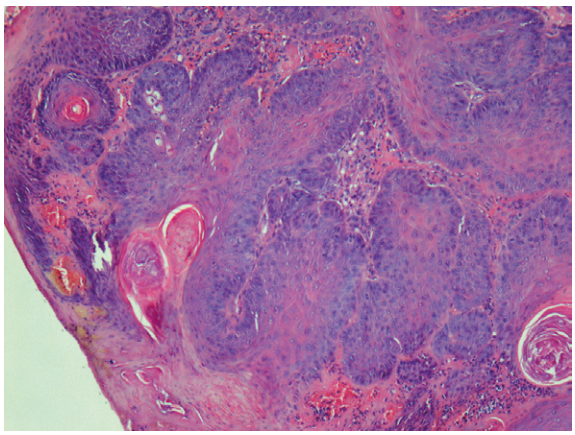

FIGURE 3. Histological presentation of squamous papilloma (Tumour 4). Hematoxylin and eosin stain, 100 x.

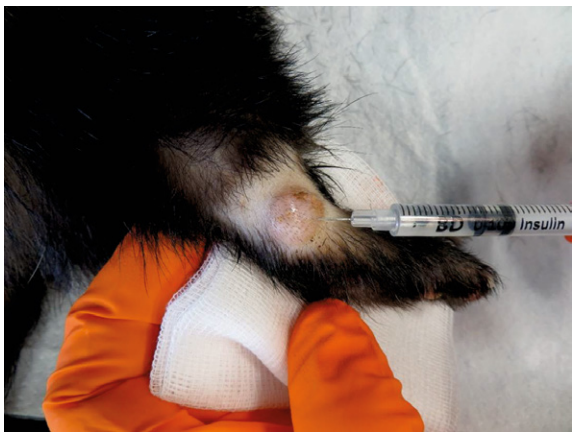

FIGURE 4. Intralessional injection of bleomycin into mast cell tumour (Tumour 2) located laterally on the right hock. Note the size of tumor and surgicaly chalenging anatomical location.

tumour composed of round cells that exhibited mild anisocytosis. Neoplastic cells had a moderate amount of pale blue cytoplasm and round nuclei that exhibited mild anisokaryosis. Additional Toluidine blue staining revealed numerous cytoplasmic metachromatic granules. Mitotic figures were rare.

Cytological samples of the tumour 2 (Figure 2) contained moderate number of the neoplastic cells with the morphology similar to neoplastic cells in the tumour 1. Single eosinophils were scattered between neoplastic cells.

Histopathology of tumour 3 (Figure 3) exhibited epithelial tumour that formed papillary projections supported by a fine to moderate fibrovascular core. Papillary projections were covered with well-differentiated squamous epithelial cells. Changes characteristic for papilloma, such as enlarged keratohyalin granules, koilocytes and intranuclear inclusions, were not present. Mitotic figures were 6 per 10 high power fields (HPF). The stroma was diffusely moderately infiltrated with neutrophils.

Histopathology of tumour 4 exhibited lobular tumour that consisted predominantly of cells with sebaceous differentiation (sebocytes) and peripheral layer of basaloid reserve cells. Sebocytes were round to oval, exhibited moderate anisocytosis and had finely vacuolated cytoplasm. Basaloid reserve cells were cuboid and had a small amount of basophilic cytoplasm, and round to oval nuclei. Mitotic figures were rare, 3 per 10 HPF, and confined to basaloid reserve cells.

In the first patient, both masses were diagnosed as MCTs, and in the second patient, squamous papilloma of hock region and sebaceous adenoma of chest region were diagnosed. Haematology, serum biochemistry, total body radiographs, and abdominal ultrasound were performed for staging. Whole body radiographs and abdominal ultrasound investigations showed no evidence of health problems or distant metastasis. In the first patient, the haematology showed no abnormal findings, most of serum biochemistry values were within reference range; only urea nitrogen (12.4 mmol/L; reference 3.93–8.93 mmol/L^{9}) and creatinine (128 umol/L; reference 26.52–70.72 μmol/L^{9}) were elevated suggesting early kidney disease. Also in the second patient, haematology results showed no abnormal findings; however, serum biochemistry showed elevated aspartate aminotransferase (248 U/L; reference 78–140 U/L^{9}) and decreased values of glucose (2.8 mmol/L; reference 5.5–7.5 mmol/L^{9}), most probably due to insulinoma and chronic gastroenteritis. The treatment possibilities, including surgery, were discussed with the owner. Due to unsuitable locations for surgical treatment and contemporary morbidities, ECT was selected as the minimally invasive treatment option. The owners were thoroughly informed about the procedure and its possible side effects and signed informed consent for application of electrochemotherapy.

Electrochemotherapy

For the ECT, patients were anesthetised using isoflurane and 0.5 mg ~ volume of 0.1 ml of bleomycin (3 mg/ml) was injected intratumourally using 29 gauge needle (Figure 4, 5). After 1–2 minutes, eight electric pulses of 100 μs duration with amplitude to electrode distance ratio of 1300 V/cm and frequency of 5 kHz were delivered using plate

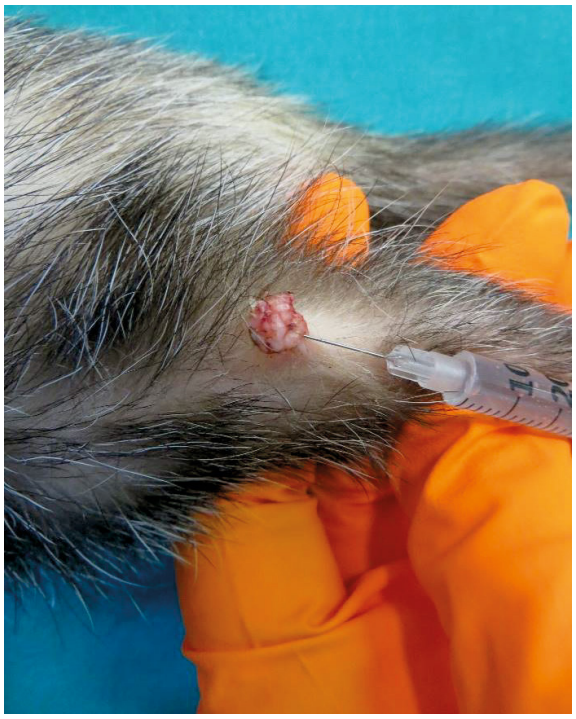

FIGURE 5. Intralessional injection of bleomycin into squamous papilloma (Tumour 4).

FIGURE 6. Electric pulses were delivered to the mast cell tumour (Tumour 2) using plate electordes.

electrodes (distance between the electrodes: 6 mm) (Figures 6,7). Good contact between the electrodes and tumour mass was obtained by application of conductive gel to the treatment area. Electric pulses were generated by the electric pulse generator (Cliniporator™ - IGEA srl, Carpi [MO], Italy). The entire tumour was exposed to electric pulses by moving the electrodes perpendicular through the whole volume of mass and the surrounding skin, starting on the tumour periphery. The duration of each ECT cycle was approximately 15 minutes, and in both cases, the recovery from anaesthesia was uneventful. Meloxicam (Loxicom; Norbrook Laboratories) in a dose 0.2 mg/kg/day[9] was prescribed for 3 consecutive days orally after every cycle of ECT to reduce pain and inflammation.

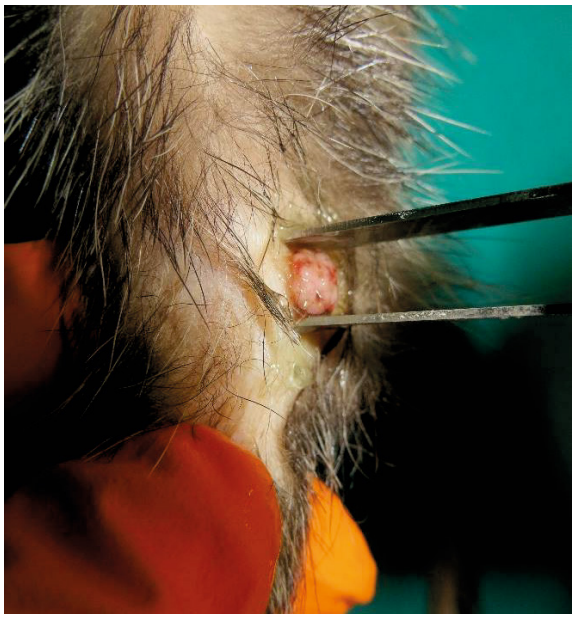

FIGURE 7. Electric pulses were delivered to the squamous papilloma (Tumour 4) using plate electordes.

Evaluation of response

After the treatment, the patients were examined at regular intervals, depending on the owner's visit of clinic, to evaluate the treatment response. At each visit, the treated tumours were examined and photographed. In the meantime, the owner observed the treated area and reported the progress.

Results

No local or/and systemic side effects were noted during or after ECT. During ECT, some muscle contractions of the patients were observed after the application of each train of electric pulses. The contractions were mild, disappearing after the end of each train of electric pulses. All tumours became necrotic and regressed. In the first patient,

FIGURE 8. Necrosis with superficial scab of squamous papilloma (Tumour 4) 8 days after electrochemotherapy.

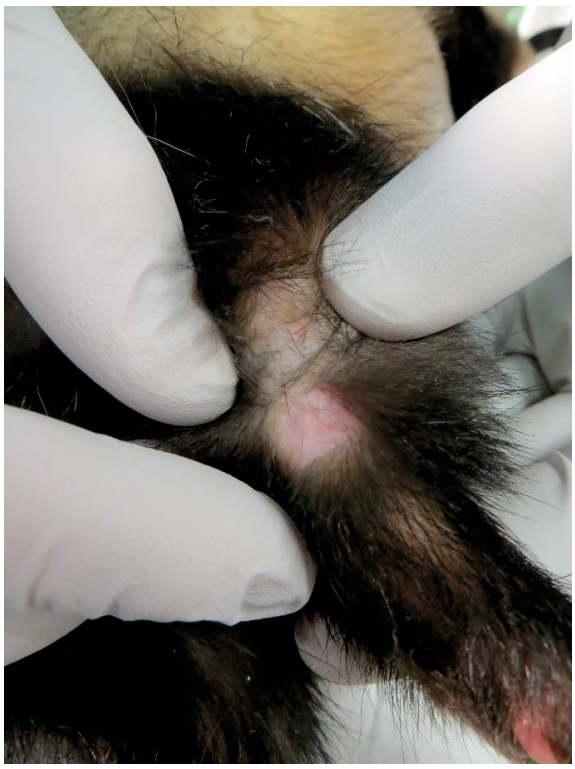

FIGURE 9. Complete response of mast cell tumour (Tumour 2) - 67 days after electrochemotherapy.

the MCT located on the laterodorsal tail base became necrotic on day 6 and a complete response (CR) was seen approximately 1 month after ECT, while the second MCT found on the lateral side of the right hock became necrotic on day 15 and CR was seen approximately two months (67 days) after ECT (Figure 9). In second patient, both tumours became necrotic on day 8 (Figure 8) and CRs were seen 70 days after ECT (Figure 10). In first patient, no tumour growth has been seen during the observation period of 15 months after ECT of the tumour located on the tail base, and 11 months after ECT of the tumour located on the right hock. In second patient, no tumour recurrence was detected 8 months after treatment.

Discussion

ECT with bleomycin as a single treatment was an effective treatment of cutaneous neoplasms; MCTs, sebaceous adenoma, and squamous papilloma in our cases. ECT was well tolerated by the patients and is a minimally invasive procedure with no major side effects noted, with excellent responses and long-lasting CR. In first patient, no tumour growth was seen during observation period of 15 months after ECT of the tumour located on the tail base, and 11 months after ECT of the tumour located on the right hock. In second patient, no tumour regrowth was seen 8 months after treatment. Different studies reported an excellent treatment response of ECT with cisplatin or bleomycin in tumours of different histology with minimal side effects in dogs[10,11], cats[12], horses[13], pet rats[14], and reptiles[15,16]. In our cases, only some muscle contractions of the patient were observed during the application of electric pulses. The contractions were mild, disappearing after the end of each train of electric pulses. In animals, pain during ECT can be avoided using sedation and/or general anaesthesia.[10-16] Gaseous anaesthesia with isoflurane was used in our cases to prevent pain and facilitate proper position of patients for tumour manipulation, the application of chemotherapeutic agent, and positioning of electrodes. Meloxicam, a nonsteroidal anti-inflammatory analgesic was prescribed to the patients before and after ECT to reduce pain and inflammation.[9] According to the literature, surgery with wide margins is advised as the first treatment option for benign skin tumours in ferrets[2,5], but this therapeutic option is not always applicable due to anatomical locations. In author's experience, some skin tumours could be quite large and located on toe, hock or footpad. Thus, aggressive surgery could result in loss of physiological function of a body part and a non-favourable cosmetic effect of therapy. In both ferrets, the tumour locations were not optimally positioned for surgery, and complications could arise with the skin defect too big for adequate closure. In that context, new therapies like ECT are highly beneficial, because of good an-

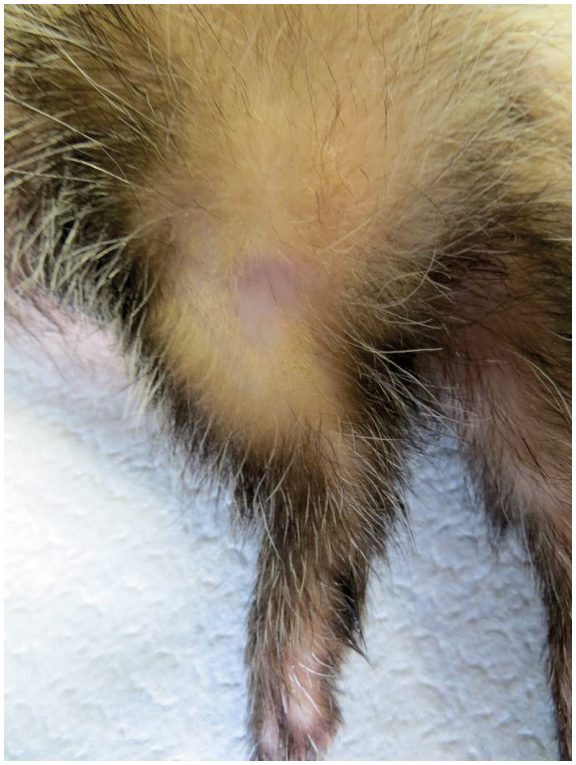

FIGURE 10. Complete response of squamous papilloma (Tumour 4) - 70 days after electrochemotherapy.

ti-tumour effectiveness, combined with excellent functional and cosmetic effects, while being less invasive than surgery.[8,10,11,12]

Neoplastic diseases are commonly seen in ferrets, and medical treatment of tumours with chemotherapy is well reported.[1,17,18] Different chemotherapeutic agents are used in ferret oncology, including bleomycin.[17,19] Bleomycin is an antitumour antibiotic commonly used in human and veterinary medicine. In exotic pets, bleomycin was used intralesionally in the treatment of SCC in a greater hedgehog tenrec (*Setifer setosus*) and in a blue fronted amazon parrot (*Amazona aestiva*) for xanthoma, respectively.[17] Recently, ECT with bleomycin was reported in a yellow bellied slider (*Trachemys scripta scripta*) and in a green sea turtle (*Chelonia mydas*) for the treatment of SCC and fibropapilloma with excellent therapeutic outcome and minimal side effects.[15,16,17] In ferret oncology, the data about this chemotherapeutic agent are scarce; however, bleomycin was used in the therapy of metastatic SCC in one animal at a dosage of 10–20 U/m^2 once a week, injected subcutaneously with moderate antitumour effectiveness.[19] In our patients, ECT using bleomycin did not induce any clinically evident systemic side effects; only mild, local tumour necrosis as a consequence of successful treatment was seen in the week following the treatment in both cases without notable effect on the patient's condition. The superficial scab developed after necrosis; it fell off within few weeks after therapy.

The drawback of our study is that it presents the ECT treatment effectiveness on only two patients. For broader acceptance of ECT in treatment of tumours in ferrets larger cohort of patients and higher number of tumours is needed. Though this study as the first provides evidence of safety and effectiveness of ECT in this specific animal species.

In conclusion, ECT with bleomycin proved to be safe and effective against cutaneous MCTs, squamous papilloma, and sebaceous gland adenoma in ferrets. Because of good effectiveness, low cost, and a relatively easy procedure ECT could represent a good treatment of choice instead of surgery for selected skin tumours in ferrets.

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References

1. Schoemaker NJ. Ferret oncology. Diseases, diagnostic, and therapeutics. In: Guzman DSM, editor. *Veterinary Clinics of North America: exotic animal practice. Exotic animal oncology.* Philadelphia: Elsevier; 2017. p. 183-208. doi: 10.1016/j.cvex.2016.07.004
2. Marini RP. Skin tumours. In: Mayer J, Donnelley TM, editors. *Clinical veterinary advisor. Birds and exotic pets*. St. Louis: Elsevier; 2013. p. 495-6.
3. Vilalta L, Meléndez-Lazo A, Doria G, Ramis A, Solano-Gallego L, Pastor J, et al. Clinical, cytological, histological and imunohistochemical features of cutaneous mast cell tumours in ferrets (*Mustela putroius furo*). *J Comp Path* 2016; **155:** 346-55. doi: 10.1016/j.jcpa.2016.07.012
4. Orcutt C. Dermatologic diseases. In: Quesenberry KE, Carpenter JW, editors. *Ferrets, rabbits and rodents. Clinical medicine and surgery*. 2nd edition. St. Louis: Saunders; 2004. p. 107-114.
5. Williams B. Neoplasia. In: Quesenberry KE, Carpenter JW, editors. *Ferrets, rabbits and rodents. Clinical medicine and surgery*. 2nd edition. St. Louis: Saunders; 2004. p. 91-106.
6. Rodrigues A, Gates L, Payne HR, Kiupel M, Mansell J. Multicentric squamous cell carcinoma in situ associated with papillomavirus in a ferret. *Vet Path* 2010; **47:** 964-8. doi: 10.1177/0300985810369899
7. Beckwith-Cohen B, Teixeira LBC, Ramos-Vara JA, Dubielzig RR. Squamous papillomas of the conjunctiva in dogs: a condition not associated with papilomavirus infection. *Vet Path* 2015; **52:** 676-80. doi: 10.1177/0300985814556185

8. Cemazar M, Tamzali Y, Sersa G, Tozon N, Mir LM, Miklavcic D, et al. Electrochemotherapy in veterinary oncology. *J Vet Intern Med* 2008; **22:** 826-31. doi: 10.1111/j.1939-1676.2008.0117.x

9. Johnson-Delaney CA. *Ferret medicine and surgery*. Washington: CRC Press; 2017.

10. Tozon N, Kodre V, Sersa G, Cemazar M. Effective treatment of perianal tumors in dogs with electrochemotherapy. *Anticancer Res* 2005; **25:** 839-46.

11. Tozon N, Sersa G, Cemazar M. Electrochemotherapy: potentiation of local antitumor effectiveness of cisplatin in dogs and cats. *Anticancer Res* 2001; **21:** 2483-6.

12. Tozon N, Pavlin D, Sersa G, Dolinsek T, Cemazar M. Electrochemotherapy with intravenous bleomycin injection: an observational study in superficial squamous cell carcinoma in cats. *J Fel Med Surg* 2014; **16:** 291-9. doi: 10.1177/1098612X13507071

13. Tozon N, Kramaric P, Kadunc Kos P, Sersa G, Cemazar M. Electrochemotherapy as a single or adjuvant treatment to surgery of cutaneous sarcoid tumours in horses: a 31-case retrospective study. *Vet Rec* 2016; **179:** 627. doi: 10.1136/vr.103867

14. Lanza A, Pettorali M, Baldi A, Spugnini EP. Surgery and electrochemotherapy treatment of incompletely excised mammary carcinoma in two male pet rats (*Rattus norvegicus*). *J Vet Med Sci* 2017; **79:** 623-5. doi: 10.1292/jvms.16-0578

15. Bruner CHM, Dutra G, Silva CB, Silviera GML, Martins MFM. Electrochemotherapy for the treatment of fibropapillomas in *Chelonia mydas*. *J of Zoo Wildl Med* 2014; **45:** 213-8.

16. Lanza A, Baldi A, Spugnini EP. Surgery and electrochemotherapy for the treatment of cutaneous squamous cell carcinoma in a yellow-bellied slider (*Trachemys scripta scripta*). *J Am Vet Med Assoc* 2015; **246:** 455-7. doi: 10.2460/javma.246.4.455

17. Harrison TM, Kitchel BE. Principles and aplications of medical oncology in exotic animals. In: Guzman DSM, editor. *Veterinary clinics of North America: exotic animal practice. Exotic animal oncology*. Philadelphia: Elsevier; 2017. p. 209-34. doi: 10.1016/j.cvex.2016.07.007

18. Mayer J, Robat C. Lymphoma. In: Mayer J, Donelley TM, editors. *Clinical veterinary advisor. Birds and exotic pets*. St. Louis: Elsevier; 2013. p. 471-5.

19. Hamilton TA, Morrison WB. Bleomycin chemotherapy for metastatic squamous cell carcinoma in a ferret. *J Am Vet Med Assoc* 1991; **198:** 107-8.

research article

The influence of genetic variability on the risk of developing malignant mesothelioma

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Background. Malignant mesothelioma is a rare cancer with poor outcome, associated with asbestos exposure. Reactive oxygen species may play an important role in the mechanism of carcinogenesis; therefore, genetic variability in antioxidative defence may modify an individual's susceptibility to this cancer. This study investigated the influence of functional polymorphisms of *NQO1, CAT, SOD2* and *hOGG1* genes, gene-gene interactions and gene-environment interactions on malignant mesothelioma risk.

Patients and methods. In total, 150 cases with malignant mesothelioma and 122 controls with no asbestos-related disease were genotyped for *NQO1, CAT, SOD2* and *hOGG1* polymorphisms.

Results. The risk of malignant mesothelioma increased with smoking, odds ratio (OR) 9.30 [95% confidence interval (CI): 4.83–17.98] and slightly with age, OR 1.10 (95% CI: 1.08–1.14). Medium and high asbestos exposures represented 7-times higher risk of malignant mesothelioma compared to low exposure, OR 7.05 (95% CI 3.59–13.83). *NQO1* rs1800566 was significantly associated with increased malignant mesothelioma risk, OR 1.73 (95% CI 1.02–2.96). Although there was no independent association between either *CAT* rs1001179 or *hOGG1* rs1052133 polymorphism and malignant mesothelioma, interaction between both polymorphisms showed a protective effect, OR_{int} 0.27 (95% CI 0.10–0.77).

Conclusions. Our findings suggest a role of both genetic variability in antioxidative defence and repair as well as the impact of gene-gene interactions in the development of malignant mesothelioma. The results of this study could add to our understanding of pathogenesis of malignant mesothelioma and contribute to prevention and earlier diagnosis of this aggressive cancer.

Key words: antioxidative enzymes; genetic polymorphism; malignant mesothelioma

Introduction

Malignant mesothelioma (MM) is a rare and aggressive disease with poor survival. It has been associated with occupational and/or environmental exposure to asbestos in more than 86% of patients with this disease.[1,2] Malignant mesothelioma most commonly arises from pleura (65%–70%), peritoneum (30%) and very rarely other serous surfaces (1%).[3,4] Global incidence is expected to peak 30 to 40 years after the peak of asbestos usage that occurred in the 1960s and 1970s.[3,5] However, recent studies still show a rise in incidence.[6]

The implication of asbestos exposure in MM has been validated, but the mechanism of carcinogenesis is not yet completely understood. Asbestos fibre components, specifically iron, are hypothesized to contribute to reactive oxygen species (ROS) production. Iron catalyses both Fenton and Haber-Weiss reactions which produce hydroxyl radical (HO) from peroxide (H_2O_2).[7] Furthermore, all types of asbestos may cause frustrated phagocytosis in

the macrofages, which produces ROS, reactive nitrogen species (RNS), cytokines, chemokines, proteases and growth factors.[8,9] This may lead to DNA damage, genomic instability and a malignant transformation of mesothelial cells.[9] A number of studies show that ROS and RNS and inflammation could have a central role in asbestos fibre toxicity.[10-13]

On the other hand, antioxidative enzymes such as catalase (CAT), superoxide dismutases (SOD-s), and NAD(P)H quinone dehydrogenase 1 (NQO1) participate in the enzymatic defence against ROS and RNS.[10] When the activity of these enzymes is decreased or changed, ROS concentrations increase and DNA damage may occur. One of the most important repair enzymes for oxidative DNA damage repair is human 8-oxoguanine glycosylase 1 (hOGG1). Functional polymorphisms that influence the expression level or activity have been reported in the genes coding for all these enzymes. CAT helps to maintain the oxidative balance by catalysing H_2O_2 to H_2O and O_2.[14,15] Numerous polymorphisms of *CAT* gene (*CAT*) have been described, rs1001179 being the most commonly studied one. It causes cytosine (C) to thymine (T) change at position -262 in the promoter region (c.262C>T).[14] Our previous study investigating the association of this polymorphism with asbestosis found a slight increase in the risk of the TT genotype.[16] Superoxide dismutases (SOD) convert superoxide into H_2O_2 and O_2. SOD2 is found in mitochondria, where the amount of ROS is very high. The most common polymorphism is rs4880, resulting in C to T substitution at position 201 (c.201C>T), which causes the change of alanine to valine at position 16 (p.Ala16Val). Several studies associate the 6q25 chromosome deletion with certain forms of cancer, which is why some authors consider *SOD2* to be a tumour suppressor gene.[17,18] HOGG1 catalyses the repair of 8-oxoguanine that may result from ROS damage to the DNA. Functional polymorphisms of the *hOGG* gene may impact DNA repair. In rs1052133 polymorphism, C replaces G in exon 7, causing the substitution of serine with cysteine in codon 326 (p.Ser326Cys). Although a changed structure of the polymorphic enzyme has not been proved, several studies have shown the association between *hOGG1* Ser326Cys polymorphism and lung cancer risk.[19,20] NQO1 catalyses the reduction of quinones to hydroquinones, preventing the formation of free radicals. The most frequently studied single nucleotide polymorphism (SNP), rs1800566, results in C to T change (c.609C>T), which causes proline to serine substitution (p.Pro187Ser).[21] Some studies found this polymorphism to be associated with an increased risk of several malignant diseases: lung cancer, colorectal cancer, breast cancer and bladder cancer.[22,23]

Only few studies have investigated the interplay between asbestos exposure and genetic variability in antioxidant defence system in MM so far.[24-26] Nevertheless, the interaction between asbestos exposure and genetic susceptibility due to genetic polymorphism of antioxidant enzymes has been shown for asbestosis.[27] We have previously described the association between *SOD2* Ala/Ala genotype and asbestosis[28] as well as association between *CAT* -262 TT genotype and asbestosis.[16] Landi *et al.* reported on the association between SOD2 and the risk of MM[25], but according to our knowledge and available literature, the impact of *NQO1*, *CAT* and *hOGG1* polymorphisms on the risk of developing MM has not been studied so far.

This study aimed to investigate whether functional polymorphisms in *NQO1*, *CAT, SOD2* and *hOGG1* genes influence the risk of MM, to investigate the interactions between genetic variability in antioxidative and DNA repair mechanisms and to investigate the interactions between asbestos exposure and the investigated polymorphisms in MM patients.

Patients and methods

Patients

The study included 159 MM patients (cases), treated at the Institute of Oncology Ljubljana between March 2007 and January 2013, along with 122 controls, who were occupationally exposed to asbestos in the asbestos cement manufacturing plant of Salonit Anhovo, Slovenia, but did not develop any disease associated with asbestos exposure. All patients and controls were from Central European Caucasian (Slovenian) population. The study was approved by the Slovenian Ethics Committee for Research in Medicine and was carried out according to the Helsinki Declaration. The subjects were included in the study after providing a written informed consent.

Methods

The diagnosis of MM was made by means of thoracoscopy or video-assisted thoracoscopic surgery (VATS) in patients with pleural MM and by means of laparoscopy or laparotomy in peritoneal MM. The diagnosis was confirmed histopathologically by an experienced pathologist.[2]

TABLE 1. Clinical characteristics of MM patients and controls

	Controls (n = 122)	MM patients (n = 159)	Test	p
Gender N (%)				
Male	88 (72.1)	123 (77.4)		
Female	34 (27.9)	36 (22.6)	$\chi^2 = 1.008$	0.315
Age (years), median (range)	54 (48–60.3)	65 (57–72)	U = 4392.000	< 0.001
No. of smokers[1] (%)	13 (10.7)	80 (52.6)	$\chi^2 = 53.185$	< 0.001
Asbestos exposure[2] N (%)				
No	0 (0.0)	25 (16.6)		
Yes	122 (100.0)	126 (83.4)		
Asbestos exposure[3] N (%)				
Low	96 (78.7)	22 (34.4)	$\chi^2 = 35.941$	< 0.001
Medium	11 (9.0)	21 (32.8)		
High	15 (12.3)	21 (32.8)		
Asbestos exposure[3] N (%)				
Low	96 (78.7)	22 (34.4)	$\chi^2 = 35.541$	< 0.001
Medium and high	26 (21.3)	42 (65.6)		

MM = Malignant mesothelioma
[1] data missing for 7 MM patients; [2] data missing for 8 MM patients; [3] data available for all controls and 64 MM patients

The diagnosis of "no asbestos related disease" in the control group was confirmed by the experts of the Board for Recognition of Occupational Asbestos Diseases at the Clinical Institute of Occupational Medicine, which consisted of an occupational physician, pulmonologist and radiologist, as previously described.[16]

A personal interview with each of the subjects was conducted to get the data about smoking using a standardized questionnaire.[29] To determine asbestos exposure, a semiquantative method was used. For all the controls, data on cumulative asbestos exposure in fibres/cm^3-years were available from the previous study.[29] Data on cumulative asbestos exposure were also available for 27 MM patients. Based on these data, we divided the subjects into three groups: low (< 11 fibres/cm^3-years), medium (11–20 fibres/cm^3-years) and high (> 20 fibres/cm^3-years) asbestos exposure. For the rest of the patients with MM, a thorough work history was obtained and where enough information was available, their exposures were compared with those from the group of patients with known cumulative asbestos exposure and were correspondingly divided into three groups with presumed low, medium and high asbestos exposures.[2] Thus, 37 MM patients were assigned to one of these three groups, but for 95 MM patients epidemiological data were not sufficient to allow the assignment of patients to one of the groups; consequently, they were only categorized as exposed or non-exposed. The influence of asbestos exposure on MM risk was determined in the subgroup of patients where the asbestos exposure was known or could be assessed.

DNA of the MM patients and some controls without asbestos related diseases was available from our previous studies[2,30], DNA of the rest of the controls was isolated from peripheral venous blood samples using FlexiGene DNA kit (Qiagen, Hilden, Germany).

Real-time polymerase chain reaction (PCR) based TaqMan assays were used for the analysis of *NQO1* rs1800566, *CAT* rs1001179, *SOD2* rs4880 and *hOGG1* rs1052133 polymorphisms as recommended by the manufacturer (Thermo Fisher Scientific, SNP genotyping assay C_2091255_30, C_11468118_10, C_8709053_10 and C_3095552_1_, respectively). Genotyping was performed blinded regarding the study endpoints and repeated in 20% of samples to check for genotyping accuracy and all the genotypes were concordant. Amplification was not successful in 11 subjects for *NQO1*, in 2 for *CAT*, in 6 for *SOD2* and in 7 subjects for *hOGG1* polymorphism.

Statistical methods

Standard descriptive statistics were first performed. Next, *t*-tests for differences of means of variables between the cases and controls were calculated, and Mann-Whitney (U) test was performed. The dominant genetic model was used for all the comparisons. To analyse the association between genotypes, cumulative asbestos exposure, and standard confounders (age, sex) and MM, univariate logistic regression was first used, followed by multivariate logistic regression modelling. A possible synergistic effect between genotypes and

TABLE 2. The distribution of antioxidative and repair gene polymorphisms in MM patients and controls and risk of MM

Polymorphism	Genotype	MM patients	Controls	Unadjusted risk		Adjusted by age		Adjusted by smoking		Adjusted by asbestos exposure	
		N (%)	N (%)	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
NQO1 rs1800566[1]	CC CT TT	98 (62.0) 57 (36.1) 3 (1.9)	82 (73.9) 27 (24.3) 2 (1.8)	**1.73 (1.02–2.96)**	**0.043**	1.63 (0.91–2.95)	0.103	**1.88 (1.04–3.41)**	**0.037**	1.72 (0.83–3.57)	0.124
CAT rs1001179	CC CT TT	79 (50.0) 64 (40.5) 15 (9.5)	70 (57.4) 47 (38.5) 5 (4.1)	1.35 (0.84–2.17)	0.220	1.21 (0.71–2.05)	0.484	1.47 (0.86–2.51)	0.159	1.45 (0.73–2.88)	0.288
SOD2 rs4880[2]	CC CT TT	44 (27.7) 81 (50.9) 31 (19.5)	31 (25.8) 52 (43.3) 37 (30.8)	0.89 (0.52–1.52)	0.661	0.76 (0.41–1.39)	0.371	0.95 (0.52–1.73)	0.857	0.81 (0.38–1.73)	0.578
hOGG1 rs1052133[3]	CC CG GG	99 (62.3) 52 (32.7) 6 (3.8)	82 (70.1) 32 (27.4) 3 (2.6)	1.37 (0.82–2.29)	0.225	1.42 (0.80–0.51)	0.232	1.36 (0.77–2.41)	0.286	1.77 (0.85–3.66)	0.125

CAT = catalase; *hOGG1* = human 8-oxoguanine glycosylase 1; MM = Malignant mesothelioma; *NQO1* = NAD(P)H quinone dehydrogenase 1; OR = odds ratio; *SOD2* = superoxide dismutase
For determining MM risk, carriers of at least one polymorphic allele were compared to non-carriers.
[1]missing data for 10 patients; [2]missing data for 2 patients; [3]mising data for 4 patients

cumulative asbestos exposure was investigated by using dummy variables. *P*-values less than 0.05 were considered as statistically significant.

Results

The clinical characteristics of MM patients and controls are presented in Table 1. There was no statistical difference in gender between the cases and controls (p = 0.315), but MM patients were notably older (p < 0.001) and a much higher number of the patients were smokers (p < 0.001). All the controls (122) and 126 (83.4%) MM patients had been exposed to asbestos. For all the controls and 64 (50.8%) MM patients, asbestos exposure could be categorized into the groups. Among the subjects with known asbestos exposure, the MM patients had a significantly higher asbestos exposure compared to asbestos exposed subjects without any asbestos related disease (p < 0.001, Table 1).

Univariate regression logistic analysis has shown that the risk of MM was influenced by smoking, age and asbestos exposure, but not by gender. The risk of MM was increased in smokers (OR = 9.30; 95% CI = 4.83–17.98; p < 0.001) and older patients (OR = 1.10; 95% CI = 1.08–1.14; p < 0.001). Compared to a low exposure to asbestos, medium and high asbestos exposures increased the risk of MM 7-fold (OR = 7.05; 95% CI = 3.59–13.83; p < 0.001). Gender did not influence MM risk (OR = 0.76; 95% CI = 0.44–1.30; p = 0.316).

Genotype frequencies for controls and MM patients are presented in Table 2. Minor allele frequencies were 13.9% for *NQO1* rs1800566, 22.4% for *CAT* rs1001179, 52.5% for *SOD2* rs4880 and 18.8% for *hOGG1* rs1052133. In controls, all SNPs were in Hardy-Weinberg equilibrium (all p > 0.05). The association between MM and the investigated polymorphisms was tested with univariate logistic regression using a dominant genetic model. The carriers of at least one polymorphic *NQO1* allele

TABLE 3. Gene-gene interactions between rs1800566 NAD(P)H quinone dehydrogenase 1 (*NQO1*), rs1001179 catalase (*CAT*), rs4880 superoxide dismutase 2 (*SOD2*), and rs1052133 human 8-oxoguanine glycosylase 1 (*hOGG1*)

Gene 1			Gene 2			Interaction	
Genotypes	**OR (95% CI)**	**p**	**Genotypes**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
***NQO1* rs1800566** CT+TT *vs*.CC	**1.73 (1.02–2.96)**	**0.043**	***hOGG1* rs1052133** CG+GG *vs*.CC	1.37 (0.82–2.29)	0.225	1.22 (0.36–4.13)	0.75
***CAT* rs1001179** CT+TT *vs*.CC	1.35 (0.84-2.17)	0.220	***hOGG1* rs1052133** CG+GG *vs*.CC	1.37 (0.82–2.29)	0.225	**0.27 (0.10–0.77)**	**0.014**
***SOD2* rs4880** CT+TT *vs*.CC	0.89 (0.52–1.52)	0.661	***hOGG1* rs1052133** CG+GG *vs*.CC	1.37 (0.82–2.29)	0.225	0.78 (0.25–2.43)	0.669

OR = odds ratio

(CT and TT genotypes) had an increased risk of MM compared to those with CC genotype (OR = 1.73; 95% CI = 1.02–2.96; p = 0.043). No association was observed between MM and other genetic polymorphisms (Table 2).

Multivariate analysis was used to determine the combined effect of genetic determinants and clinical variables such as smoking, age and asbestos exposure. The association between *NQO1* and MM risk remained significant after adjustment for smoking, but the risk was slightly lower when adjusted by age or asbestos exposure. The association between other investigated polymorphisms and MM risk remained nonsignificant also after taking into account the effect of age, smoking and asbestos exposure (Table 2).

Next, gene-gene interactions between the investigated *NQO*, *CAT*, *SOD2* and *hOGG1* genotypes and the interactions between genotypes and asbestos exposure were calculated. The interaction between *CAT* rs1001179 and *hOGG1* rs1052133 had a protective effect on the risk of MM (OR_{int} = 0.27; 95% CI = 0.10–0.77; p = 0.014). On the other hand, no gene-gene interactions were observed between other investigated polymorphisms (Table 3).

Finally, we investigated the influence of interactions between polymorphisms and asbestos exposure on the risk of MM, but no interaction was found (Table 4).

TABLE 4. The influence of interactions between the investigated polymorphisms and asbestos exposure on risk of malignant mesothelioma

Polymorphism	OR	CI (95%)	p
***NQO1* rs1800566**	1.56	0.35–6.86	0.560
***CAT* rs1001179**	1.57	0.39–6.29	0.522
***SOD2* rs4880**	1.13	0.24–5.18	0.880
***hOGG1* rs1052133**	0.50	0.12–2.14	0.352

CAT = catalase; *hOGG1* = human 8-oxoguanine glycosylase 1; *NQO1* = NAD(P)H quinone dehydrogenase 1; OR = odds ratio; *SOD2* = superoxide dismutase 2

Discussion

The association between asbestos exposure and MM has been clearly proved, but not much has been known about the influence of genetic polymorphisms that may modify the risk of developing this aggressive cancer. Our present study investigated the effect of genetic polymorphisms of some of the most important enzymes involved in removal of ROS and RNS (NQO1, CAT, SOD2) and DNA damage repair (hOGG1) on the risk of MM, as well as the impact of interactions between the observed genetic polymorphisms and between genetic polymorphisms and asbestos exposure on the risk of developing this cancer.

In the study, we have found that smoking increased the risk of MM. It has been well proved that exposure to asbestos fibres results in an increased generation of ROS.[8,9] Many studies have also investigated the association between ROS and carcinogenesis, caused by tobacco smoke.[31] According to the free radical hypothesis of aging, ROS and RNS can drive the accumulation of cell and DNA damage[32] leading to carcinogenesis and cancer.[33-36] The combined effect of both asbestos and smoking may thus greatly increase the amount of ROS in the cells and may cause more DNA damage than smoking or asbestos exposure alone. That could explain the observed higher risk of MM among smokers exposed to asbestos compared to non-smokers.

Our study also showed a slight increase in MM susceptibility in older patients, which is in line with other studies in which MM is found predominantly as disease of the elderly.[37] Mortality due to pleural MM increased between 75 and 89 years of age and in peritoneal MM between 65 and 84 years of age.[37] This may be due to the long latency time, which is the period from the first exposure to the diagnosis of MM, and can range from 20 to over 50 years.[38] There are many factors affecting the latency period, including dose response, age, gender and location of MM.[39]

An important finding of our study is that medium and high asbestos exposures increase the risk of MM by 7-fold compared to low asbestos exposure. This is in line with the results of some studies that have also reported that the MM risk is related to the amount of exposure.[40-43] An Australian study reported an increased risk of MM with higher and longer occupational or environmental exposure to asbestos.[40,41] A Norwegian study also observed a correlation between the duration of occupational exposure and risk of MM[42,43] However, in our previous study, low levels of asbestos exposure were reported in almost 36% of patients with MM.[2]

Another important finding of the current study indicates a higher risk of MM among subjects with the *NQO1* rs1800566 T allele. According to the available literature, the association between *NQO1* polymorphisms and MM has not been investigated yet. However, some studies have found an increased risk of lung cancer[21], colorectal can-

cer[44] and bladder cancer[22] among the carriers of the polymorphic allele. On the other hand, a risk of MM was not statistically significantly increased for other investigated polymorphisms. Contrary to the findings of this study, the only other study investigating the *SOD2* polymorphism in relation to MM risk[25] showed an increased risk of pleural MM in *SOD2* Ala/Ala genotype. Regarding other asbestos related diseases, we have previously reported an association between *SOD2* Ala/Ala genotype and higher risk of asbestosis.[28] Furthermore, a significantly higher risk of lung cancer was reported in carriers of both Ala/Val and Val/Val genotypes.[45,46]

Even though there was no association between *CAT* rs1001179 or *hOGG1* rs1052133 alone and MM, one of the key findings of this study was that the interactions between *CAT* rs1001179 and *hOGG1* rs1052133 have a protective effect on the risk of MM. This can be explained by the fact that CAT as an antioxidative enzyme constitutes a part of the primary defence system against ROS, while hOGG1 as a repair enzyme removes oxidized bases such as 8-oxoguanine. According to the abovementioned mechanisms of defence against ROS, we can consider our observations as biologically plausible. We have also previously reported slightly increased risk of asbestosis among the carriers of the *CAT* rs1001179 TT genotype.[16] Furthermore, Erculj *et al*. have observed an association between *hOGG1* Ser326Cys polymorphism and higher DNA damage levels in healthy young population.[47]

A limitation of this study was that MM patients were significantly older than controls, however we accounted for that with adjustment for age in the statistical analysis. Furthermore, cumulative asbestos exposure could not be determined for all MM patients, as proper assessment is very difficult, especially for environmental or occasional exposure. Therefore, some of the analyses were only performed on the subgroup of MM patients. On the other hand, our study is one of the few that investigated gene-gene as well as gene-environment interactions in MM patients.[48] Neri *et al*. analysed a different set of genes, including several glutathione S-transferases that also contribute to antioxidative defence mechanisms and also showed the presence of gene-gene interactions as well as gene-environment interactions in the development of MM.[48] Therefore, further studies including a larger number of subjects with well-defined asbestos exposure are needed to elucidate the role of gene-environment interactions in the development of MM. Considering that pathogenesis of MM is still not completely understood, polymorphisms of other enzymes that could affect the removal of ROS and RNS and other DNA repair mechanisms, also need to be investigated.

In conclusion, our study showed for the first time that *NQO1* polymorphism influences the risk of MM both independently and after adjustment by smoking. Another key observation is the protective effect of the interaction between *CAT* rs1001179 and *hOGG1* rs1052133 polymorphisms, indicating the importance of interaction between antioxidative and DNA repair mechanisms. The results of this and future studies will improve our understanding of MM pathogenesis and may consequently enable better preventive measures for the exposed populations, earlier diagnosis and new approaches to treatment of this aggressive malignant disease.

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References

1. Zellos L, Christiani DC. Epidemiology, biologic behavior, and natural history of mesothelioma. *Thorac Surg Clin* 2004; **14:** 469-77. doi: 10.1016/j.thorsurg.2004.06.011
2. Franko A, Dolzan V, Kovac V, Arneric N, Dodic-Fikfak M. Soluble mesothelin-related peptides levels in patients with malignant mesothelioma. *Dis Markers* 2012; **32:** 123-31. doi: 10.3233/DMA-2011-0866
3. Burdorf A, Dahhan M, Swuste P. Occupational characteristics of cases with asbestos-related diseases in the Netherlands. *Ann Occup Hyg* 2003; **47:** 485-92. doi: 10.1093/annhyg/meg062
4. Bridda A, Padoan I, Mencarelli R, Frego M. Peritoneal mesothelioma: a review. *MedGenMed* 2007; **9:** 32.
5. O'Reilly KM, Mclaughlin AM, Beckett WS, Sime PJ. Asbestos-related lung disease. *Am Fam Physician* 2007; **75:** 683-90.
6. Plato N, Martinsen JI, Sparen P, Hillerdal G, Weiderpass E. Occupation and mesothelioma in Sweden: updated incidence in men and women in the 27 years after the asbestos ban. *Epidemiol Health* 2016; **38:** e2016039. doi: 10.4178/epih.e2016039
7. Aung W, Hasegawa S, Furukawa T, Saga T. Potential role of ferritin heavy chain in oxidative stress and apoptosis in human mesothelial and mesothelioma cells: implications for asbestos-induced oncogenesis. *Carcinogenesis* 2007; **28:** 2047-52. doi: 10.1093/carcin/bgm090
8. Liu G, Cheresh P, Kamp DW. Molecular basis of asbestos-induced lung disease. *Annu Rev Pathol* 2013; **8:** 161. doi: 10.1146/annurev-pathol-020712-163942
9. Pietrofesa RA, Velalopoulou A, Albelda SM, Christofidou-Solomidou M. Asbestos induces oxidative stress and activation of Nrf2 signaling in murine macrophages: chemopreventive role of the synthetic lignan secoisolariciresinol diglucoside (LGM2605). *Int J Mol Sci* 2016; **17:** 322. doi: 10.3390/ijms17030322
10. Kinnula V. Oxidant and antioxidant mechanisms of lung disease caused by asbestos fibres. *Eur Respir J* 1999; **14:** 706-16.
11. Weitzman SA, Graceffa P. Asbestos catalyzes hydroxyl and superoxide radical generation from hydrogen peroxide. *Arch Biochem Biophys* 1984; **228:** 373-6. doi: https://doi.org/10.1016/0003-9861(84)90078-x

12. Pezerat H, Zalma R, Guignard J, Jaurand M. Production of oxygen radicals by the reduction of oxygen arising from the surface activity of mineral fibres. *IARC Sci Publ* 1988; **(90):** 100-11.

13. Shukla A, Gulumian M, Hei TK, Kamp D, Rahman Q, Mossman BT. Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. *Free Radic Biol Med* 2003; **34:** 1117-29. doi: https://doi.org/10.1016/s0891-5849(03)00060-1

14. Forsberg L, Lyrenäs L, Morgenstern R, de Faire U. A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. *Free Radic Biol Med* 2001; **30:** 500-5. doi: https://doi.org/10.1016/s0891-5849(00)00487-1

15. Quick SK, Shields PG, Nie J, Platek ME, McCann SE, Hutson AD, et al. Effect modification by catalase genotype suggests a role for oxidative stress in the association of hormone replacement therapy with postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2008; **17:** 1082-7. doi: 10.1158/1055-9965.EPI-07-2755

16. Franko A, Dolžan V, Arnerić N, Dodič-Fikfak M. Asbestosis and catalase genetic polymorphism. *Arh Hig Rada Toksikol* 2008; **59:** 233-40. doi: 10.2478/10004-1254-59-2008-1907

17. Chuang T-C, Liu J-Y, Lin C-T, Tang Y-T, Yeh M-H, Chang S-C, et al. Human manganese superoxide dismutase suppresses HER2/neu-mediated breast cancer malignancy. *FEBS Lett* 2007; **581:** 4443-9. doi: 10.1016/j.febslet.2007.08.021

18. Cullen JJ, Weydert C, Hinkhouse MM, Ritchie J, Domann FE, Spitz D, et al. The role of manganese superoxide dismutase in the growth of pancreatic adenocarcinoma. *Cancer Res* 2003; **63:** 1297-303.

19. Li H, Hao X, Zhang W, Wei Q, Chen K. The hOGG1 Ser326Cys polymorphism and lung cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2008; **17:** 1739-45. doi: 10.1158/1055-9965.EPI-08-0001

20. Zhong D, Li G, Long J, Wu J, Hu Y. The hOGG1Ser326Cys polymorphism and increased lung cancer susceptibility in Caucasians: an updated meta-analysis. *Sci Rep* 2012; **2:** 548. doi: 10.1038/srep00548

21. Chao C, Zhang Z-F, Berthiller J, Boffetta P, Hashibe M. NAD (P) H: quinone oxidoreductase 1 (NQO1) Pro187Ser polymorphism and the risk of lung, bladder, and colorectal cancers: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006; **15:** 979-87. doi: 10.1158/1055-9965.EPI-05-0899

22. Basma HA, Kobeissi LH, Jabbour ME, Moussa MA, Dhaini HR. CYP2E1 and NQO1 genotypes and bladder cancer risk in a Lebanese population. *Int J Mol Epidemiol Genet* 2013; **4:** 207-17.

23. Stoehr CG, Nolte E, Wach S, Wieland WF, Hofstaedter F, Hartmann A, et al. NAD (P) H: Quinone Oxidoreductase 1 (NQO1) P187S Polymorphism and prostate cancer risk in Caucasians. *Int J Mol Sci* 2012; **13:** 10959-69. doi: 10.3390/ijms130910959

24. Gemignani F, Neri M, Bottari F, Barale R, Canessa PA, Canzian F, et al. Risk of malignant pleural mesothelioma and polymorphisms in genes involved in the genome stability and xenobiotics metabolism. *Mutat Res* 2009; **671:** 76-83. doi: 10.1016/j.mrfmmm.2009.09.003

25. Landi S, Gemignani F, Neri M, Barale R, Bonassi S, Bottari F, et al. Polymorphisms of glutathione-S-transferase M1 and manganese superoxide dismutase are associated with the risk of malignant pleural mesothelioma. *Int J Cancer* 2007; **120:** 2739-43. doi: 10.1002/ijc.22590

26. Kinnula VL, Torkkeli T, Kristo P, Sormunen R, Soini Y, Paakko P, et al. Ultrastructural and chromosomal studies on manganese superoxide dismutase in malignant mesothelioma. *Am J Respir Cell Mol Biol* 2004; **31:** 147-53. doi: 10.1165/rcmb.2003-0409OC

27. Franko A, Dolžan V, Arnerić N, Dodič-Fikfak M. The influence of gene-gene and gene-environment interactions on the risk of asbestosis. *Biomed Res Int* 2013; **2013:** 1-7. doi: 10.1155/2013/405743

28. Franko A, Dodič-Fikfak M, Arnerić N, Dolžan V. Manganese and extracellular superoxide dismutase polymorphisms and risk for asbestosis. *Biomed Res Int* 2009; **2009:** 1-6. doi: 10.1155/2009/493083

29. Fikfak MD, Kriebel D, Quinn M, Eisen E, Wegman D. A case control study of lung cancer and exposure to chrysotile and amphibole at a Slovenian asbestos-cement plant. *Ann Occup Hyg* 2007; **51:** 261-8. doi: 10.1093/annhyg/mem003

30. Erčulj N, Kovač V, Hmeljak J, Dolžan V. The influence of platinum pathway polymorphisms on the outcome in patients with malignant mesothelioma. *Ann Oncol* 2011; **23:** 961-7. doi: 10.1093/annonc/mdr324

31. Durham A, Adcock I. The relationship between COPD and lung cancer. *Lung Cancer* 2015; **90:** 121-7. doi: 10.1016/j.lungcan.2015.08.017

32. Harman D. Free radical theory of aging: an update. *Ann N Y Acad Sci* 2006; **1067:** 10-21. doi: 10.1196/annals.1354.003

33. Jung M, Davis WP, Taatjes DJ, Churg A, Mossman BT. Asbestos and cigarette smoke cause increased DNA strand breaks and necrosis in bronchiolar epithelial cells in vivo. *Free Radic Biol Med* 2000; **28:** 1295-9. doi: 10.1016/S0891-5849(00)00211-2

34. Jackson J, Schraufstatter I, Hyslop P, Vosbeck K, Sauerheber R, Weitzman S, et al. Role of oxidants in DNA damage. Hydroxyl radical mediates the synergistic DNA damaging effects of asbestos and cigarette smoke. *J Clin Invest* 1987; **80:** 1090-5. doi: 10.1172/JCI113165

35. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. *Int J Env Res Public Health* 2009; **6:** 445-62. doi: 10.3390/ijerph6020445

36. Kamp DW, Graceffa P, Pryor WA, Weitzman SA. The role of free radicals in asbestos-induced diseases. *Free Radic Biol Med* 1992; **12:** 293-315.

37. Delgermaa V, Takahashi K, Park E-K, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bull World Health Organ* 2011; **89:** 716-24. doi: 10.2471/BLT.11.086678

38. Tomasson K, Gudmundsson G, Briem H, Rafnsson V. Malignant mesothelioma incidence by nation-wide cancer registry: a population-based study. *J Occup Med Toxicol* 2016; **11:** 1-6. doi: 10.1186/s12995-016-0127-4

39. Whitmer M. Mesothelioma latency period. 2016. Available at: https://www.asbestos.com/mesothelioma/latency-period.php. Accessed 25 Avg 2016.

40. Hansen J, De Klerk NH, Eccles JL, William Musk A, Hobbs MS. Malignant mesothelioma after environmental exposure to blue asbestos. *Int J Cancer* 1993; **54:** 578-81. doi: 10.1002/ijc.2910540410

41. Armstrong B, De Klerk N, Musk A, Hobbs M. Mortality in miners and millers of crocidolite in Western Australia. *Br J Ind Med* 1988; **45:** 5-13.

42. Ulvestad B, Kjærheim K, Martinsen JI, Damberg G, Wannag A, Mowe G, et al. Cancer incidence among workers in the asbestos-cement producing industry in Norway. *Scand J Work Environ Health* 2002; **28:** 411-7. doi: 10.5271/sjweh.693

43. Ulvestad B, Kjærheim K, Martinsen JI, Mowe G, Andersen A. Cancer incidence among members of the Norwegian trade union of insulation workers. *J Occup Environ Med* 2004; **46:** 84-9. doi: 10.1097/01.jom.0000105981.46987.42

44. Ding R, Lin S, Chen D. Association of NQO1 rs1800566 polymorphism and the risk of colorectal cancer: a meta-analysis. *Int J Colorectal Dis* 2012; **27:** 885-92. doi: 10.1007/s00384-011-1396-0

45. Wang LI, Miller DP, Sai Y, Liu G, Su L, Wain JC, et al. Manganese superoxide dismutase alanine-to-valine polymorphism at codon 16 and lung cancer risk. *J Natl Cancer Inst* 2001; **93:** 1818-21.

46. Zejnilovic J, Akev N, Yilmaz H, Isbir T. Association between manganese superoxide dismutase polymorphism and risk of lung cancer. *Cancer Genet Cytogenet* 2009; **189:** 1-4. doi: 10.1016/j.cancergencyto.2008.06.017

47. Erčulj N, Zadel M, Dolžan V. Genetic polymorphisms in base excision repair in healthy slovenian population and their influence on DNA damage. *Acta Chim Slov* 2010; **57:** 182-8.

48. Neri M, Filiberti R, Taioli E, Garte S, Paracchini V, Bolognesi C, et al. Pleural malignant mesothelioma, genetic susceptibility and asbestos exposure. *Mutat Res* 2005; **592:** 36-44. doi: 10.1016/j.mrfmmm.2005.06.003

research article

Voluntary deep inspiration breath-hold reduces the heart dose without compromising the target volume coverage during radiotherapy for left-sided breast cancer

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Background. During radiotherapy of left-sided breast cancer, parts of the heart are irradiated, which may lead to late toxicity. We report on the experience of single institution with cardiac-sparing radiotherapy using voluntary deep inspiration breath hold (V-DIBH) and compare its dosimetric outcome with free breathing (FB) technique.

Patients and methods. Left-sided breast cancer patients, treated at our department with postoperative radiotherapy of breast/chest wall +/- regional lymph nodes between May 2015 and January 2017, were considered for inclusion. FB-computed tomography (CT) was obtained and dose-planning performed. Cases with cardiac V25Gy ≥ 5% or risk factors for heart disease were coached for V-DIBH. Compliant patients were included. They underwent additional CT in V-DIBH for planning, followed by V-DIBH radiotherapy. Dose volume histogram parameters for heart, lung and optimized planning target volume (OPTV) were compared between FB and BH. Treatment setup shifts and systematic and random errors for V-DIBH technique were compared with FB historic control.

Results. Sixty-three patients were considered for V-DIBH. Nine (14.3%) were non-compliant at coaching, leaving 54 cases for analysis. When compared with FB, V-DIBH resulted in a significant reduction of mean cardiac dose from 6.1 +/- 2.5 to 3.2 +/- 1.4 Gy ($p < 0.001$), maximum cardiac dose from 51.1 +/- 1.4 to 48.5 +/- 6.8 Gy ($p = 0.005$) and cardiac V25Gy from 8.5 +/- 4.2 to 3.2 +/- 2.5% ($p < 0.001$). Heart volumes receiving low (10–20 Gy) and high (30–50 Gy) doses were also significantly reduced. Mean dose to the left anterior coronary artery was 23.0 (+/- 6.7) Gy and 14.8 (+/- 7.6) Gy on FB and V-DIBH, respectively ($p < 0.001$). Differences between FB- and V-DIBH-derived mean lung dose (11.3 +/- 3.2 *vs.* 10.6 +/- 2.6 Gy), lung V20Gy (20.5 +/- 7 *vs.* 19.5 +/- 5.1 Gy) and V95% for the OPTV (95.6 +/- 4.1 *vs.* 95.2 +/- 6.3%) were non-significant. V-DIBH-derived mean shifts for initial patient setup were ≤ 2.7 mm. Random and systematic errors were ≤ 2.1 mm. These results did not differ significantly from historic FB controls.

Conclusions. When compared with FB, V-DIBH demonstrated high setup accuracy and enabled significant reduction of cardiac doses without compromising the target volume coverage. Differences in lung doses were non-significant.

Key words: breast cancer; radiotherapy; heart dose; heart sparing

Introduction

Worldwide, breast cancer is the most commonly diagnosed female malignancy and the leading cause of cancer mortality in women.[1,2] Radiotherapy (RT) is an essential component of multimodal breast cancer treatment. Adjuvant irradiation to the residual breast after wide local excision of the primary tumor provides equivalent outcomes to mastectomy while ensuring superior cosmesis.[3-5] In pa-

tients with risk factors after mastectomy, adjuvant radiotherapy improves overall survival and local control.[6,7] Due to improvements in breast cancer treatment, the number of long-term survivors has increased over the past decades.[8] With larger numbers surviving, more patients become at risk of developing a wide range of late radiation-related side effects. Postoperative radiotherapy in patients with left-sided breast cancer is characterized by exposure of significant portion of the heart volume to high doses of irradiation.[9] Pathophysiology of radiotherapy-induced cardiac toxicity involves damage of blood vessels and interstitial fibrosis, leading to coronary artery disease, valvular abnormalities, myocardial dysfunction, pericardial disease and conductive disturbances. These changes can become clinically manifest several years or even decades after treatment, leading to increased risk for cardiac morbidity and death.[10-24] The increased risk is proportional to the dose received by the heart, begins within years after exposure and continues for decades.[12] Various radiotherapy techniques, including breath hold (BH) during treatment have been proposed to reduce the cardiac dose.[25,26] It is expected that these maneuvers will result in reduced probability of late clinical manifestations of cardiac events.[12,27,28] Voluntary deep inspiration breath hold (V-DIBH) radiotherapy has been studied in the setting of breast conserving treatment and post-mastectomy.[25,26] Using this technique, the distance from the chest wall to the heart increases during deep inspiration, resulting in a decrease of cardiac volume in the radiotherapy field. While consistency and stability of V-DIBH has been demonstrated, real-time positional monitoring is advocated in daily practice to apply corrective actions due to intra-fractional movements.[29,30] In 2015, we implemented V-DIBH for patients undergoing left-sided breast cancer radiotherapy, based on a prospective observational study protocol. This implementation in routine practice was based on the existent body of evidence in favor of V-DIBH.[25,26] We aimed to ensure controlled transition to the new routine technique and to report on feasibility of this approach in our clinical setting and its dosimetric impact. Our hypothesis was that V-DIBH, when compared with free-breathing (FB) technique, will result in statistically significant reduction of the commonly reported cardiac dose-volume histogram (DVH) parameters without compromising the coverage of the target volume with prescribed dose. We also hypothesized that V-DIBH treatment results in non-inferior set-up accuracy when compared with FB. Our study was approved by the institutional Medical Research Center (Study No. 15330/15), on 14. 10. 2015 by the Hamad Medical Corporation Medical Research Centre.

Patients and methods

Patients and CT scanning

Formal calculation of the sample size was not performed. Instead, all consecutive left-sided breast cancer patients, treated at our department with postoperative radiotherapy between May 2015 and January 2017, were considered for V-DIBH. In this way, a clinically relevant patient cohort was enrolled during the period of V-DIBH implementation. Informed consent to treatment according to the protocol was obtained from all patients. Metastatic disease, compromised respiratory function, Eastern Cooperative Group performance status >2, need for sedation during treatment and patient refusal were exclusion criteria. Patients with cardiac V25Gy ≥ 5% on FB treatment plan were offered V-DIBH. In addition, selected cases with lower V25Gy were entered on the V-DIBH protocol. This selection was performed at discretion of the treating radiation oncologist by considering patient-related factors such as age, pre-existent ischemic cardiac events and other co-morbidities, application of cardio-toxic medications, history of smoking, diabetes mellitus, hyperlipidemia and arterial hypertension.

Our V-DIBH approach was adapted from the technique used in the UK HeartSpare study and was based on visual confirmation of the borders of the light fields, marked on the patient as surrogates of the isocenter.[31] Planning scans were obtained with a 64-slice Siemens Somatom Definition CT scanner, using 5 mm slice thickness. During scanning, Patients were positioned supine with both arms above the head, using the breast board and knee rest (CIVCO Medical Solutions, © 2017 USA). Standard CT planning marks were used in all cases. They included four tattoos (superior, inferior, medial and lateral) and wires to delineate surgical scar and patient midline. First, FB CT was obtained. Following completion of FB CT, the patients, still in simulation position, underwent V-DIBH coaching. During coaching, patient's ability to hold breath for the duration of treatment was checked. In addition, geometric consistency of BH was visually assessed using in-room lasers and skin marks. Finally, the patients were asked to practice V-DIBH technique overnight and returned the following day to complete V-DIBH CT scan. V-DIBH scans were com-

pleted using the same basic set up parameters as FB scans. During imaging, the therapists communicated with the patients by using in-room intercom. Video connection with closed-circuit camera was used for visual assessment of skin marks to ensure BH consistency; distance from tattoos to BH marks was recorded.

Contouring and dose optimization

Contouring and treatment planning was performed with Varian External Beam Planning system, version 13.7 (© 1996-2016 Varian Medical Systems, Inc, Palo Alto, USA). Planning target volume (PTV), heart and lung were contoured on FB and V-DIBH CT scans by five different radiation oncologists according to our departmental contouring guidelines, adapted from the published recommendations.[32] As per our departmental practice, internal mammary lymph node chains were not included in the treatment volume. Left anterior descending coronary artery (LAD) was contoured based on the recently published contouring atlas.[33] Optimized PTV (OPTV) was created by subtracting 5 mm from PTV at the skin. Analysis of contouring uncertainties was limited to volumetric comparisons (mean volumes and relative standard deviations) of delineated regions of interest between FB and V-DIBH and within each approach.

Treatment planning was completed according to our institutional practice (see below) separately for FB and V-DIBH scans. Our standard prescription was 50 Gy in 25 fractions to the OPTV. When indicated, 45 Gy in 25 fractions were applied simultaneously with breast / chest wall irradiation to the ipsilateral supra-clavicular region. OPTV irradiation was followed by electron boost of 16 Gy in 8 fractions to lumpectomy bed or post-mastectomy scar. Photon boost was not used. Dose contribution from electron boost was not included in the analysis. Dose optimization did not differ between FB and V-DIBH approach and consisted of forward-planned intensity modulated field in field technique. Subfields were fitted on a weighted pair of tangents to attain OPTV dose homogeneity. Planning aims were to cover ≥ 95% of the OPTV with ≥ 95% of prescribed dose and to keep the proportion of ipsilateral lung irradiated to 20 Gy (V20Gy) < 25%, cardiac V25Gy < 5% and mean cardiac dose < 5 Gy. For hypo-fractionation (40 Gy in 15 fractions), linear quadratic model with α/β of 3Gy was applied to calculate the biologically equivalent dose constraints for the lung (V18Gy < 22%–25%) and heart (V23Gy ≤ 5% and mean D ≤ 4Gy). DVH parameters of FB and V-DIBH treatment plans were recorded and compared.

Treatment

For daily treatments, patients were positioned and immobilized identical to planning CT. BH consistency was checked in the room by using skin marks to reflect the measurements from CT and in-room lasers. Outside the treatment room, closed-circuit television camera was zoomed in to clearly define BH skin marks. Next, patients were asked to complete BH using the intercom system. Skin marks were visually checked through video connection to quantify inspiration and to ensure that the planned inspiration depth was reproduced during daily treatments. Set up verification and correction was performed through daily pre-port tangential megavoltage images and cine loop images (Varian On board imager 1.6 © 2015, Switzerland) to confirm both isocenter position and BH consistency. If corrections were required, they were applied in the room with the patient in BH position and new marks were placed on the patient's skin. Set up errors were assessed offline for every fraction. For the first 18 patients treated with the V-DIBH technique, mean shifts and systematic and random errors were calculated. The results were compared with a retrospective cohort of patients treated at our department using the FB technique.

Statistical analysis

Mean values and standard deviations were used to present continuous numerical variables and paired sample t-test was used to test for significance of differences. Statistical tests were double sided with p-value of < 0.05 considered as the limit for significance. Miscrosoft Office Excel software was used for data analysis and statistics.

Results

Patients and treatment

Sixty-three patients were considered for V-DIBH radiotherapy. Nine (14.3%) were excluded at the time of coaching due to non-compliance with the V-DIBH protocol. Additional two (3.2%) were unable to hold breath after the treatment start and reverted from V-DIBH to FB technique, but their DVH parameters are included in final analysis. In summary, the overall ability to complete radiotherapy using the V-DIBH technique was 82.5% and 54

cases were included in the DVH analysis. All patients were female and median age was 41 years (range: 30-64 years). The irradiated volume included residual breast after organ conserving surgery in 31 (57%) and chest wall after mastectomy in 23 (43%) cases. All patients received electron boost of 16 Gy in 8 fractions to the lumpectomy cavity or mastectomy scar. Left supra-clavicular region was included in the radiation fields in all 24 (100%) post-mastectomy and in 7 (22.6%) post-lumpectomy cases. Patients were required to perform 11 breath holds on an average daily treatment. Mean couch shifts and setup errors for the V-DIBH technique were not significantly different when compared with our historic cohort of patients, treated with FB approach (Table 1). Largest mean shift for initial patient setup was in longitudinal direction (2.7 mm), followed by the lateral (2.1 mm) and vertical direction (1.2 mm). Population systematic and random error was the highest for the longitudinal direction (2.1 and 0.7 mm, respectively).

TABLE 1. Vertical, longitudinal and lateral couch shifts and corresponding systematic and random errors for the initial 18 patients treated with voluntary deep inspiration breath-hold (V-DIBH) and a historic control treated with free-breathing (FB) technique. Differences between the two approaches were non-significant.

	Vertical [mm]		Longitudinal [mm]		Lateral [mm]	
Setup parameter	**FB**	**V-DIBH**	**FB**	**V-DIBH**	**FB**	**V-DIBH**
Mean shift	1	1.2	2.8	2.7	1.9	2.1
Systematic error	0.7	1.5	1.6	2.1	0.8	1.3
Random error	0.6	0.6	2.1	0.7	1.1	0.4

FB = free breathing; V-DIBH = voluntary deep inspiration breath hold

Dose volume histogram parameters

V-DIBH technique resulted in a significant increase of delineated left lung volume when compared with FB (1557 +/- 389 cm^3 *vs*. 914 +/- 207.7 cm^3; $p < 0.001$). Inter-observer variation of lung contouring was comparable between the two approaches with a relative standard deviation of 23% and 25% on FB and V-DIBH CT, respectively. Global volumetric analysis revealed statistically significant inter-approach (intra-observer) variation of contoured cardiac volumes: mean volume of the heart on FB and V-DIBH CT was 567 +/- 82 cm^3 and 547 +/-91 cm^3, respectively ($p < 0.05$) (Figure 1). Inter-observer variation of cardiac and LAD volumes was comparable between the FB and V-DIBH scans as demonstrated by non-significantly different relative standard deviations (heart volume: 14.4% *vs*. 16.7%, LAD volume: 29.5% on both scans). Mean volume of PTV contours on FB CT did not differ significantly from the PTV as delineated on V-DIBH scans (985 +/- 405 cm^3 *vs*. 960 +/- 369 cm^3; $p = 0.08$). Results of the DVH parameters analysis are presented in Table 2. When compared with FB, V-DIBH resulted in a statistically significant reduction of all analyzed DVH parameters for the heart and LAD. Differences between FB- and V-DIBH-derived lung doses and V95% for the OPTV were non-significant (Table 2). Impact of elective nodal radiotherapy on the analyzed cardiac and lung DVH parameters is summarized in Table 3. There was no significant difference in cardiac DVH parameters between patients receiving left supraclavicular fossa radiotherapy and patients treated with breast/chest wall radiotherapy alone. Mean dose to the left lung and lung volumes receiving 10, 20 and 30 Gy, were significantly higher in subgroup with inclusion of supraclavicular fossa both in V-DIBH and FB treatment plans (Table 3).

Discussion

Adjuvant radiotherapy improves the treatment outcome after breast cancer surgery, but it also carries a risk for late cardiac toxicity in left sided tumors.[3-7,10-24] Various techniques were suggested to reduce this effect.[25,26] In our present study, the implementation of V-DIBH technique achieved statistically significant reduction of cardiac doses without affecting the PTV coverage. V-DIBH ra-

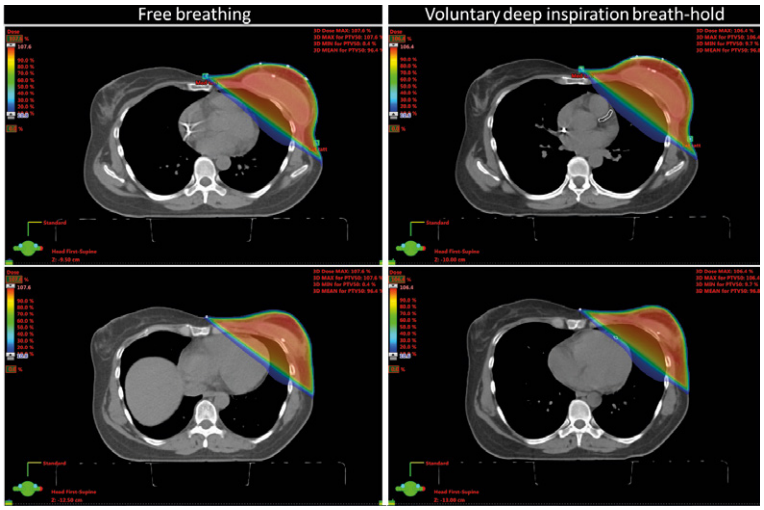

FIGURE 1. Impact of deep inspiration on cardiac dose during postoperative radiotherapy for left-sided breast cancer. Doses from 0% to three-dimensional dose maximum are depicted by color wash. Upper two slices are taken at mid-breast level and the lower pair 6 slices below. At both levels, the proportion of cardiac volume is reduced by voluntary deep inspiration breath-hold.

TABLE 2. Mean values +/- standard deviations of dose volume histogram (DVH) parameters for heart, left anterior descending coronary artery (LAD), lung and optimized planning target volume (OPTV) achieved by the free breathing and breath-hold technique.

DVH parameter	Free breathing	Breath-hold	P-value
	Heart		
D_{mean} [Gy]	6.1 +/- 2.5	3.2 +/- 1.4	
D_{max} [Gy]	51.1 +/- 1.4	48.5 +/- 6.8	
V50Gy [%]	0.7 +/- 1.1	0.2 +/- 0.6	
V40Gy [%]	6.2 +/- 3.5	2.1 +/- 1.9	
V30Gy [%]	7.8 +/- 4	2.8 +/- 2.3	< 0.05
V25Gy [%]	8.5 +/- 4.2	3.2 +/- 2.5	
V20Gy [%]	9.2 +/- 4.4	3.6 +/- 2.7	
V15Gy [%]	10 +/- 4.6	4.1 +/- 2.9	
V10Gy [%]	11.2 +/- 5	4.9 +/- 3.2	
	Left lung		
D_{mean} [Gy]	11.3 +/- 3.2	10.6 +/- 2.6	
D_{max} [Gy]	51.6 +/- 1.8	50.6 +/- 1.1	
V30Gy [%]	17.9 +/- 6.3	17 +/- 4.6	NS
V20Gy [%]	20.5 +/- 7	19.5 +/- 5.1	
V10Gy [%]	25.9 +/- 8.1	25.4 +/- 5.8	
	LAD		
D_{mean} [Gy]	23.0 +/- 6.7	14.8 +/- 7.6	
D_{max} [Gy]	49.7 +/- 3.4	44.3 +/- 12.2	< 0.05
D50% [Gy]	20.4 +/- 17.6	8.4 +/- 11.1	
	OPTV		
V95% [%]	95.6 +/- 4.1	95.2 +/- 6.3	NS

D_{max} = maximal dose; D_{mean} = mean dose; Dx% = dose received by x% of volume; LAD = left anterior descending coronary artery; NS = non-significant; VxGy = relative volume, receiving a dose of x Gy; Vx% = relative volume, receiving x% of the prescribed dose

diotherapy was characterized by excellent patient compliance and high set-up accuracy which was non-inferior to the historic FB control.

We found that V-DIBH, when compared with FB technique, achieved significant reduction of all analyzed DVH parameters for LAD and heart (Table 2). In our patient cohort, the mean cardiac dose was reduced by 50% and V25Gy by 64% (Table 2). The heart-sparing effect afforded by the V-DIBH did not come at a cost of inferior dose-coverage of the OPTV when compared with the FB treatment plans (Table 2). Covariates that impact the cardiac dose during radiotherapy include the radiotherapy technique (intensity modulated *vs*. 3D conformal), use of cardiac sparing techniques, patient position, regional irradiation and boost.[34] It should be emphasized that direct comparisons between different studies and our current report are challenging due to differences in the listed factors, including treatment volumes and heart sparing methodologies used. Hjelstuen *et al*. analyzed the DVH parameters of 17 patients treated with DIBH technique using a commercially available gating system. When compared with the FB technique, DIBH reduced the planned mean heart dose from 6.2 to 3.1 Gy and cardiac V25Gy from 6.7% to 1.2% ($p < 0.001$). Mean V95% for the PTV did not differ significantly between the FB (98.9 +/- 0.5%) and DIBH (98.8 +/- 0.5) plans. Of note, regional lymph nodes, including the internal mammary chain, were included in the target volume in all patients in this study.[35] In our work, internal mammary chain was not included, making direct comparisons challenging. In another study of left-sided breast cancer patients treated with DIBH or FB, similar reduction of cardiac doses was obtained while the target volume coverage was even slightly improved.[36] In a cohort of 22 patients, Stranzl *et al*. found a low mean heart dose of 2.3 Gy on FB, which further improved to 1.3 Gy with DIBH using the Real-time Positioning Management System™ (RPM; © Varian Medical Systems).[24] Using V-DIBH, we achieved significant reduction of all analyzed DVH parameters for LAD (Table 2). In breast cancer radiotherapy, damage to left anterior ventricular wall and LAD play an important role, given their anatomical position in relation to the radiation fields.[23] In a study by Wang *et al*., mean dose to LAD was 20.47 Gy on FB compared to 5.94 Gy on DIBH plans, with a relative reduction of 71%.[37] Hayden at al. achieved a 31% dose reduction for the mean LAD dose using DIBH technique.[38] Several other studies demonstrated similar improvements for different cardiac DVH parameters, including dose to LAD.[39-41] Keeping the challenges related to comparisons of mono-institutional retrospective studies in mind, we can summarize that our results compare favourably with the published reports.

In patients without previous cardiac events, we used the heart V25Gy ≥ 5% as threshold for inclusion on the V-DIBH protocol. But the evidence suggests that there is no threshold dose below which the late cardiac effects do not occur. A recent study by Darby *et al.* used a population-based case-control model to look at major coronary events and ischemic cardiac deaths following breast cancer radiotherapy. The investigators estimated the cardiac doses in 963 patients with major coronary events and 1205 controls. Dosimetric findings were corre-

TABLE 3. Impact of supraclavicular fossa (SCF) radiotherapy on heart and lung dose volume histogram (DVH) parameters

DVH parameter	*Free breathing*		p-value	*Breath-hold*		p-value
	No SCF (n = 23)	SCF (n = 31)		No SCF (n = 23)	SCF (n = 31)	
	Heart			**Heart**		
D_{mean} [Gy]	5.5 +/- 2.2	6.6 +/- 2.7		2.9 +/- 1.1	3.5 +/- 1.6	
D_{max} [Gy]	51.1 +/- 1.5	51.1 +/- 1.3		48.2 +/- 7.8	48.8 +/- 5.9	
V50Gy [%]	1 +/- 1.3	0.5 +/- 0.9		0.3 +/- 0.7	0.2 +/- 0.3	
V40Gy [%]	5.9 +/- 3.6	6.5 +/- 3.4	NS	1.6 +/- 1.4	2.4 +/- 2.2	NS
V30Gy [%]	7.2 +/- 4.1	8.3 +/- 3.9		2.3 +/- 1.8	3.3 +/- 2.6	
V25Gy [%]	7.8 +/- 4.2	9.1 +/- 4.1		2.6 +/- 1.9	3.7 +/- 2.8	
V20Gy [%]	8.4 +/- 4.4	9.8 +/- 4.4		2.9 +/- 2.1	4.2 +/- 3	
V15Gy [%]	9.2 +/- 4.7	10.6 +/- 4.5		3.4 +/- 2.3	4.7 +/- 3.2	
V10Gy [%]	10.4 +/- 5.1	12 +/- 4.8		4.2 +/- 2.6	5.6 +/- 3.5	
	Lung			**Lung**		
D_{mean} [Gy]	9 +/- 2.6	13.2 +/- 2.2	< 0.05	9.3 +/- 3.2	11.8 +/- 2.4	< 0.05
D_{max} [Gy]	51.1 +/- 1.4	52 +/- 2.1	NS	50.4 +/- 1.1	50.8 +/- 1.1	NS
V30Gy [%]	13.4 +/- 4.9	21.7 +/- 4.7		14 +/- 4	19.6 +/- 3.3	
V20Gy [%]	15.5 +/- 5.3	24.9 +/- 5.1	< 0.05	16.3 +/- 4.4	22.3 +/- 3.8	< 0.05
V10Gy [%]	19.8 +/- 6.1	31.2 +/- 5.5		21.5 +/- 5.5	28.8 +/- 3.6	

NS = non-significant

lated with clinical outcomes. The study suggested that the probability of major coronary events increases linearly with increasing mean heart dose at a rate of 7.4% / Gy (95% confidence interval 2.9–14.5; $p < 0.01$). This increase began within 5 years after treatment and continued for at least 20 years. The relative effect per Gray was independent of the presence of cardiac risk factors, but the absolute increase was higher in women with pre-existing morbidity.[12] Therefore, all left-sided breast cancer patients requiring radiotherapy should in principle be offered one of the cardiac sparing treatment techniques.[25] We suggest that implementation of new methods such as V-DIBH is carefully planned, because it demands time and additional human resources, especially during the learning curve period. The V25Gy inclusion threshold of 5% used in our study was selected based on our infrastructural capabilities. Analysis of our workforce and linear accelerator capacities was balanced against the projected workload during the study. This analysis showed that setting the V25Gy threshold at 5% leads to inclusion of approximately 33% of patients with highest cardiac doses, which was the maximal acceptable workload increase. Based on the positive results of our present study and the favorable experience gained, we adopted V-DIBH radiotherapy as standard treatment for all left-sided breast cancer patients. This implementation was reflected in a corresponding increase of our planned staffing requirements. However, it required no infrastructural investments because the V-DIBH technique can be applied without any additional special equipment. Relatively high average number of breath-holds observed in our study (11 breath holds per daily treatment) can be attributed to the learning curve at the early stage of V-DIBH implementation.

Average cardiac volume as delineated on V-DIBH scans (547 +/-91 cm3) was significantly smaller when compared with FB scans (567 +/- 82 cm^3) ($p = 0.016$), which could be attributed to the physiologic effect of V-DIBH. While statistically significant, the absolute average difference between contoured volumes was small (20 cm^3), but there was a substantial spread of individual differences (st. dev: 61 cm^3), indicating large variation between FB and V-DIBH based cardiac volumes in individual study cases. Contouring variation is one of the major sources of uncertainties in radiotherapy. In spite of the use of contouring guidelines, high quality imaging and participation

of trained observers, complete elimination of contouring variation is an unrealistic aim.[42] Therefore, the magnitude of contouring variation needs to be quantified and considered during the interpretation of DVH results. While the DVH parameters reported in our present study were based on relative cardiac volumes, the mean absolute volume was smaller on V-DIBH when compared with FB. Therefore, cardiac sparing afforded by V-DIBH technique is likely to be an underestimation of the actual sparing effect. This can be regarded as a supporting argument for the confirmation of our study hypothesis. The inter-observer (intra-approach) variation of cardiac contouring was comparable between the FB and V-DIBH scans as demonstrated by similar relative standard deviation of around 15%. Consequently, the impact of contouring variation on uncertainties of the DVH parameters was similar for both simulation approaches, making our results clinically relevant.

Our V-DIBH technique requires no additional equipment, ensures precise setup and is feasible, as demonstrated by the 82.5% compliance with coaching instructions. We found that the mean shifts for initial patient setup with V-DIBH technique were from 1.2 to 2.8 mm and the systematic and random setup errors were ≤ 2.1 mm. These favorable results did not differ significantly from our past experience with FB approach (Table 1). Real-time monitoring ensured high precision setup throughout the beam-on time. Although not formally analyzed, our experience with the V-DIBH confirms excellent reproducibility, constancy and stability of this treatment technique.[29,30] Our results compare favorably with reports by other authors using similar approaches. The HeartSpare study was a randomized comparison between V-DIBH and deep-inspiratory breath-hold with Active Breathing Coordinator™ (ABC-DIBH; © Elekta).[31] Twenty three patients were randomized to receive one technique for the first seven and the second technique for the following 8 fractions of hypofractionated regimen delivering 40 Gy in 15 fractions. Differences between V-DIBH and ABC-DIBH based setup errors were non-significant. Systematic errors derived from electronic portal imaging were ≤ 1.8 mm for v-DIBH and ≤ 2 mm for ABC-DIBH, while the respective random errors were ≤ 2.5 mm and ≤ 2.2 mm. Furthermore, V-DIBH was preferred by patients and staff, took less time to deliver and achieved similar normal tissue sparing at lower cost when compared with the ABC-DIBH.[31] Similarly, Borst *et al.* reported on high feasibility and small setup variability of V-DIBH technique, with the largest systematic (2.9 mm) and random error (2 mm) in direction perpendicular to the field.[40] In a study by Gierga *et al.*, three-dimensional surface imaging was used to correct the daily set up of 20 patients treated with 443 fractions of DIBH radiotherapy. Mean shifts for initial patient setups were from 0.3 to 2 mm in different directions, while random and systematic errors were less than 4 mm.[43]

Conclusions

When compared with free-breathing radiotherapy, voluntary deep inspiration breath-hold enabled significant reduction of cardiac doses without compromising the target volume coverage in our cohort of left-sided breast cancer patients. Treatment setup shifts and population systematic and random errors were small and not significantly different from the historic controls treated with the free-breathing technique. Our systematic approach to patient coaching was reflected in low rate of conversion to free-breathing radiotherapy. Based on the positive results of our present study and experience gained, we adopted V-DIBH radiotherapy as standard treatment for all left-sided breast cancer patients. Long follow up is needed to confirm the clinical impact of the presented favorable dosimetric benefit.

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References

1. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends - an update. *Cancer Epidemiol Biomarkers Prev* 2016; **25:** 16-27. doi: 10.1158/1055-9965

2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49:** 1374-403. doi: 10.1016/j.ejca.2012.12.027

3. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. *Lancet* 2005; **366:** 2087-106. doi: 10.1016/S0140-6736(05)67887-7.

4. Fisher B, Anderson S, Bryant J, Margoloese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347:** 1233-41. doi: 10.1056/NEJMoa022152

5. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after breast conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; **378:** 1707-16. doi: 10.1016/S0140-6736(11)61629-2

6. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383:** 2127-35. doi: 10.1016/S0140-6736(14)60488-8

7. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006; **24:** 2268-75. doi: 10.1200/JCO.2005.02.8738

8. Kanapuru B, Ershler WB, Hesdorffer C, Jemal A, Yates JW. Long-term survival of older breast cancer patients: population-based estimates over three decades. *Breast Cancer Res Treat* 2012; **134:** 853-7. doi: 10.1007/s10549-012-2115-4

9. Taylor CW, Brønnum D, Darby SC, Gagliardi G, Hall P, Jensen MB, et al. Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977-2001. *Radiother Oncol* 2011; **100:** 176-83. doi: 10.1016/j.radonc.2011.01.020

10. Duma MN, Molls M, Trott KR. From heart to heart for breast cancer patients - cardiovascular toxicities in breast cancer radiotherapy. *Strahlenther Onkol* 2014; **190:** 5-7. doi: 10.1007/s00066-013-0465-4

11. Carlson RG, Mayfield WR, Normann S, Alexander JA. Radiation-associated valvular disease. *Chest* 1991; **99:** 538-45. doi: http://dx.doi.org/10.1378/chest.99.3.538

12. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; **368:** 987-98. doi: 10.1056/NEJMoa1209825

13. Heidenreich PA, Hancock SL, Vagelos RH, Lee BK, Schnittger I. Diastolic dysfunction after mediastinal irradiation. *Am Heart J* 2005; **150:** 977-82. doi: 10.1016/j.ahj.2004.12.026

14. Orzan F, Brusca A, Gaita F, Giustetto C, Figliomeni MC, Libero L. Associated cardiac lesions in patients with radiation-induced complete heart block. *Int J Cardiol* 1993; **39:** 151-6. doi: 10.1016/0167-5273(93)90027-E

15. Larsen RL, Jakacki RI, Vetter VL, Meadows AT, Silber JH, Barber G. Electrocardiographic changes and arrhythmias after cancer therapy in children and young adults. *Am J Cardiol* 1992; **70:** 73-7. doi: 10.1016/0002-9149(92)91393-I

16. Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagy GN, Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst* 2005; **97:** 419-24. doi: 10.1093/jnci/dji067

17. Cheng YJ, Nie XY, Ji CC, Lin XX, Liu J, Chen XM, et al. Long-Term Cardiovascular Risk After Radiotherapy in Women With Breast Cancer. *J Am Heart Assoc* 2017; **6:** e005633. doi: 10.1161/JAHA.117.005633

18. Højris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. *Lancet* 1999; **354:** 1425-30. doi: 10.1016/S0140-6736(99)02245-X.

19. McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol* 2011; **100:** 167-75. doi: 10.1016/j.radonc.2011.06.016

20. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017; **35:** 1641-9. doi: 10.1200/JCO.2016.72.0722

21. Paszat LF, Mackillop WJ, Groome PA, Boyd C, Schulze K, Holowaty E. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. *J Clin Oncol* 1998; **16:** 2625-31. doi: 10.1200/JCO.1998.16.8.2625

22. Lee MS, Finch W, Mahmud E. Cardiovascular complications of radiotherapy. *Am J Cardiol* 2013; **112:** 1688-96. doi: 10.1016/j.amjcard.2013.07.031

23. Correa CR, Litt HI, Hwang WT, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol* 2007; **25:** 3031-7. doi: 10.1200/JCO.2006.08.6595

24. Stranzl H, Zurl B. Postoperative irradiation of left-sided breast cancer patients and cardiac toxicity. *Strahlenther Onkol* 2008; **184:** 354-8. doi: 10.1007/s00066-008-1852-0

25. Shah C, Badiyan S, Berry S, Khan AJ, Goyal S, Schulte K, et al. Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy. *Radiother Oncol* 2014; **112:** 9-16. doi: 10.1016/j.radonc.2014.04.009

26. Latty D, Stuart KE, Wang W, Ahern V. Review of deep inspiration breath-hold technique for the treatment of breast cancer. *J Med Radiat Sci* 2015; **62:** 74-81. doi: 10.1002/jmrs.96

27. Marks LB, Yorke ED, Jackson A Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010; **76:** 10-9. doi: 10.1016/j.ijrobp.2009.07.1754

28. Korreman SS, Pederson AN, Aarup LR, Nøttrup TJ, Specht L, Nyström H. Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2006; **65:** 1375-80. doi: 10.1016/j.ijrobp.2006.03.046

29. Colgan R, James M, Bartlett FR, Kirby AM, Donovan EM. Voluntary breath-holding for breast cancer radiotherapy is consistent and stable. *Br J Radiol* 2015; **88:** 1-8. doi: 10.1259/bjr.20150309

30. Kapanen M, Laaksomaa M, Pehkonen J, Haltamo M, Luukkanen H, et al. Effects of multiple breath hold reproducibility on treatment localization and dosimetric accuracy in radiotherapy of left-sided breast cancer with voluntary deep inspiration breath hold technique. *Med Dosim* 2017; **42:** 177-84. doi: 10.1016/j.meddos.2017.02.004

31. Bartlett FR, Colgan RM, Carr K, Donovan EM, McNAir HA, Locke I, et al. The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiother Oncol* 2013; **108:** 242-7. doi: 10.1016/j.radonc.2013.04.021

32. Radiation Therapy Oncology Group (RTOG). Breast cancer atlas for radiation therapy planning: consensus definitions. [cited 15 Avg 2017]. Available at: http://www.rtog.org/LinkClick.aspx?fileticket=vzJFhPaBipE%3d&tabid=236

33. Duane F, Aznar M, Bartlett F, Cutter DJ, Darby SC, Jagsi R, et al. A cardiac contouring atlas for radiotherapy. *Radiother Oncol* 2017; **122:** 416-22. doi: 10.1016/j.radonc.2017.01.008

34. Pierce LJ, Feng M, Griffith KA, Jaqsi R, Boike T, Dryden D, et al. Recent time trends and predictors of heart dose from breast radiation therapy in a large quality consortium of radiation oncology practices. *Int J Radiat Oncol Biol Phys* 2017; **99:** 1154-61. doi: 10.1016/j.ijrobp.2017.07.022

35. Hjelstuen MH, Mjaaland I, Vikstrom J, Dybvik Kl. Radiation during deep inspiration allows loco-regional treatment of left breast and axillary, supraclavicular, and internal mammary lymph nodes without compromising target coverage or dose restrictions to organs at risk. *Acta Oncol* 2012; **51:** 333-44. doi: 10.3109/0284186X.2011.618510

36. Nissen HD, Appelt AL. Improved heart, lung, and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. *Radiother Oncol* 2013: **106:** 28-32. doi: 10.1016/j.radonc.2012.10.016

37. Wang W, Purdie TG, Rahman M, Marshal A, Liu FF, Fyles A. Rapid automated treatment planning process to select breast cancer patients for active breathing control to achieve cardiac dose reduction. *Int J Radiat Oncol Biol Phys* 2012; **82:** 386-93. doi: 10.1016/j.ijrobp.2010.09.026

38. Hayden AJ, Rains M, Tiver K. Deep inspiration breath hold technique reduces heart dose from radiotherapy for left-sided breast cancer. *J Med Imaging Radiat Oncol* 2012; **56:** 462-72. doi: 10.1111/j.1754-9485.2012.02405.x

39. Reardon KA, Read PW, Morris MM, Reardon MA, Geesy C, Wijesooriya K. A comparative analysis of 3D conformal deep inspiratory-breath hold and free-breathing intensity-modulated radiation therapy for left-sided breast cancer. *Med Dosim* 2013; **38:** 190-5. doi: 10.1016/j.meddos.2013.01.002

40. Borst GR, Sonke JJ, den Hollander S, Betgen A, Remeijer P, van Giersbergen A, et al. Clinical results of image-guided deep inspiration breath hold breast irradiation. *Int J Radiat Oncol Biol Phys* 2010; **78:** 1345-51. doi: 10.1016/j.ijrobp.2009.10.006

41. McIntosh A, Soushtari AN, Benedict SH, Read PW, Wijesooriya K. Quantifying the reproducibility of heart position during treatment and corresponding delivered heart dose in voluntary deep inspiration breath hold for left breast cancer patients treated with external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; **81:** 569-76. doi: 10.1016/j.ijrobp.2011.01.044

42. Segedin B, Petric P. Uncertainties in target volume delineation in radiotherapy - are they relevant and what can we do about them? *Radiol Oncol* 2016; **50:** 254-62. doi: 10.1515/raon-2016-0023.

43. Gierga DP, Turcotte JC, Sharp GC, Sedlacek DE, Cotter CR, Taghian AG. A voluntary breath-hold treatment technique for the left breast with unfavorable cardiac anatomy using surface imaging. *Int J Radiation Oncol Biol Phys* 2012; **84:** 663-8. doi: 10.1016/j.ijrobp.2012.07.2379

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Rezultati zdravljenja okužbe s Helicobacter v Sloveniji v obdobju 2013–2015 kot del Evropskega registra zdravljenja okužbe Helicobacter pylori

Tepeš B, Kastelic M, Vujasinovič M, Lampič P, Šeruga M, Brglez Jurečič N, Olga PN, Donday MG, O'Morain C, Megraud F, Mc Nicholl AG, Javier GP

Izhodišča. Okužba s *Helicobacter pylori* (*H. pylori*) je najpogostejša kronična bakterijska okužba. Okuženih je 50 % svetovne populacije. *H. pylori* je karcinogen I.reda, odgovoren za nastanek 89 % želodčnega raka, brez raka kardije.

Bolniki in metode. Slovenija je vključena v Evropski register *Helicobacter pylori* od njegove ustanovitve. V sedmih medicinskih centrih smo v obdobju od 16. 4. 2013 do 15. 5. 2016 zbirali podatke o uspehih zdravljenja okužbe s *H. pylori* pri 1774 bolnikih. Podatki so bili primerni za modificirano analizo z namenom ozdravitve (mITT) pri 1519 bolnikih in za analizo po protokolu (PP) pri 1346 bolnikih.

Rezultati. Pri zdravljenju v celoti ni sodelovalo 11,4 % bolnikov. Uspeh sedemdnevnega zdravljenja z zaviralcem protonske črpalke (ZPČ) + klaritromicinom (K) + amoksicilinom (A) je bil 88,7 % PP in 72,0 % mITT; v primeru sheme ZPČ + K + metronidazol (M) 85,2 % PP in 84,4 % mITT. V drugem poiskusu zdravljenja smo najpogosteje uporabili dvotedensko zdravljenje ZPČ + A + Levofloxacin z 92,3 % uspehom ozdravitve PP in 87,1 % mITT. Štiritirno zdravljenje 10 do 14 dni z bizmutom smo uporabili v tretjem poizkusu zdravljenja. Vse bolnike, ki so sodelovali pri zdravljenju, smo ozdravili okužbe s *H.pylori*.

Zaključki. Visoka stopnja nesodelovanja pri zdravljenju terja posebno analizo. Ker je rezistenca *H. pylori* na klaritromicin v Sloveniji še vedno < 15 %, so uspehi sedemdnevnega trotirnega zdravljenja > 85 % PP še zadovoljivi, uspehi zdravljenja po mITT pa so nezadovoljivi.

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Predrakave želodčne spremembe pri bolnikih vključenih v Nacionalni program presejanja na rak in predrakave spremembe debelega črevesja in danke

Tepeš B, Šeruga M, Vujasinovič M, Urlep D, Ljepovič L, Brglez Jurečič N, Forte A, Kek Ljubec A, Škvarč M

Izhodišča. Želodčni rak je peti najpogostejši rak na svetu. Okužba z bakterijo *Helicobacter pylori* (*H. pylori*) povzroča 89 % vseh želodčnih rakov ne upoštevajoč rakov kardije. Kronična okužba povzroči nastanek predredrakavih sprememb, kot sta atrofija in intestinalna metaplazija. Sekundarna preventiva želodčnega raka je možna z presejalnimi gastroskopijami, kar pa je drago in pri preiskovancih slabo sprejeto. Druga možnost je določitev nivoja pepsinogena I in II v serumu, ugotavljanje razmerja pepsinogen I/II z namenom najti bolnike s predrakavimi spremembami, ki jih potem spremljamo endoskopsko.

Bolniki in metode. V multicentrično raziskavo smo vključili 288 bolnikov (154 moških; 53.5 %), povprečne starosti 60,68 let, ki so bili napoteni na kolonoskopijo v okviru Nacionalnega programa presejanja na rak debelega črevesja in danke SVIT. Uporabili smo Gastropanel (BioHit, Finland) za test serološke biopsije.

Rezultati. Našli smo 24 bolnikov (12 moških; povprečne starosti 63,7 let), ki so imeli razmerje pepsinogen I/II < 3 in/ali pepsinogen I < 30μg/L. Histološko smo potrdili predrakave spremembe želodčne sluznice pri 21 bolnikih (7.3 %). Operativno povezavo z ocenjevanjem želodčne intestinalne metaplazije (*Operative Link on Gastric Intestinal Metaplasia Assessment*, OLGIM) > 1 smo našli pri 20 bolnikih; operativno povezavo za oceno gastritisa (*Operative Link for Gastritis Assessment*, OLGA) > 1 pa smo našli pri 19 bolnikih. Skupna natančnost ugotavljanja predrakavih sprememb je bila 87,5 %. Serološka preiskava na okužbo s *H. pylori* je bila pozitivna pri 219 bolnikih (76 %).

Zaključki. Test Gastropanel se je pokazal kot zanesljiva metoda ugotavljanja predrakavih sprememb želodca, ki lahko najde bolnike, ki potrebujejo endoskopijo. V naši skupini bolnikov ugotavljamo visoko prekuženost z bakterijo *H. pylori*.

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Napovedna vrednost računalniško tomografskih perfuzijskih parametrov za odgovor na zdravljenje in preživetje bolnikov z jetrnoceličnim rakom, zdravljenih s transarterijsko kemoembolizacijo

Popovič P, Leban A, Kregar K, Garbajs M, Dežman R, Bunc M

Izhodišča. Namen raziskave je bilo ugotoviti, ali lahko z računalniško tomografskimi perfuzijskimi (CTPI) parametri bolnikov z jetrnoceličnim rakom (HCC), ki smo jih pridobili pred zdravljenjem z eluiranjem zdravila s transarterijsko kemoembolizacijo (DEBTACE), napovemo odgovor tumorja na zdravljenje in preživetje bolnikov po zdravljenju.

Bolniki in metode. V retrospektivno opazovalno raziskavo smo vključili 18 bolnikov (17 moških; srednja starost, 69 ± 5,8 let) s HCC, pri katerih smo ugotovili vmesni stadij bolezni po barcelonski klasifikaciji (*Barcelona Clinic Liver Cancer Classification*). Bolnikom smo med decembrom 2010 in januarjem 2013 naredili preiskavo jeter CTPI v povprečju 22 ± 49,7 dni pred zdravljenjem s superselektivno DEBTACE. Odgovor na zdravljenje smo slikovno vrednotili v povprečju 4,9 ± 3,3 mesece po TACE. Na kontrolnem slikanju smo upoštevali prilagojene kriterije za oceno odgovora v solidnih tumorjih (*mRECIST*) in razdelili bolnike na tiste, ki so odgovorili s popolnim odgovorom in tiste ki niso tako odgovorili. Uporabili smo Studentov t-test, da smo smo s parametri slikanja CTPI primerjali bolnike s popolnim in delnim odgovorom. Pri ugotavljanju vpliva posameznih parametrov CTPI na preživetja pa smo uporabili metodo Kaplan-Meier.

Rezultati. Primerjava perfuzijskih parametrov lezij s popolnim ter lezij z delnim odgovorom na TACE ni pokazala statistično značilnih razlik. Preživetje pa je bilo statistično značilno boljše pri bolnikih s pretokom krvi (BF) nižjim od 50,44 ml/100ml/min (p = 0,033), volumnom krvi (BV) nižjim od 13,32 ml/100ml (p = 0,028), časom do največjega obarvanja (TTP) daljšim od 19,035 s (p = 0,015).

Zaključki. Preiskava CTPI bi lahko na podlagi vrednosti perfuzijskih parametrov BF, BV in TTP, ki smo jih pridobili pred zdravljenjem s TACE, napovedala preživetje. Potrebne so dodatne klinične raziskave, ki bi dodatno ovrednotile napovedno vrednost CTPI pri bolnikih s HCC zdravljenih s TACE.

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Predperativna intenzitetno modulirana kemoradioterapija s simultanim integriranim dodatkom doze pri raku danke. Dvoletno sledenje bolnikov v raziskavi II. faze

But-Hadžić J, Velenik V

Izhodišča. Namen raziskave je bil ugotoviti učinkovitost in varnost eksperimentalne frakcionacije ob uporabi intenzitetno modulirane radioterapije s simultano integriranim dodatkom doze (IMRT-SID) pri lokalno napredovalem raku danke. Na ta način lahko skrajšamo celokupni čas obsevanja in ne povišamo celokupne doze pri predoperativni radiokemoterapiji.

Bolniki in metode. Med januarjem 2014 in novembrom 2015 smo predoperativno obsevali 51 bolnikov z operabilnim rakom danke v II.–III. stadiju. Z obsevalno tehniko IMRT so prejeli 41,8 Gy na medenico, s simultanim dodatkom doze pa do 46,2 Gy na T2/3 in 48,8 Gy na T4 tumor v 22-ih dnevnih frakcijah. Sočasno so prejemali standardni odmerek kapecitabina. Zdravljenje je po protokolu zaključilo 50 bolnikov in 47/50 je bilo operiranih. Srednji čas sledenja bolnikov je bil 35 mesecev.

Rezultati. Stopnja zgodnje toksičnosti G ≥ 3 je bila 2,4 %. Celokupno znižanje stadija smo ugotovili pri 89 % bolnikov, resekcijo R0 pa pri 98 %. Patološko popolni odgovor smo dosegli pri 25,5 % bolnikov, ki so imeli 100 % 2 letno lokalno kontrolo bolezni, preživetje brez ponovitve bolezni in celokupno preživetje. Analiza preživetja pri vseh 51 bolnikih, ki smo jih zdravili, je pokazala stadij pN kot negativni napovedni dejavnik za preživetje brez ponovitve bolezni in celokupno preživetje. Dvoletna lokalna kontrola bolezni, preživetje brez ponovitve bolezni in celokupno preživetje za vse bolnike so bili 100 %, 90 % (95 % CI 98,4–81,6) in 92,2 % (95 % CI 99,6–84,7).

Zaključki. Eksperimentalni obsevalni režim je v tej raziskavi omogočil doseganje visoke stopnje patološko popolnih odgovorov z nizko stopnjo zgodnje toksičnosti. Dvoletna lokalna kontrola bolezni, preživetje brez ponovitve bolezni in celokupno preživetje so bili zelo spodbudni.

Radiol Oncol 2018; 52(1): 30-35.
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Vpliv regresije tumorja na dolgoročno preživetje bolnikov z lokalno napredovalim rakom danke po predoperativni radiokemoterapiji

Omejc M, Potisek M

Izhodišča. Rak danke pogosto odkrijemo v lokalno napredovalem stadiju (UICC II, III). Zdravljenje vključuje predoperativno radiokemoterapijo, kateri sledi čez 6-8 tednov resekcija danke ter pooperativna kemoterapija. Namen pričujoče raziskave je bil ugotoviti, ali odgovor tumorja na predoperativno kemoradioterapijo vpliva na dolgotrajno preživetje pri bolnikih z lokalno napredovalim rakom danke.

Bolniki in metode. V retrospektivno raziskavo smo vključili 202 bolnikov z lokalno napredovalim nemetastatskim rakom danke, ki so bili med letoma 2006 in 2010 zdravljeni z predoperativno radiokemoterapijo, resekcijo in poperativno kemoterapijo. Klinične in patohistološke podatke smo vključili v univariatno in multivariatno analizo. Preživetje smo ocenjevali po metodi Kaplan Meier.

Rezultati. Mediano spremljanje bolnikov je bilo 53,2 meseca. Popolna regresija tumorja (ypT0N0, pCR) je bila dosežena pri 14,8 % bolnikov. 5-letno preživetje bolnikov z popolno regresijo tumorja (pCR) je bilo > 90 %. V univariatni analizi so se pokazali ypT, ypN in pooperativni stadij kot pomemben napovedni dejavnik celokupnega preživetja. Edini neodvisni napovedni dejavnik v multivariatni analizi pa je bil odgovor tumorja na neoadjuvantno zdravljenje (p = 0,003).

Zaključki. Patohistološko ugotovljen odgovor tumorja na predoperativno zdravljenje je pomemben napovedni dejavnik za dolgoročno preživetje bolnikov z lokalno napredovalim rakom danke.

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Laparoskopska parenhim ohranjajoča resekcija jeter zaradi zasevkov raka debelega črevesa in danke

Aghayan DL, Pelanis E, Fretland AA, Kazaryan AM, Sahakyan MA, Røsok BI, Barkhatov L, Bjørnbeth BA, Elle OJ, Edwin B

Izhodišča. Laparoskopsko resekcijo jeter zaradi zasevkov raka debelega črevesa in danke izvajamo v specializiranih centrih. Pri multidisciplinarnem zdravljenju raka debelega črevesa in danke težimo k parenhim ohranjajočem načinu zdravljenja, kljub temu pa je vloga takšnega zdravljenja nejasna. Namen raziskave je bil prikazati kratko- in dolgoročne rezultate laparoskopske parenhim ohranjajoče jetrne resekcije v posamični ustanovi.

Bolniki in metode. V obdobju od avgusta 1998 do marca 2017 smo v Univerzitetni bolnišnici Oslo – Rikshospitalet opravili 951 laparoskopskih resekcij jeter. V raziskavo smo vključili tiste bolnike, kjer smo primarno naredili parenhim ohranjujočo resekcijo jeter zaradi zasevkov raka debelega črevesa in danke. Laparoskopsko parenhim ohranjajočo jetrno resekcijo smo opredelili kot ne-anatomsko laparoskopsko resekcijo jeter. Tako smo iz raziskave izključili hemihepatektomije in sekcionektomije. Analizirali smo perioperativne zaplete in izhod bolezni. Zaplete po operaciji smo razvrstili po klasifikaciji Accordian. Srednji čas sledenja je znašal 40 mesecev.

Rezultati. Pri 296 bolnikih smo naredili primarno laparoskopsko parenhim ohranjajočo jetrno resekcijo zaradi zasevkov raka debelega črevesa in danke. Pri 204 bolnikih smo naredili eno resekcijo, pri 92 pa smo hkrati opravili več resekcij. 5 laparoskopskih posegov smo nadaljevali z odprto operacijo. Srednji čas operacije je znašal 134 minut, izguba krvi 200 ml in čas hospitalizacije 3 dni. 90-dnevne smrtnosti ni bilo. Delež zapletov po operaciji je znašal 14,5 %. Pri 189 bolnikih se je bolezen ponovila. Ponovitev je nastopila v jetrih pri 146 bolnikih (49 %), izmed katerih smo 85 bolnikov ponovno zdravili kirurško (z resekcijo jeter [n = 69], z ablacija [n = 14] in s transplantacijo jeter [n = 2]). Pet-letno celokupno preživetje je bilo 48 % srednje celokupno preživetje pa 56 mesecev.

Zaključki. V izkušenih rokah je laparoskopska parenhim ohranjajoča jetrna resekcija varna metoda zdravljenja zasevkov raka debelega črevesa in danke. Tehnika omogoča ponovne kirurške posege, ki lahko izboljšajo preživetje takšnih bolnikov.

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doi: 10.1515/raon-2017-0047

Simultane popolne laparoskopske resekcije primarnega raka debelega črevesa in danke ter sinhronih jetrnih zasevkov. Izkušnje posamične ustanove z analizo uravnoteženega vzorca

Ivanecz A, Krebs B, Stožer, Jagrič T, Plahuta I, Potrč S

Izhodišča. Namen raziskave je bila primerjava popolne laparoskopske in odprte simultane resekcije primarnega raka debelega črevesa in danke ter sinhronih jetrnih zasevkov.

Bolniki in metode. V obdobju od leta 2000 do 2016 smo vse bolnike, ki smo jih zdravili s simultano resekcijo, vključili v opisano klinično ne-randomizirano raziskavo. Z metodo uravnoteženega vzorca smo primerjali obe skupini, ki smo ju operirali laparoskopsko ali odprto. Primarni cilji analize so bili perioperativni in onkološki rezultati zdravljenja. Sekundarna cilja analize sta bila celokupno preživetje in preživetje brez bolezni.

Rezultati. 82 bolnikov smo zdravili s simultano resekcijo primarnega raka debelega črevesa in danke ter sinhronih jetrnih zasevkov. Med njimi smo 10 bolnikov operirali laparoskopsko. Vseh 10 bolnikov se je po metodi uravnoteženega vzorca ujemalo z 10 bolniki iz skupine, ki smo jo zdravili z odprto operacijo. V skupini laparoskopsko zdravljenih je bil čas bivanja v bolnišnici bistveno krajši (P = 0,044) in uživanje trdne hrane hitrejše (P = 0,006). Pri nobenem bolniku, ki smo ga operirali laparoskopsko ni bilo potrebno operacije nadaljevati z odprtim posegom. Ni bilo razlik v času operacije, izgubi krvi, transfuziji, potrebi po narkotičnih analgetikih, med kliničnimi dejavniki tveganja, resekcijskih robovih, deležu R0 resekcij, v zapletih, smrtnosti in pojavu brazgotinskih kil. Skupini se nista razlikovali niti glede deleža 3-letnega celokupnega preživetja (90 proti 75 %; P = 0,842) in preživetja brez bolezni (60 proti 57 %; P = 0,724).

Zaključki. Laparoskopska operacija je skrajšala čas bivanja v bolnišnici in omogočila zmožnost hitrejšega uživanja trdne hrane. Onkološki rezultati in preživetja so bili primerljivi. Laparoskopski poseg je upravičen pri skrbno izbranih bolnikih v rokah izkušenega kirurga v terciarnem referenčnem centru.

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Dejavniki vpliva za perioperativno obolevnost in smrtnost ter posledice perioperativne obolevnosti in dolgoročno preživetje po resekcijah glave trebušne slinavke

Potrč S, Ivanecz A, Pivec V, Marolt U, Rudolf S, Ilijevec B, Jagrič T

Izhodišča. Cilj raziskave je bil odkriti dejavnike tveganja za perioperativno obolevnost in smrtnost, kot tudi posledice perioperativne obolevnosti na dolgoročno preživetje po resekcijah glave trebušne slinavke.

Bolniki in metode. V retrospektivni raziskavi 240 bolnikov po resekciji glave trebušne slinavke ali popolni odstranitvi trebušne slinavke smo analizirali kliničnopatološke dejavnike in njihovo povezavo z perioperativno obolevnostjo, 30- in 90-dnevno smrtnostjo in dolgoročnim preživetjem. Glede na Clavien-Dindo klasifikacijo so bili vsi zapleti s stopnjo II ali več opredeljeni kot vsesplošni zapleti. Raziskovali smo korelacijo kliničnopatoloških dejavnikov z vsesplošnimi zapleti, kirurškimi, splošnimi in nekaterimi posebnimi zapleti, kot so puščanje anastomoze črevesa in trebušne slinavke, fistule trebušne slinavke (tip A, B, C), puščanja drugih anastomoz, krvavitve in ognojki.

Rezultati. V obdobju 9-ih let smo opravili resekcijo trebušne slinavke pri 240 bolnikih. Vsesplošnih zapletov je bilo 37,1 %, kirurških 29,2 % in splošnih 15,8 %. Med kirurškimi zapleti smo ugotovili puščanje anastomoze črevesa in trebušne slinavke, puščanje drugih anastomoz, krvavitve ter ognojke pri 19 % bolnikov (od 208 resekcij glave trebušne slinavke), 5,8 %, 5,8 % in 2,5 % za vsak zaplet posebej. Starost, vrednost ASA, amilaza iz drenov in fistule trebušne slinavke tipa B in C so bili pomembno povezani z različnimi tipi zapletov. Vsesplošni 30- in 90-dnevni smrtnosti sta bili 5 % in 7,9 % v obdobju P1 in sta se zmanjšali na 3,5 % in 5 % v obdobju P2.

Zaključki. Visoka vrednost amilaze po drenih in posledični fistuli trebušne slinavke tipa B in C, vsesplošni zapleti, puščanje anastomoze med črevesom in trebušno slinavko ter krvavitev so bili neodvisni kazalci obolevnosti, medtem ko sta se puščanje anastomoze med črevesom in trebušno slinavko ter krvavitev pokazali kot neodvisni napovednik 30-dnevne smrtnosti, vsesplošni zapleti in fistula trebušne slinavke tipa C pa tudi kot napovednik 90-dnevne smrtnosti.

Radiol Oncol 2018; 52(1): 65-74.
doi:10.1515/raon-2017-003

Rezultati kirurškega zdravljenja žleznega raka kardije želodca. Izkušnje posamičnega centra

Potrč S, Ivanecz A, Krebs B, Marolt U, Ilijevec B, Jagrič T

Izhodišča. Žlezni raki kardije želodca so biološko agresivni tumorji s slabim dolgoročnim preživetjem po kurativni resekciji. Pri resektabilnih žleznih rakih kardije največkrat naredimo razširjeno totalno gastrektomijo ali pa proksimalno gastrektomija z distalno ezofagektomijo. Še vedno pa ni dorečeno, ali je bolj primeren transabdominalni ali transtorakalni kirurški pristop. Namen raziskave je bil ovrednotili možne razlike navedenih kirurških zdravljenj in upoštevati klinično pomembne podatke, ki so vplivali na postoperativno obolevnost, smrtnost in dolgoročno preživetje.

Bolniki in metode. Med 844 gastrektomijami, ki smo jih opravili med januarjem 2000 in decembrom 2016, smo naredili 166 posegov zaradi žleznega raka kardije želodca. Pri analizi smo uporabili metodo Coxove regresije.

Rezultati. Naredili smo 136 totalnih gastrektomij z distalno ezofagektomijo in 125 proksimalnih gastrektomij z distalno ezofagektomijo. D2 limfadenektomija je bila opravljena pri 88,2 %, splenektomija pri 47,2 % in multiorganske resekcije pri 12,4 % bolnikov. Stopnja R0 resekcij je bila 95,7 %. Srednja vrednost bližnjega resekcijskega roba na požiralniku je bila 42,45 mm, manj kot 21 mm je bila pri 9 bolnikih. Skupna obolevnost glede na Clavien-Dindo klasifikacijo (> 1) je znašala 28,6 %. Kirurških zapletov je bilo 15,5 % in internističnih 21,1 %. 30-dnevna smrtnost je bila 2,2 %. 5-letno preživetje pri R0 resekcijah je bilo 33,4 %. V raziskavi so se multiorganska resekcija, globina infiltracije tumorja, stadij bezgavk in resekcije v zdravo pokazali za neodvisne napovedne dejavnike za zaplete in preživetje.

Zaključki. Transhiatalni pristop pri resekciji žleznega raka kardije želodca je varen poseg pri bolnikih s Siewert II in III tumorjem glede na pooperativno obolevnost in smrtnost. Tudi dolgoročno preživetje je primerljivo s torakoabdominalnim pristopom. Zapletom, povezanim s torakoabdominalnim pristopom, se tako lahko izognemo brez vpliva na stopnjo lokalne ponovitve bolezni.

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Vpliv rednih ambulantnih kontrol bolnikov z alkoholno jetrno cirozo na stopnjo hospitalizacije in preživetje

Majc D, Tepeš B

Izhodišča. V raziskavi smo želeli ugotoviti, ali imajo redne ambulantne kontrole bolnikov z alkoholno jetrno cirozo vpliv na stopnjo hospitalizacije in smrtnost.

Bolniki in metode. V prospektivno študijsko skupino smo vključili bolnike z alkoholno jetrno cirozo, ki so imeli redne ambulantne kontrole. V nerandomizirano retrospektivno kontrolno skupino smo vključili bolnike z alkoholno jetrno cirozo, ki so imeli kontrole le v primeru zapletov. Raziskava je potekala med leti 2006 in 2011.

Rezultati. V študijsko skupino smo vključili 98 bolnikov, v kontrolno pa 101 bolnika.V študijski skupini smo imeli več ambulantnih pregledov kot v kontrolni (5,54 vs. 2,27 pregledov, p = 0.000). Bolniki v študijski skupini so imeli 25 hospitalizacij manj (10,2 %; p = 0,612). Srednje preživetje bolnikov v študijski skupini je bilo 4,6 let, v kontrolni skupini pa 2,9 (p = 0,021). Bolniki z cirozo Child A so imeli v študijski skupini v povprečju 1 leto daljše preživetje (p = 0,035). Ni bilo razlik v preživetju med skupinama v skupini s cirozo Child B. Bolniki s cirozo Child C so imeli v študijski skupino povprečno 1,6 let daljše preživetje (p = 0,006). Uživanje alkohola je bilo manjše v študijsji skupini (p =0.018).

Zaključki. Ugotovili smo, da so bolniki v študijski skupini uživali statistično značilno manj alkohola, imeli so manj hospitalizacij in s statistično značilno daljše preživetje. S tem smo potrdili potrebo po rednem ambulantnem spremljanju bolnikov z alkoholno jetrno cirozo.

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Prehrana bonikov z nevrološko okvaro

Orel A, Homan M, Blagus R, Benedik E, Orel R, Fidler Mis N

Izhodišča. Strokovne smernice priporočajo za prehrano bolnikov s težko nevrološko okvaro, ki imajo gastrostomo, komercialne enteralne prehranske pripravke. Kljub temu bolniki pogosto uporabljajo doma pripravljeno pasirano hrano. Zdi se, da njena popularnost v nekaterih skupinah bolnikov celo narašča. Primerjali smo učinkovitost komercialnih enteralnih pripravkov in pasirane hrane za hranjenje po gastrostomi pri zdravljenju podhranjenosti.

Bolniki in metode. V 6-mesečno intervencijsko raziskavo smo vključili 37 podhranjenih otrok, adolescentov in mladih odraslih (starost 2–26 let) s težko nevrološko okvaro (po klasifikaciji *GMFCS* stopnja V). Bolnike smo hranili po gastrostomi s komercialnimi enteralnimi pripravki (n = 17) ali s pasirano hrano (n = 20). Z meritvami smo ocenili prehranski status pred in ob koncu intervencije.

Rezultati. Porast vrednosti Z telesne teže za starost in indeksa telesne mase je bil večji pri skupini hranjeni s komercialnimi enteralnimi pripravki kot pri skupini na pasirani hrani (2,07 proti 0,70, p = 0,0012; in 3,75 proti 0,63, p = 0,0014). Tudi sprememba indeksa telesne maščobe je bila večja pri skupini hranjeni z enteralnimi pripravki (1,12 kg/m^2 proti 0,38 kg/m^2; p = 0,0012). Medtem ko se je pri bolnikih s komercialnimi enteralnimi pripravki povečal tudi indeks puste telesne mase (za 0,70 kg/m^2), pri bolnikih na pasirani hrani ni prišlo do porasta (-0,06 kg/m^2) (p = 0,0487).

Zaključki. Rezultati raziskave kažejo, da je pri prehranski rehabilitaciji podhranjenih bolnikov s težko nevrološko okvaro prehrana po gastrostomi s pasirano hrano, tudi če je strokovno načrtovana, manj učinkovita od prehrane s komercialnimi enteralnimi pripravki. Te rezultate bo potrebno potrditi še z večjimi in po možnosti randomiziranimi kliničnimi raziskavami.

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MR in ^{11}C acetat PET/CT za napoved zasevkov v področnih bezgavkah pri novoodkritem raku prostate

von Below C, Wassberg C, Grzegorek R, Kullberg J, Gestblom C, Sörensen J, Waldén M, Ahlström H

Izhodišča. Namen raziskave je bil ovrednotiti kvantitativne in kvalitativne parametre MR in ^{11}C acetat PET/CT za napoved zasevkov v področnih bezgavkah pri novoodkritem raku prostate.

Bolniki in metode. Analizirali smo bolnike z rakom prostate, ki smo ga opredelili z vmesnim (n = 6) in visokim tveganjem (n = 47). Pred razširjeno pelvično bezgavčno disekcijo smo jih slikali s 3T MR-jem (40 bolnikov) in ^{11}C acetat PET/CT-jem (53 bolnikov). Pri vsakem bolniku smo ocenili povprečni viden difuzijski koeficient (ADCpovprečni), maksimalno standardizirano vrednost prevzema (SUVmaksimalni), velikost in obliko z MR najbolj sumljive bezgavke, stadij T primarnega tumorja ter ADCpovprečni in SUVmaksimalni v tumorju. Parametre smo presojali z enostavno in multiplo logistično regresijo.

Rezultati. Vsi parametri razen ADCpovprečni in SUVmaksimalni primarnega tumorja so bili neodvisni napovedni kazalci zasevkov v bezgavkah. V multipli logistični regresijski analizi je bil najboljši model ADCpovprečni v kombinaciji s MR stadijem T. Oba parametra sta bila neodvisna napovedna kazalca zasevkov v bezgavkah. AUC obeh napovednih kazalcev je bil 0,81, kar je več kot AUC samega ADCpovprečni, kjer je znašal 0,65 in več kot AUC samega MR stadija T, kjer je bil 0,69.

Zaključki. Različni kvalitativni in kvantitativni slikovni parametri napovedujejo zasevke v področnih bezgavkah pri raku prostate. S kombinacijo ADCpovprečni bezgavke in MR stadija T je bila napovedna vrednost višja kot vsakega parametra zase.

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Elektrokemoterapija – učinkovita metoda zdravljenja nekaterih kožnih tumorjev pri belem dihurju (Mustela putorius furo)

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Izhodišča. Mastocitom, adenom žlez lojnic ter redkeje ploščatocelični papilom so kožni tumorji pri belem dihurju (Mustela putorius furo). Za njihovo zdravljenje najpogosteje svetujemo kirurško odstranitev s primernim varnostnim robom. V članku smo opisali elektrokemoterapijo, kot minimalno invazivno nekirurško metodo zdravljenja nekaterih kožnih tumorjev pri belem dihurju.

Marteriali in metode. Prvi pacient je bil petletni, kastriran samec pri katerem smo pri dveh pregledih v razmaku 4 mesecev ugotovili kožni tumor. Lokacija prvega tumorja je bila laterodorzalna stran korena repa, lokacija drugega tumorja pa na zunanji strani desnega skočnega sklepa. Pri drugem pacientu, sedemletni, sterilizirani samici smo pri enem pregledu ugotovili dva kožna tumorja. Prvi tumor je ležal lateralno na levem skočnem sklepu, drugi pa dorzolateralno na levi strani prsnega koša. Pri prvem pacientu sta bili obe tumorski masi mastocitoma, pri drugem pacientu pa je bil en tumor ploščatocelični papilom in drugi adenom žlez lojnic. Vse tumorje smo zdravili z elektrokemoterapijo z bleomicinom.

Rezultati. Pri obeh pacientih smo pri vseh štirih tumorjih opazili popolni odgovor na terapijo. Pri prvem pacientu sta v opazovanem obdobju 15 mesecev oba tumorja še vedno v remisiji; prvi tumor 15 mesecev, drugi tumor pa 11 mesecev po terapiji. Tudi pri drugem pacientu sta v opazovanem obdobju 8 mesecev oba tumorja v remisiji; oba 8 mesecev po zdravljenju z elektrokemoterapijo.

Zaključki. Elektrokemoterapija z bleomicinom je varna in učinkovita metoda zdravljenja nekaterih kožnih tumorjev pri belih dihurjih. Zdravljenje je učinkovito, sorazmerno enostavno in poceni in bi lahko v določenih primerih nadomestilo kirurgijo, kar velja predvsem za tumorje, ki jih zaradi neugodne lokacije težje kirurško odstranimo.

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Vpliv genetske variabilnosti na tveganje za razvoj malignega mezotelioma

Franko A, Kotnik N, Goričar K, Kovač V, Dodič-Fikfak M, Dolžan V

Izhodišča. Maligni mezoteliom je redek rak s slabo napovedjeo poteka bolezni. Povezan je z izpostavljenostjo azbestu. Ker imajo reaktivne kisikove spojine pomembno vlogo v mehanizmu karcinogeneze, lahko genetska variabilnost v antioksidativni obrambi spremeni posameznikovo dovzetnost za razvoj tega raka. V raziskavi smo proučevali vpliv funkcionalnih polimorfizmov *NQO1*, *CAT, SOD2* in *hOGG1*, gensko-genskih in gensko-okoljskih interakcij na tveganje za pojav malignega mezotelioma.

Bolniki in metode. Pri 150 primerih z malignim mezoteliomom in 122 kontrolah, ki niso imeli nobene bolezni, povezane z izpostavljenostjo azbestu, smo z genetsko analizo določili polimorfizme *NQO1*, *CAT*, *SOD2* in *hOGG1*.

Rezultati. Tveganje za razvoj malignega mezotelioma je naraščalo s kajenjem, razmerje obetov (RO) 9,30 (interval zaupanja [IZ) 4,83–17,98] in nekoliko tudi z starostjo, RO 1,10 (95% IZ: 1,08–1,14). Srednja in visoka izpostavljenost azbestu je predstavljala 7-krat večje tveganje za razvoj malignega mezotelioma v primerjavi z nizko izpostavljenostjo, RO 7,05 (95% IZ 3,59–13,83). *NQO1* rs1800566 je bil pomembno povezan s tveganjem za maligni mezoteliomom, RO = 1,73 (95% IZ 1,02–2,96). Kljub temu, da ni bilo neodvisne povezave med polimorfizmom *CAT* rs1001179 ali polimorfizmom *hOGG1* rs1052133 in malignim mezoteliomom, pa je interakcija med obema polimorfizmoma pokazala zaščitni učinek, RO_{int} 0,27 (95 % IZ 0,10–0,77).

Zaključki. Ugotovitve raziskave kažejo, da imajo tako genetska variabilnost v antioksidativni obrambi in v popravljanih mehanizmih poškodb DNA, kot tudi gensko-genske interakcije lahko pomembno vlogo pri razvoju malignega mezotelioma. Rezultati raziskave lahko prispevajo k boljšemu razumevanju patogeneze malignega mezotelioma ter k preprečevanju in zgodnejši diagnozi tega agresivnega tumorja.

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Obsevanje levostranskega raka dojke v zadržanem globokem vdihu zmanjša dozo na srce brez okrnjenega pokritja tarčnega volumna

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Izhodišča. Med obsevanjem levostranskega raka dojke so deli srca izpostavljeni obsevalni dozi, kar lahko vodi v pozne zaplete zdravljenja. V pričujoči raziskavi smo opravili primerjavo izpostavljenosti srca med obsevanjem v zadržanem globokem vdihu (ang. *voluntary deep inspiration breath hold,* V-DIBH) in prostem dihanju (ang. *Free breathing,* FB).

Bolniki in metode. V raziskavo smo vključili bolnice z rakom leve dojke, zdravljene na našem oddelku s pooperativnim obsevanjem med majem 2015 in januarjem 2017. Najprej smo opravili dozno načrtovanje na podlagi računalniških tomografskih (CT) slik pridobljenih z načinom FB. Bolnice z dozno volumskim parametrom za srce V25Gy ≥ 5 % na FB-CT smo vključili v program učenja tehnike V-DIBH. Pri tistih, ki so program uspešno opravile, smo ponovili dozno načrtovanje in nato obsevanje na podlagi CT s pristopom V-DIBH. Dozno volumske parametre za srce, pljuča in optimizirani načrtovalni tarčni volumen (ang. *optimized planning target volume,* OPTV), pridobljene z obema načinoma FB in V-DIBH, smo primerjali med seboj. Premike pri nastavitvah bolnic pred vsakodnevnim V-DIBH obsevanjem in tako nastale sistemske in naključne napake smo primerjali s kontrolno skupino bolnic, zdravljenih s pristopom FB.

Rezultati. V protokol V-DIBH smo vključili 63 bolnic. Devet (14,3 %) smo jih iz končne analize izključili zaradi neustreznega vzdrževanja globokega vdiha, tako da je v raziskavi ostalo 54 bolnic. V primerjavi s tehniko FB smo z V-DIBH statistično značilno znižali srednjo dozo na srce iz 6,1 +/- 2,5 na 3,2 +/- 1,4 Gy ($p < 0,001$), maksimalno srčno dozo iz 51,1 +/- 1,4 na 48,5 +/- 6,8 Gy ($p = 0,005$) in parameter V25Gy iz 8,5 +/- 4,2 na 3,2 +/- 2,5 % ($p < 0,001$). Prostornine srca, izpostavljene nizkim (10−20 Gy) in visokim (30−50 Gy) dozam, so bile s tehniko V-DIBH statistično značilno nižje kot s FB. Srednja doza na levo descendentno koronarno arterijo je bila 23,0 (+/- 6,7) Gy in 14,8 (+/- 7,6) Gy v načinih FB in V-DIBH ($p < 0,001$). Razlike med FB in V-DIBH v srednji pljučni dozi (11,3 +/- 3,2 vs. 10,6 +/- 2,6 Gy), pljučnem parametru V20Gy (20,5 +/- 7 vs. 19,5 +/- 5,1 Gy) in V95% za OPTV (95,6 +/- 4,1 vs. 95,2 +/- 6,3 %) so bile statistično neznačilne. Srednji premiki pri nastavitvah med obsevanjem so bili ≤ 2,7 mm, naključne in sistematične napake so bile ≤ 2,1 mm in ti rezultati se niso statistično značilno razlikovali od rezultatov tehnike FB.

Zaključki. V primerjavi s tehniko FB smo z V-DIBH dosegli statistično značilno in klinično pomembno znižanje obsevalne doze na srce, ne da bi bila ob tem okrnjena dozna pokritost tarčnega volumna. Tehnika V-DIBH je omogočala visoko natančnost nastavitev bolnic med obsevanji.

Fundacija "Docent dr. J. Cholewa"
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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the first quarter of 2018

Doc. dr. Josip Cholewa Foundation for cancer research and education continues with its planned activities in the first quarter of 2018 and is commencing to prepare for the activities the whole year. Its primary focus remains the provision of grants and scholarships and other forms of financial assistance for basic, clinical and public health research in the field of oncology. An analysis of the ongoing activities in the last year was made in order to make an assessment of the impact of Foundation's activities, thus providing a basis for developing new strategies and approaches in its scope of fight against cancer.

The Foundation continues to provide support for »Radiology and Oncology«, a quarterly scientific magazine with a respectable impact factor that publishes research and review articles about all aspects of cancer. The magazine is edited and published in Ljubljana, Slovenia. »Radiology and Oncology« is an open access journal available to everyone free of charge. Its long tradition represents a guarantee for the continuity of international exchange of ideas and research results in the field of oncology for all in Slovenia that are interested and involved in helping people affected by many different aspects of cancer.

The Foundation makes great efforts to provide financial and other kinds of support for the organisation of various forms of meetings to extend and broaden the knowledge about prevention of cancer, early detection of various types of cancer, its treatment and rehabilitation of cancer patients. The advances in knowledge of all aspects of dealing with cancer should be in Foundation's opinion available to all the professionals that treat cancer patients, to the patients themselves and their closest relatives and friends, and finally also to the general public.

The problems associated with cancer affect more and more people and their relatives in Slovenia and elsewhere. The Foundation will therefore continue with its activities in the years to come. Treatment of cancer is ever more successful with many patients surviving decades after the start of their treatment and many new problems and challenges have thus come into place. Longer survival of an increasing number of patients with previously incurable cancer conditions adds many new dimensions to their life and to the life of their families. It also confronts cancer specialists, all the other experts and lay public dealing with cancer with new challenges and new goals to achieve.

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Odmerjanje: Priporočeni odmerek zdravila Alecensa je 600 mg dvakrat na dan s hrano. *Trajanje zdravljenja:* Zdravljenje z zdravilom Alecensa je treba nadaljevati do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. *Prilagoditve odmerka:* Obvladovanje neželenih učinkov lahko obsega zmanjšanje odmerka, začasno prekinitev uporabe ali ukinitev zdravljenja z zdravilom Alecensa. Odmerek zdravila Alecensa je treba zmanjševati v korakih po 150 mg dvakrat na dan, upoštevaje prenašanje. Zdravljenje z zdravilom Alecensa je treba ukiniti, če bolnik ne prenese odmerka 300 mg dvakrat na dan. Smernice za prilagoditev odmerka so opisane v povzetku glavnih značilnosti zdravila. Način uporabe: zdravilo Alecensa je namenjeno peroralni uporabi. Trde kapsule mora bolnik pogoltniti cele in jih ne sme odpirati ali raztapljati. Vzeti jih mora s hrano. **Kontraindikacije:** preobčutljivost za alektinib ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Intersticijska bolezen pljuč (IBP)/pnevmonitis: Bolnike je treba kontrolirati glede pljučnih simptomov, ki kažejo na pnevmonitis. Bolnikom, pri katerih je diagnosticirana IBP/pnevmonitis, je treba zdravljenje z zdravilom Alecensa nemudoma prekiniti; če ni mogoče ugotoviti drugih možnih vzrokov za IBP/pnevmonitis, je treba zdravljenje ukiniti. Hepatotoksičnost: Delovanje jeter, vključno z ALT, AST in celokupnim bilirubinom, je treba kontrolirati izhodiščno in nato na 2 tedna prve 3 mesece zdravljenja. Kasneje je treba spremljanje izvajati periodično, ker se dogodki lahko pojavijo po več kot 3 mesecih; pri bolnikih, ki se jim pojavi zvišanje aminotransferaz in bilirubina, morajo biti kontrole pogostejše. Glede na izrazitost neželenega učinka je treba uporabo zdravila Alecensa začasno prekiniti in zdravilo znova uvesti v manjšem odmerku, ali pa ga je treba ukiniti. Huda mialgija in zvišanja kreatin-fosfokinaze (CPK): Bolnikom je treba naročiti, naj poročajo o vseh nepojasnjenih mišičnih bolečinah, občutljivosti ali šibkosti. Koncentracije CPK je treba določiti vsaka dva tedna v prvem mesecu zdravljenja, pri bolnikih, ki poročajo o simptomih, pa kot je klinično indicirano. Glede na izrazitost zvišanja CPK je treba uporabo zdravila Alecensa začasno prekiniti in zdravilo znova uvesti v manjšem odmerku. Bradikardija: Srčno frekvenco in krvni tlak je treba kontrolirati, kot je klinično indicirano. Če se bolniku pojavijo simptomatska bradikardija ali življenjsko ogrožujoči dogodki, je treba oceniti sočasna zdravila, za katera je znano, da povzročajo bradikardijo, in antihipertenzivna zdravila, odmerjanje zdravila Alecensa pa je treba prilagoditi. Fotosenzibilnost: Bolnikom je treba naročiti, naj se med jemanjem zdravila Alecensa in vsaj še 7 dni po koncu zdravljenja izogibajo dolgotrajnejšemu izpostavljanju soncu. Prav tako jim je treba naročiti, naj za preprečitev sončnih opeklin uporabljajo širokospektralno sredstvo za sončenje in mazilo za ustnice, ki ščitita pred ultravijoličnimi žarki A in B. Ženske v rodni dobi: zdravilo Alecensa lahko škoduje plodu, če je uporabljeno med nosečnostjo. Bolnice v rodni dobi morajo med zdravljenjem in še vsaj 3 mesece po zadnjem odmerku zdravila Alecensa uporabljati visoko učinkovito kontracepcijsko zaščito. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Vplivi drugih zdravil na alektinib: *Induktorji CYP3A4:* Glede na učinke na skupno izpostavljenost alektinibu in M4 med sočasno uporabo zdravila Alecensa in induktorjev CYP3A odmerka ni treba prilagoditi. Priporočljivo je ustrezno spremljanje bolnikov, ki sočasno jemljejo močne induktorje CYP3A. *Zaviralci CYP3A4:* Glede na učinke na skupno izpostavljenost alektinibu in M4 med sočasno uporabo zdravila Alecensa in zaviralcev CYP3A odmerka ni treba prilagoditi. Priporočljivo je ustrezno spremljanje bolnikov, ki sočasno jemljejo močne zaviralce CYP3A. *Zdravila, ki zvišujejo pH v želodcu:* večkratni odmerki esomeprazola, zaviralca protonske črpalke, 40 mg enkrat na dan, niso imeli klinično pomembnega vpliva na skupno izpostavljenost alektinibu in M4. Vpliv prenašalcev na odstranjevanje alektiniba: M4 je substrat P-gp. Ker alektinib zavira P-gp, ni pričakovati, da bi sočasna uporaba z zaviralci P-gp pomembno vplivala na izpostavljenost M4. Učinki alektiniba na druga zdravila: *Substrati P-gp:* Če zdravilo Alecensa uporabljamo sočasno s substrati P-gp, je priporočljiv ustrezen nadzor. *Substrati BCRP:* Če zdravilo Alecensa uporabljamo sočasno s substrati BCRP, je priporočljiv ustrezen nadzor. *Substrati CYP:* Alektinib in M4 *in vitro* kažeta šibko časovno odvisno zavrtje CYP3A4; alektinib je v kliničnih koncentracijah pokazal šibek indukcijski potencial na CYP3A4 in CYP2B6. Tveganja za indukcijo encimov CYP2B6 in drugih encimov, reguliranih s PXR, razen encima CYP3A4, ni mogoče povsem izključiti. Učinkovitost sočasno uporabljenih peroralnih kontraceptivov se lahko zmanjša. *Neželeni učinki: Zelo pogosti:* anemija, driska, bruhanje, zaprtost, navzea, zvišana AST, ALT in zvišan bilirubin, izpuščaj, mialgija, zvišana kreatin-fosfokinaza v krvi, edemi in povečanje telesne mase. *Pogosti:* disgevzija, motnje vida, bradikardija, stomatitis, zvišana alkalna fosfataza, fotosenzibilnost, akutna poškodba jeter in zvišan kreatinin v krvi. Poročanje o domnevnih neželenih učinkih: Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na: Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. **Režim izdaje zdravila:** Rp/Spec. **Imetnik dovoljenja za promet:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, Velika Britanija. **Verzija: 3.0/17. Informacija pripravljena:** januar 2018. Samo za strokovno javnost.

PG-119-0118-ALC

Literatura: 1. Povzetek glavnih značilnosti zdravila ALECENSA. Dostopano januar 2018 na: http://www.ema.europa.eu/docs/sl_SI/document_library/EPAR_-_Product_Information/human/004164/WC500225707.pdf

DODATNE INFORMACIJE SO NA VOLJO PRI:
Roche farmacevtska družba d.o.o., Vodovodna cesta 109, 1000 Ljubljana

Roche

PRVA REGISTRIRANA TERAPIJA V 2. LINIJI ZA ZDRAVLJENJE ADENOKARCINOMA ŽELODCA ALI GASTRO-EZOFAGEALNEGA PREHODA[1]

CYRAMZA®
(ramucirumab)

UKREPAJTE ZDAJ

USPOSOBLJENI ZA SPREMEMBE, ZA NEPRIMERLJIVE IZKUŠNJE

Skrajšan povzetek glavnih značilnosti zdravila

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

Cyramza 10 mg/ml koncentrat za raztopino za infundiranje

En mililiter koncentrata za raztopino za infundiranje vsebuje 10 mg ramucirumaba. Ena 10-mililitrska viala vsebuje 100 mg ramucirumaba. **Terapevtske indikacije** Zdravilo Cyramza je v kombinaciji s paklitakselom indicirano za zdravljenje odraslih bolnikov z napredovalim rakom želodca ali adenokarcinomom gastro-ezofagealnega prehoda z napredovalo boleznijo po predhodni kemoterapiji, ki je vključevala platino in fluoropirimidin. Monoterapija z zdravilom Cyramza je indicirana za zdravljenje odraslih bolnikov z napredovalim rakom želodca ali adenokarcinomom gastro-ezofagealnega prehoda z napredovalo boleznijo po predhodni kemoterapiji s platino ali fluoropirimidinom, za katere zdravljenje v kombinaciji s paklitakselom ni primerno. Zdravilo Cyramza je v kombinaciji s shemo FOLFIRI indicirano za zdravljenje odraslih bolnikov z metastatskim kolorektalnim rakom (mCRC), z napredovanjem bolezni ob ali po predhodnem zdravljenju z bevacizumabom, oksaliplatinom in fluoropirimidinom. Zdravilo Cyramza je v kombinaciji z docetakselom indicirano za zdravljenje odraslih bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim rakom, z napredovanjem bolezni po kemoterapiji na osnovi platine. **Odmerjanje in način uporabe** Zdravljenje z ramucirumabom morajo uvesti in nadzirati zdravniki z izkušnjami v onkologiji. Odmerjanje *Rak želodca in adenokarcinom gastro-ezofagealnega prehoda* Priporočeni odmerek ramucirumaba je 8 mg/kg 1. in 15. dan 28-dnevnega cikla, pred infuzijo paklitaksela. Priporočeni odmerek paklitaksela je 80 mg/m^2 in se daje z intravenskim infundiranjem, ki traja približno 60 minut, 1., 8. in 15. dan 28-dnevnega cikla. Pred vsakim infundiranjem paklitaksela je treba pri bolnikih pregledati celotno krvno sliko in izvide kemičnih preiskav krvi, da se oceni delovanje jeter. Priporočeni odmerek ramucirumaba kot monoterapije je 8 mg/kg vsaka 2 tedna. *Kolorektalni rak* Priporočeni odmerek ramucirumaba je 8 mg/kg vsaka 2 tedna, dan z intravensko infuzijo pred dajanjem sheme FOLFIRI. Pred kemoterapijo je treba bolnikom odvzeti kri za popolno krvno sliko. *Nedrobnocelični pljučni rak (NSCLC)* Priporočeni odmerek ramucirumaba je 10 mg/kg na 1. dan 21-dnevnega cikla, pred infuzijo docetaksela. Priporočeni odmerek docetaksela je 75 mg/m^2, dan z intravensko infuzijo v približno 60 minutah na 1. dan 21-dnevnega cikla. *Premedikacija* Pred infundiranjem ramucirumaba je priporočljiva premedikacija z antagonistom histaminskih receptorjev H1. Način uporabe Po redčenju se zdravilo Cyramza daje kot intravenska infuzija v približno 60 minutah. Zdravila ne dajajte v obliki intravenskega bolusa ali hitre intravenske injekcije. Da boste dosegli zahtevano trajanje infundiranja približno 60 minut, največja hitrost infundiranja ne sme preseči 25 mg/minuto, saj morate sicer podaljšati trajanje infundiranja. Bolnika je med infundiranjem treba spremljati glede znakov reakcij, povezanih z infuzijo, zagotoviti pa je treba tudi razpoložljivost ustrezne opreme za oživljanje. **Kontraindikacije** Pri bolnikih z NSCLC je ramucirumab kontraindiciran, kjer gre za kavitacijo tumorja ali prepletenost tumorja z glavnimi žilami. **Posebna opozorila in previdnostni ukrepi** Trajno prekinite zdravljenje z ramucirumabom pri bolnikih, pri katerih se pojavijo resni arterijski trombembolični dogodki, gastrointestinalne perforacije, krvavitev stopnje 3 ali 4, če zdravstveno pomembne hipertenzije ni mogoče nadzirati z antihipertenzivnim zdravljenjem ali če se pojavi fistula, raven beljakovin v urinu > 3 g/24 ur ali v primeru nefrotskega sindroma. Pri bolnikih z neuravnano hipertenzijo zdravljenja z ramucirumabom ne smete uvesti, dokler oziroma v kolikor obstoječa hipertenzija ni uravnana. Pri bolnikih s ploščatoceličnо histologijo obstaja večje tveganje za razvoj resnih pljučnih krvavitev. Če se pri bolniku med zdravljenjem razvijejo zapleti v zvezi s celjenjem rane, prekinite zdravljenje z ramucirumabom, dokler rana ni povsem zaceljena. V primeru pojava stomatitisa je treba takoj uvesti simptomatsko zdravljenje. Pri bolnikih, ki so prejemali ramucirumab in docetaksel za zdravljenje napredovalega NSCLC z napredovanjem bolezni po kemoterapiji na osnovi platine, so opazili trend manjše učinkovitosti z naraščajočo starostjo. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Med ramucirumabom in parlitakselom niso opazili medsebojnega delovanja. **Plodnost, nosečnost in dojenje** Ženskam v rodni dobi je treba svetovati, naj se izogn ejo zanositvi med zdravljenjem z zdravilom Cyramza in jih je treba seznaniti z možnim tveganjem za nosečnost in plod. Ni znano, ali se ramucirumab izloča v materino mleko. **Neželeni učinki** *Zelo pogosti (≥ 1/10)* nevtropenija, levkopenija, trombocitopenija, hipoalbuminemija, hipertenzija, epistaksa, gastrointestinalne krvavitve, stomatitis, driska, proteinurija, utrujenost/astenija, periferni edem, bolečina v trebuhu. *Pogosti (≥ 1/100 do < 1/10)* hipokaliemija, hiponatriemija, glavobol. **Rok uporabnosti** 3 leta **Posebna navodila za shranjevanje** Shranjujte v hladilniku (2 °C–8 °C). Ne zamrzujte. Vialo shranjujte v zunanji ovojnini, da zagotovite zaščito pred svetlobo. **Pakiranje** 2 viali z 10 ml **IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, Nizozemska **DATUM ZADNJE REVIZIJE BESEDILA** 25.01.2016
Režim izdaje: Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah.

Pomembno obvestilo:

Pričujoče gradivo je namenjeno **samo za strokovno javnost**. Zdravilo Cyramza se izdaja le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem zdravila Cyramza vas vljudno prosimo, da preberete celotni Povzetek glavnih značilnosti zdravila Cyramza. Podrobnejše informacije o zdravilu Cyramza in o zadnji reviziji besedila Povzetka glavnih značilnosti zdravila so na voljo na sedežu podjetja Eli Lilly (naslov podjetja in kontaktni podatki spodaj) in na spletni strani European Medicines Agency (EMA): www.ema.europa.eu. in na spletni strani European Commission http://ec.europa.eu/health/documents/community-register/html/alfregister.htm.

Eli Lilly farmacevtska družba, d.o.o., Dunajska cesta 167, 1000 Ljubljana, telefon: (01) 5800 010, faks: (01) 5691 705

Referenca: 1. https://pharmaphorum.com/news/lilly-s-cyramza-approved-in-eu-for-stomach-cancer/?epoch=1505121044344

PP-RB-SI-0002, 17.11.2017.

Lilly

ICLUSIG® je zaviralec tirozin-kinaze 3. generacije, ki zagotavlja HITER, GLOBOK in TRAJEN odgovor.[1-3]

ICLUSIG® ▼
(ponatinib) tablete

Zdravilo Iclusig je na tržišču v dveh jakostih

- **15 mg** - na voljo v vsebnikih s 60 filmsko obloženimi tabletami
- **45 mg** - na voljo v vsebnikih s 30 filmsko obloženimi tabletami

incyte

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.
Iclusig 15 mg filmsko obložene tablete
Iclusig 45 mg filmsko obložene tablete
Sestava: Ena filmsko obložena tableta vsebuje 15 mg ali 45 mg ponatiniba (v obliki ponatinibijevega klorida). **Terapevtske indikacije:** Zdravilo Iclusig je indicirano pri odraslih bolnikih s kronično mieloidno levkemijo (KML) v kronični fazi, pospešeni fazi ali blastni fazi, ki so odporni na dasatinib ali nilotinib; ki ne prenašajo dasatiniba ali nilotiniba in pri katerih nadaljnje zdravljenje z imatinibom ni klinično ustrezno; ali ki imajo mutacijo T315I, ter pri odraslih bolnikih z akutno limfoblastno levkemijo s prisotnim kromosomom Philadelphia (Ph+ ALL), ki so odporni na dasatinib; ki ne prenašajo dasatiniba in pri katerih nadaljnje zdravljenje z imatinibom ni klinično ustrezno; ali ki imajo mutacijo T315I. **Odmerjanje in način uporabe:** Terapijo mora uvesti zdravnik z izkušnjami v diagnosticiranju in zdravljenju bolnikov z levkemijo. Med zdravljenjem se lahko bolniku nudi hematološka podpora v obliki transfuzije trombocitov in hematopoetskega rastnega faktorja, če je to klinično indicirano. Pred začetkom zdravljenja s ponatinibom je treba oceniti kardiovaskularni status bolnika, vključno z anamnezo in telesnim pregledom, in aktivno obravnavati kardiovaskularne dejavnike tveganja. Kardiovaskularni status je treba še naprej spremljati in med zdravljenjem s ponatinibom optimizirati zdravljenje z zdravili in podporno zdravljenje stanj, ki prispevajo h kardiovaskularnim tveganjem. Odmerjanje: Priporočeni začetni odmerek ponatiniba je 45 mg enkrat na dan. Zdravljenje je treba nadaljevati, dokler se pri bolniku ne pokažejo znaki napredovanja bolezni ali nesprejemljive toksičnosti. Pri bolnikih je treba spremljati njihov odgovor v skladu s standardnimi kliničnimi smernicami. Če v 3 mesecih (90 dneh) ni celovitega hematološkega odgovora, je treba razmisliti o ukinitvi ponatiniba. Tveganje arterijskih okluzivnih dogodkov je verjetno povezano z odmerkom. Treba je razmisliti o zmanjšanju odmerka zdravila Iclusig na 15 mg pri bolnikih s KML v kronični fazi, ki so dosegli bistven citogenetski odgovor. Pri teh bolnikih je treba pri oceni koristi in tveganj za posameznika upoštevati naslednje dejavnike: kardiovaskularno tveganje, neželene učinke zdravljenja s ponatinibom, čas do citogenetskega odgovora in ravni transkriptov BCR-ABL. Če se odmerek zmanjša, se priporoča skrbno spremljanje odgovora. Obravnava toksičnosti: Pri obravnavi hematoloških in nehematoloških toksičnosti je treba razmisliti o prilagoditvi ali prekinitvi odmerjanja. V primeru hudih neželenih učinkov je treba z zdravljenjem začasno prenehati. Pri bolnikih, pri katerih neželeni učinki izzvenijo ali se njihova resnost zmanjša, se lahko zdravljenje nadaljuje, in če je klinično ustrezno, se lahko odmerek stopnjuje nazaj do dnevnega odmerka, doseženega pred neželenim učinkom. *Mielosupresija:* Za prilagajanje odmerka v primeru nevtropenije (ANC < 1,0 x 10^9/l) ali trombocitopenije (trombociti < 50 x 10^9/l), ki nista povezani z levkemijo, glejte celoten Povzetek glavnih značilnosti zdravila. *Arterijska okluzija in venska trombembolija:* Zdravljenje z zdravilom Iclusig je treba pri sumu, da se je pri bolniku razvil arterijski okluzivni dogodek ali venska trombembolija, takoj prekiniti. *Pankreatitis in hepatotoksičnost:* Za prilagajanje odmerka pri neželenih reakcijah, povezanih s trebušno slinavko in hepatotoksičnostjo glejte celoten Povzetek glavnih značilnosti zdravila. Starejši bolniki: Verjetnost neželenih učinkov pri starejših bolnikih večja. Okvara jeter: Bolniki z okvarjenim delovanjem jeter lahko prejemajo priporočeni začetni odmerek, vendar se priporoča previdnost. Okvara ledvic: Pri dajanju zdravila Iclusig bolnikom z ocenjenim očistkom kreatinina < 50 ml/min ali ledvično boleznijo v zadnjem stadiju se priporoča previdnost. Pediatrična populacija: Varnost in učinkovitost zdravila Iclusig pri bolnikih, starih do 18 let, še nista bili dokazani. Način uporabe: Peroralna uporaba. Tablete je treba pogoltniti cele. Bolniki tablet ne smejo drobiti ali raztapljati. Zdravilo Iclusig se lahko jemlje s hrano ali brez nje. **Kontraindikacije**: Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pomembne neželene reakcije: *Mielosupresija:* Zdravilo Iclusig je povezano s hudo (3. ali 4. stopnje po Poenotenih kriterijih za neželene učinke Nacionalnega inštituta za rak) trombocitopenijo, nevtropenijo in anemijo. Prve 3 mesece je treba vsaka 2 tedna opraviti pregled celotne krvne slike, nato pa mesečno ali kot je klinično indicirano. *Arterijska okluzija:* Neželeni učinki arterijske okluzije so bili pogostejši pri starejših bolnikih in pri bolnikih z ishemijo, hipertenzijo, sladkorno boleznijo ali hiperlipidemijo v anamnezi. Zdravila Iclusig se ne sme uporabljati pri bolnikih z miokardnim infarktom, predhodno revaskularizacijo ali možgansko kapjo v anamnezi, razen če so možne koristi zdravljenja večje od možnih tveganj. Pri teh bolnikih je treba pred začetkom zdravljenja s ponatinibom razmisliti tudi o alternativnih možnostih zdravljenja. *Venska trombembolija:* Spremljati je treba znake trombembolije in zdravljenje z zdravilom Iclusig takoj prekiniti v primeru trombembolije. Pri odločitvi o ponovni uvedbi zdravljenja z zdravilom Iclusig je treba upoštevati oceno koristi in tveganj. *Hipertenzija:* Med zdravljenjem z zdravilom Iclusig je treba ob vsakem obisku zdravnika spremljati krvni tlak in zdraviti hipertenzijo, da se vrne na normalno raven. Zdravljenje z zdravilom Iclusig je treba začasno prekiniti, če hipertenzija ni pod zdravniškim nadzorom. Za hipertenzijo, povezano z zmedenostjo, glavobolom, bolečinami v prsih ali zasoplostjo, bo morda potrebna nujna klinična intervencija. *Kongestivno srčno popuščanje:* Bolnike je treba spremljati glede znakov ali simptomov, ki kažejo na srčno popuščanje, in jih zdraviti, kot je klinično ustrezno, vključno s prekinitvijo zdravljenja z zdravilom Iclusig. *Pankreatitis in serumska lipaza:* Pogostnost pankreatitisa je večja prva 2 meseca uporabe. Prva 2 meseca vsaka 2 tedna preverjajte serumsko lipazo, nato pa periodično. Morda bo treba odmerek prekiniti ali zmanjšati. Pri bolnikih s pankreatitisom ali alkoholizmom v anamnezi se priporoča previdnost. *Hepatotoksičnost:* Pri večini bolnikov, pri katerih se je pojavila hepatotoksičnost, se je stanje prvič pojavilo v prvem letu zdravljenja. Teste delovanja jeter je treba opraviti pred uvedbo zdravljenja in nato periodično, kot je klinično indicirano. *Krvavitev:* Incidenca težkih krvavitev je bila večja pri bolnikih z AP-KML, BP-KML in Ph+ ALL. Največ krvavitev, vendar ne vse, se je pojavilo pri bolnikih s trombocitopenijo 3./4. stopnje. Zdravljenje z zdravilom Iclusig je treba prekiniti in bolnika oceniti glede pojava resne ali hude krvavitve. *Reaktivacija hepatitisa B:* Bolnike je treba pred začetkom zdravljenja z zdravilom Iclusig testirati glede okužbe z virusom hepatitisa B. Pri bolnikih s pozitivno serologijo na hepatitis B (vključno z bolniki z aktivno boleznijo) in bolnikih, pri katerih se med zdravljenjem test glede okužbe z virusom hepatitisa B izkaže za pozitivnega, se je treba pred začetkom zdravljenja posvetovati s strokovnjaki za obolenja jeter in zdravljenje hepatitisa B. Pri prenašalcih virusa hepatitisa B, pri katerih je potrebno zdravljenje z zdravilom Iclusig, je treba med zdravljenjem in nekaj mesecev po njegovem zaključku skrbno spremljati pojav znakov in simptomov aktivne okužbe z virusom hepatitisa B. Podaljšanje intervala QT: Celovitih študij v zvezi z intervalom QT niso izvajali, zato klinično pomembnih učinkov na interval QT ni mogoče izključiti. Laktoza: To zdravilo vsebuje laktozo monohidrat. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Snovi, ki lahko povečajo koncentracijo ponatiniba v serumu: *Zaviralci CYP3A:* Pri sočasni uporabi močnih zaviralcev CYP3A, kot so klaritromicin, indinavir, itrakonazol, ketokonazol, nefazodon, nelfinavir, ritonavir, sakvinavir, telitromicin, troleandomicin, vorikonazol in sok grenivke, je potrebna previdnost, razmisliti pa je treba tudi o zmanjšanju začetnega odmerka zdravila Iclusig na 30 mg. Snovi, ki lahko zmanjšajo koncentracijo ponatiniba v serumu: *Induktorji CYP3A:* Sočasni uporabi močnih induktorjev CYP3A4, kot so karbamazepin, fenobarbital, fenitoin, rifabutin, rifampicin in šentjanževka s ponatinibom, se je treba izogniti in poiskati alternative induktorju CYP3A4, razen če so koristi večje od možnega tveganja za premajhno izpostavljenost ponatinibu. Snovi, ki jim lahko ponatinib spremeni koncentracije v serumu: *Substrati prenašalcev:* Ponatinib lahko zviša koncentracije sočasno uporabljenih substratov P-gp (npr. digoksin, dabigatran, kolhicin, pravastatin) ali BCRP (npr. metotreksat, rosuvastatin, sulfasalazin) v plazmi in poveča njihov terapevtski učinek in neželene učinke. Pri dajanju ponatiniba s temi zdravili se priporoča skrbno klinično spremljanje. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi/kontracepcija pri moških in ženskah: Ženskam v rodni dobi, ki se zdravijo z zdravilom Iclusig, je treba svetovati, da naj v času zdravljenja z zdravilom Iclusig ne zanosijo, moškim pa, da naj ne zaplodijo otroka. Med zdravljenjem je treba uporabljati učinkovito metodo kontracepcije. Ni znano, ali ponatinib vpliva na učinkovitost sistemskih hormonskih kontraceptivov. Uporabljati je treba alternativno ali dodatno metodo kontracepcije. Nosečnost: Zdravilo Iclusig je dovoljeno med nosečnostjo uporabljati le, če je to nujno potrebno. Dojenje: Z dojenjem je treba med zdravljenjem z zdravilom Iclusig prenehati. Plodnost: Pri ljudeh ni podatkov o vplivu ponatiniba na plodnost. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo Iclusig ima blag vpliv na sposobnost vožnje in upravljanja strojev, zato je pri vožnji ali upravljanju strojev potrebna previdnost. **Neželeni učinki:** Zelo pogosti: okužbe zgornjih dihal, anemija, zmanjšane število trombocitov, zmanjšanje števila nevtrofilcev, zmanjšan apetit, nespečnost, glavobol, omotica, hipertenzija, dispneja, kašelj, bolečine v trebuhu, driska, bruhanje, zaprtje, navzea, zvišanje ravni lipaz, zvišanje ravni alanin-aminotransferaze, zvišanje ravni aspartat-aminotransferaze, izpuščaj, suha koža, bolečine v kosteh, artralgija, mialgija, bolečine v okončinah, bolečine v hrbtu, mišični krči, utrujenost, astenija, periferni edem, pireksija, bolečine. Pogosti: pljučnica, sepsa, folikulitis, celulitis, pancitopenija, febrilna nevtropenija, zmanjšanje števila levkocitov, zmanjšano število limfocitov, hipotiroza, dehidracija, zastajanje tekočine, hipokalciemija, hiperglikemija, hiperurikemija, hipofosfatemija, hipertrigliceridemija, hipokaliemija, zmanjšanje telesne mase, hiponatriemija, cerebrovaskularni dogodek, cerebralni infarkt, periferna nevropatija, letargija, migrena, hiperestezija, hipoestezija, parestezija, prehodni ishemični napad, zamegljen vid, suhe oči, periorbitalni edem, edem veke, konjunktivitis, srčno popuščanje, miokardni infarkt, kongestivno srčno popuščanje, bolezen koronarnih arterij, angina pektoris, perikardni izliv, atrijska fibrilacija, zmanjšanje iztisnega deleža, akutni koronarni sindrom, atrijska undulacija, periferna arterijska okluzivna bolezen, periferna ishemija, stenoza periferne arterije, intermitentna klavdikacija, globoka venska tromboza, vročinski oblivi, zariplost, pljučna embolija, plevralni izliv, epistaksa, disfonija, pljučna hipertenzija, pankreatitis, zvišanje amilaz v krvi, gastroezofagealna refluksna bolezen, stomatitis, dispepsija, trebušna distenzija, nelagodje v trebuhu, suha usta, krvavitev v želodcu, zvišanje ravni bilirubina v krvi, zvišanje ravni alkalne fosfataze v krvi, zvišanje ravni gama-glutamiltransferaze, pruritični izpuščaj, eksfoliativni izpuščaj, eritem, alopecija, pruritis, eksfoliacija kože, nočno potenje, hiperhidroza, petehija, ekhimoza, boleča koža, eksfoliativni dermatitis, hiperkeratoza, hiperpigmentacija kože, mišično-skeletne bolečine, bolečine v vratu, mišično-skeletne bolečine v prsnem košu, erektilna disfunkcija, mrzlica, gripi podobna bolezen, nekardiogena bolečina v prsnem košu, tiplji vozlič, obrazni edem. Občasni: sindrom tumorske lize, cerebralna arterijska stenoza, možganska krvavitev, intrakranialna krvavitev, tromboza mrežnične vene, okluzija mrežnične vene, okluzija mrežnične arterije, okvara vida, miokardna ishemija, kardialno nelagodje, ishemična kardiomiopatija, spazem koronarnih arterij, disfunkcija levega prekata, slaba periferna cirkulacija, vranični infarkt, venska embolija, venska tromboza, hipertenzivna kriza, stenoza ledvične arterije, hepatotoksičnost, odpoved jeter, zlatenica. **Način in režim predpisovanja in izdaje**: Rp/Spec – Zdravilo se izdaja le na recept, uporablja pa se po navodilu in pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Incyte Biosciences UK Ltd., Riverbridge House, Guildford Road, Leatherhead , Surrey KT22 9AD, Velika Britanija **Datum zadnje revizije besedila**: 12/2017. Lokalni predstavnik: Angelini Pharma d.o.o., Koprska ulica 108 A.
Pred predpisovanjem se seznanite s celotnim Povzetkom glavnih značilnosti zdravila.

Samo za strokovno javnost.
Datum priprave informacije: februar 2018

ANGELINI

PR/ANGSI/PON/2018/001

Lokalni predstavnik:
Angelini Pharma d.o.o, Koprska ulica 108A, 1000 Ljubljana

Literatura:
1. Cortes, et al. Am Soc Clin Oncol 2016: Abstr 7013.
2. Müller MC, et al. Am Soc Clin Oncol 2016: Abstr 7053.
3. Cortes JE, et al. N Engl J Med 2013; 369: 1783–1796.

Zdravilo za predhodno že zdravljene bolnike z mKRR

Več časa za trenutke, ki štejejo

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mKRR = metastatski kolorektalni rak

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Ta vključujejo kemoterapijo na osnovi fluoropirimidina, oksaliplatina in irinotekana, zdravljenje z zaviralci žilnega endotelijskega rastnega dejavnika (VEGF - Vascular Endothelial Growth Factor) in zaviralci receptorjev za epidermalni rastni dejavnik (EGFR - Epidermal Growth Factor Receptor). **ODMERJANJE IN NAČIN UPORABE*:** Priporočeni začetni odmerek zdravila Lonsurf pri odraslih je 35 mg/m^2/odmerek peroralno dvakrat dnevno na 1. do 5. dan in 8. do 12. dan vsakega 28-dnevnega cikla zdravljenja, najpozneje 1 uro po zaključku jutranjega in večernega obroka. Odmerjanje, izračunano glede na telesno površino, ne sme preseči 80 mg/odmerek. Možne prilagoditve odmerka glede na varnost in prenašanje zdravila: dovoljena so največ 3 zmanjšanja odmerka na najmanjši odmerek 20 mg/m^2 dvakrat dnevno. Potem ko je bil odmerek zmanjšan, povečanje ni dovoljeno. **KONTRAINDIKACIJE*:** Preobčutljivost na zdravilni učinkovini ali katero koli pomožno snov. **OPOZORILA IN PREVIDNOSTNI UKREPI*:** Supresija kostnega mozga: Pred uvedbo zdravljenja, pred vsakim ciklom zdravljenja in po potrebi je treba pregledati celotno krvno sliko. Zdravljenja ne smete začeti, če je absolutno število nevtrofilcev < 1,5 x 10^9/l, če je število trombocitov < 75 x 10^9/l ali če se je pri bolniku zaradi predhodnih zdravljenj pojavila klinično pomembna nehematološka toksičnost 3. ali 4. stopnje, ki še traja. Bolnike je treba skrbno spremljati zaradi morebitnih okužb, uvesti je treba ustrezne ukrepe, kot je klinično indicirano. Toksičnost za prebavila: Potrebna je uporaba antiemetikov, antidiaroikov ter drugih ukrepov, kot je klinično indicirano. Če je potrebno, prilagodite odmerke. Ledvična okvara: Zdravilo Lonsurf ni primerno za uporabo pri bolnikih s hudo ledvično okvaro ali končno stopnjo ledvične okvare. Bolnike z zmerno ledvično okvaro je treba zaradi hematološke toksičnosti bolj pogosto spremljati. Jetrna okvara: Uporaba zdravila Lonsurf pri bolnikih z obstoječo zmerno ali hudo jetrno okvaro ni priporočljiva. Proteinurija: Pred začetkom zdravljenja in med njim je priporočljivo spremljanje proteinurije z urinskimi testnimi lističi. Pomožne snovi: Zdravilo vsebuje laktozo. **INTERAKCIJE*:** Zdravila, ki medsebojno delujejo z nukleozidnimi prenašalci CNT1, ENT1 in ENT2, zaviralci OCT2 ali MATE1, substrati humane timidin-kinaze (npr. zidovudinom), hormonskimi kontraceptivi. **PLODNOST*, NOSEČNOST IN DOJENJE*:** Ni priporočljivo. **KONTRACEPCIJA*:** Ženske in moški morajo uporabljati učinkovito metodo kontracepcije med zdravljenjem in do 6 mesecev po zaključku zdravljenja. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI*:** Med zdravljenjem se lahko pojavijo utrujenost, omotica ali splošno slabo počutje. **NEŽELENI UČINKI*:** *Zelo pogosti:* nevtropenija, levkopenija, anemija, trombocitopenija, zmanjšan apetit, diareja, navzea, bruhanje, utrujenost. *Pogosti:* okužba spodnjih dihal, okužba zgornjih dihal, febrilna nevtropenija, limfopenija, monocitoza, hipoalbuminemija, nespečnost, disgevzija, periferna nevropatija, omotica, glavobol, vročinski oblivi, dispneja, kašelj, bolečina v trebuhu, zaprtje, stomatitis, bolezni ustne votline, hiperbilirubinemija, sindrom palmarne plantarne eritrodisestezije, izpuščaj, alopecija, pruritus, suha koža, proteinurija, piriksija, edem, vnetje sluznice, splošno slabo počutje, zvišanje jetrnih encimov, zvišanje alkalne fosfataze v krvi, zmanjšanje telesne mase. *Občasni:* septični šok, infekcijski enteritis, pljučnica, okužba žolčevoda, gripa, okužba sečil, vnetje dlesni, herpes zoster, tinea pedis, kandidiaza, bakterijska okužba, okužba, bolečina zaradi raka, pancitopenija, granulocitopenija, monocitopenija, eritropenija, levkocitoza, dehidracija, hiperglikemija, hiperkaliemija, hipokaliemija, hipofosfatemija, hipernatriemija, hiponatriemija, hipokalciemija, protin, anksioznost, nevrotoksičnost, disestezija, hiperestezija, hipoestezija, sinkopa, parestezija, pekoč občutek, letargija, zmanjšana ostrina vida, zameglien vid, diplopija, kataraka, konjunktivitis, suho oko, vrtoglavica, neugodje v ušesu, angina pektoris, aritmija, palpitacije, embolija, hipertenzija, hipotenzija, pljučna embolija, plevralni izliv, izcedek iz nosu, disfonija, orofaringealna bolečina, epistaksa, hemoragični enterokolitis, krvavitev v prebavilih, akutni pankreatitis, ascites, ileus, subileus, kolitis, gastritis, refluksni gastritis, ezofagitis, moteno praznjenje želodca, abdominalna distenzija, analno vnetje, razjede v ustih, dispepsija, gastroezofagealna refluksna bolezen, proktalgija, bukalni polip, krvavitev dlesni, glositis, parodontalna bolezen, bolezen zob, siljenje na bruhanje, flatulenca, slab zadah, hepatotoksičnost, razširitev žolčnih vodov, luščenje kože, urtikarija, preobčutljivostne reakcije na svetlobo, eritem, akne, hiperhidroza, žulj, bolezni nohtov, otekanje sklepov, artralgija, bolečina v kosteh, mialgija, mišično-skeletna bolečina, mišična oslabelost, mišični krči, bolečina v okončinah, občutek teže, ledvična odpoved, neinfektivni cistitis, motnje mikcije, hematurija, levkociturija, motnje menstruacije, poslabšanje splošnega zdravstvenega stanja, bolečina, občutek spremembe telesne temperature, kseroza, zvišanje kreatinina v krvi, podaljšanje intervala QT na elektrokardiogramu, povečanje mednarodnega umerjenega razmerja (INR), podaljšanje aktiviranega parcialnega tromboplastinskega časa (aPTČ), zvišanje sečnine v krvi, zvišanje laktatne dehidrogenaze v krvi, znižanje celokupnih proteinov, zvišanje C-reaktivnega proteina, zmanjšan hematokrit. *Post-marketinške izkušnje:* pri bolnikih, zdravljenih z zdravilom Lonsurf na Japonskem, so poročali o primerih intersticijske bolezni pljuč. **PREVELIKO ODMERJANJE*:** Neželeni učinki, o katerih so poročali v povezavi s prevelikim odmerjanjem, so bili v skladu z uveljavljenim varnostnim profilom. Glavni pričakovani zaplet prevelikega odmerjanja je supresija kostnega mozga. **FARMAKODINAMIČNE LASTNOSTI*:** *Farmakoterapevtska skupina:* zdravila z delovanjem na novotvorbe, antimetaboliti, oznaka ATC: L01BC59. Zdravilo Lonsurf sestavljata antineoplastični timidinski nukleozidni analog, trifluridin, in zaviralec timidin-fosforilaze (TPaze), tipiracilijev klorid. Po privzemu v rakave celice timidin-kinaza fosforilira trifluridin. Ta se v celicah nato presnovi v substrat deoksiribonukleinske kisline (DNA), ki se vgradi neposredno v DNA ter tako preprečuje celično proliferacijo. TPaza hitro razgradi trifluridin in njegova presnova po peroralni uporabi je hitra zaradi učinka prvega prehoda, zato je v zdravilo vključen zaviralec TPaze, tipiracilijev klorid. **PAKIRANJE*:** 20 filmsko obloženih tablet. **NAČIN PREDPISOVANJA IN IZDAJE ZDRAVILA:** Rp/ Spec. **Imetnik dovoljenja za promet:** Les Laboratoires Servier, 50, rue Carnot, 92284 Suresnes cedex, Francija. **Številka dovoljenja za promet z zdravilom:** EU/1/16/1096/001 (Lonsurf 15 mg/6,14 mg), EU/ 1/16/1096/004 (Lonsurf 20 mg/8,19 mg). **Datum zadnje revizije besedila: avgust 2017. * Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila. Celoten povzetek glavnih značilnosti zdravila in podrobnejše informacije so na voljo pri: Servier Pharma d.o.o., Podmilščakova ulica 24, 1000 Ljubljana, tel: 01 563 48 11, www.servier.si.**

Datum priprave informacije: februar 2018.
LNF17/18C2AD2 Samo za strokovno javnost.

Instructions for authors

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Preparation of manuscripts

Radiology and Oncology will consider manuscripts prepared according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by International Committee of Medical Journal Editors (www.icmje.org). The manuscript should be written in grammatically and stylistically correct language. Abbreviations should be avoided. If their use is necessary, they should be explained at the first time mentioned. The technical data should conform to the SI system. The manuscript, excluding the references, tables, figures and figure legends, must not exceed 5000 words, and the number of figures and tables is limited to 8. Organize the text so that it includes: Introduction, Materials and methods, Results and Discussion. Exceptionally, the results and discussion can be combined in a single section. Start each section on a new page, and number each page consecutively with Arabic numerals.

The Title page should include a concise and informative title, followed by the full name(s) of the author(s); the institutional affiliation of each author; the name and address of the corresponding author (including telephone, fax and E-mail), and an abbreviated title (not exceeding 60 characters). This should be followed by the abstract page, summarizing in less than 250 words the reasons for the study, experimental approach, the major findings (with specific data if possible), and the principal conclusions, and providing 3-6 key words for indexing purposes. Structured abstracts are required. Slovene authors are requested to provide title and the abstract in Slovene language in a separate file. The text of the research article should then proceed as follows:

Introduction should summarize the rationale for the study or observation, citing only the essential references and stating the aim of the study.

Materials and methods should provide enough information to enable experiments to be repeated. New methods should be described in details.

Results should be presented clearly and concisely without repeating the data in the figures and tables. Emphasis should be on clear and precise presentation of results and their significance in relation to the aim of the investigation.

Discussion should explain the results rather than simply repeating them and interpret their significance and draw conclusions. It should discuss the results of the study in the light of previously published work.

Charts, Illustrations, Images and Tables

Charts, Illustrations, Images and Tables must be numbered and referred to in the text, with the appropriate location indicated. Charts, Illustrations and Images, provided electronically, should be of appropriate quality for good reproduction. Illustrations and charts must be vector image, created in CMYK color space, preferred font "Century Gothic", and saved as .AI, .EPS or .PDF format. Color charts, illustrations and Images are encouraged, and are published without additional charge. Image size must be 2.000 pixels on the longer side and saved as .JPG (maximum quality) format. In Images, mask the identities of the patients. Tables should be typed double-spaced, with a descriptive title and, if appropriate, units of numerical measurements included in the column heading. The files with the figures and tables can be uploaded as separate files.

References

References must be numbered in the order in which they appear in the text and their corresponding numbers quoted in the text. Authors are responsible for the accuracy of their references. References to the Abstracts and Letters to the Editor must be identified as such. Citation of papers in preparation or submitted for publication, unpublished observations, and personal communications should not be included in the reference list. If essential, such material may be incorporated in the appropriate place in the text. References follow the style of Index Medicus, DOI number (if exists) should be included.

All authors should be listed when their number does not exceed six; when there are seven or more authors, the first six listed are followed by "et al.". The following are some examples of references from articles, books and book chapters:

Dent RAG, Cole P. In vitro maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95. doi: 10.1038/bjc.1981.71

Chapman S, Nakielny R. *A guide to radiological procedures*. London: Bailliere Tindall; 1986.

Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

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When reporting experiments on human subjects, authors should state whether the procedures followed the Helsinki Declaration. Patients have the right to privacy; therefore the identifying information (patient's names, hospital unit numbers) should not be published unless it is essential. In such cases the patient's informed consent for publication is needed, and should appear as an appropriate statement in the article. Institutional approval and Clinical Trial registration number is required. Retrospective clinical studies must be approved by the accredited Institutional Review Board/Committee for Medical Ethics or other equivalent body. These statements should appear in the Materials and methods section.

The research using animal subjects should be conducted according to the EU Directive 2010/63/EU and following the Guidelines for the welfare and use of animals in cancer research (Br J Cancer 2010; 102: 1555 – 77). Authors must state the committee approving the experiments, and must confirm that all experiments were performed in accordance with relevant regulations.

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IBRANCE + zaviralec aromataze in IBRANCE + fulvestrant[1]

Z ZDRUŽENIMI MOČMI, VEČ KOT 2-LETNO mPFS

S kombinacijo zdravila IBRANCE in letrozola, **prelomnim zdravljenjem 1. linije** za metastatskega raka dojke, je ugotovljeno **več kot 2-letno mPFS.**[*†2] In v kombinaciji s fulvestrantom prinaša **večjo učinkovitost za širok krog bolnikov.**[*3]

Zdravilo IBRANCE je indicirano za zdravljenje lokalno napredovalega ali metastatskega na hormonske receptorje pozitivnega (HR+) in na receptorje humanega epidermalnega rastnega faktorja 2 negativnega (HER2-) raka dojk:

- v kombinaciji z zaviralcem aromataze,
- v kombinaciji s fulvestrantom pri ženskah, ki so prejele predhodno endokrino zdravljenje .

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

IBRANCE 75 mg, 100 mg, 125 mg trde kapsule

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o kateremkoli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih.

Sestava in oblika zdravila: Ena trda kapsula vsebuje 75 mg, 100 mg ali 125 mg palbociklibа in 56 mg, 74 mg ali 93 mg laktoze (v obliki monohidrata). **Indikacije:** Zdravljenje lokalno napredovalega ali metastatskega na hormonske receptorje (HR – *Hormone Receptors*) pozitivnega in na receptorje humanega epidermalnega rastnega faktorja 2 (HER2 – *Human Epidermal growth factor Receptor 2*) negativnega raka dojk: v kombinaciji z zaviralcem aromataze ali v kombinaciji s fulvestrantom pri ženskah, ki so prejele predhodno endokrino zdravljenje. Pri ženskah v pred- in perimenopavzi je treba endokrino zdravljenje kombinirati z agonistom gonadoliberina. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Priporočeni odmerek je 125 mg enkrat na dan 21 zaporednih dni, sledi 7 dni brez zdravljenja (shema 3/1), celotni ciklus traja 28 dni. Zdravljenje je treba nadaljevati, dokler ima bolnik od zdravljenja klinično korist ali dokler se ne pojavi nesprejemljiva toksičnost. Pri sočasnem dajanju s palbociklibom je priporočeni odmerek letrozola 2,5 mg peroralno enkrat na dan, neprekinjeno vseh 28 dni ciklusa, glejte SmPC za letrozol. Pri sočasnem dajanju s palbociklibom je priporočeni odmerek fulvestranta 500 mg intramuskularno 1., 15. in 29. dan ter nato enkrat na mesec, glejte SmPC za fulvestrant. Prilagajanja odmerkov: Za prilagajanja odmerkov zaradi hematološke toksičnosti glejte preglednico 2, zaradi nehematološke toksičnosti pa preglednico 3 v SmPC-ju. Posebne skupine bolnikov: *Starejši:* Prilagajanje odmerka ni potrebno. *Okvara jeter ali ledvic*: Pri bolnikih z blago okvaro jeter ali blago ali zmerno okvaro ledvic prilagajanje odmerka ni potrebno. *Pediatrična populacija*: Varnost in učinkovitost pri otrocih in mladostnikih, starih ≤ 18 let, nista bili dokazani. Način uporabe: Peroralna uporaba. Jemanje s hrano, priporočljivo z obrokom. Ne smemo jemati z grenivko ali grenivkinim sokom. Kapsule zdravila je treba pogoltniti cele. **Kontraindikacije:** Preobčutljivost na učinkovino ali katerokoli pomožno snov. Uporaba pripravkov s šentjanževko. **Posebna opozorila in previdnostni ukrepi:** Ženske v pred- in perimenopavzi: Kadar zdravilo uporabljamo v kombinaciji z zaviralcem aromataze je obvezna ovarijska ablacija ali supresija z agonistom gonadoliberina. Hematološke bolezni: Pri nevtropeniji stopnje 3 ali 4 je priporočljiva prekinitev odmerjanja, zmanjšanje odmerka ali odložitev začetka ciklusov zdravljenja, bolnike pa je treba ustrezno spremljati. Okužbe: Zdravilo lahko poveča nagnjenost k okužbam, zato je bolnike treba spremljati glede znakov in simptomov okužbe ter jih ustrezno zdraviti. Okvara jeter ali ledvic: Bolnike z zmerno ali hudo okvaro jeter ali hudo okvaro ledvic zdravimo samo po skrbni oceni morebitnih koristi in tveganj, ter jih skrbno spremljamo glede znakov toksičnosti. Laktoza: Vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze-galaktoze tega zdravila ne smejo jemati. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Učinki drugih zdravil na farmakokinetiko palbociklibа: *Zaviralci CYP3A:* Sočasni uporabi močnih zaviralcev CYP3A, med drugim klaritromicina, indinavirja, itrakonazola, ketokonazola, lopinavirja/ritonavirja, nefazodona, nelfinavirja, posakonazola, sakvinavirja, telaprevirja, telitromicina, vorikonazola in grenivke ali grenivkinega soka, se je treba izogibati. *Induktorji CYP3A:* Sočasni uporabi močnih induktorjev CYP3A, med drugim karbamazepina, enzalutamida, fenitoina, rifampicina in šentjanževke, se je treba izogibati. Učinek zdravil za zmanjševanje kisline: Ni pričakovati nobenega klinično pomembnega učinka na izpostavljenost palbociklibu, če palbociklib zaužijemo s hrano. Učinki palbociklibа na farmakokinetiko drugih zdravil: Pri sočasni uporabi bo morda treba zmanjšati odmerek občutljivih substratov CYP3A z ozkim terapevtskim indeksom (npr. alfentanil, ciklosporin, dihidroergotamin, ergotamin, everolimus, fentanil, pimozid, kinidin, sirolimus in takrolimus), saj IBRANCE lahko poveča izpostavljenost tem zdravilom. Študije *in vitro* s prenašalci: palbociklib lahko zavira prenos, posredovan s P-gp v prebavilih in beljakovino odpornosti za raka dojk. Uporaba palbociklibа z zdravili, ki so substrati P-gp (npr. digoksin, dabigatran, kolhicin, pravastatin) ali BCRP (npr. rosuvastatin, sulfasalazin) lahko poveča njihov terapevtski učinek in neželene učinke. Palbociklib lahko zavira privzemni prenašalec organskih kationov OCT1. **Plodnost, nosečnost in dojenje:** Med zdravljenjem in vsaj 3 tedne (ženske) oziroma 14 tednov (moški) po koncu zdravljenja je treba uporabljati ustrezne kontracepcijske metode. Zdravila ne uporabljajte pri nosečnicah in ženskah v rodni dobi, ki ne uporabljajo kontracepcije. Bolnice, ki prejemajo palbociklib, ne smejo dojiti. Zdravljenje s palbociklibom lahko ogrozi plodnost pri moških. Pred začetkom zdravljenja naj moški zato razmislijo o hrambi sperme.**Vpliv na sposobnost vožnje in upravljanja s stroji:** Ima blag vpliv na sposobnost vožnje in upravljanja strojev. Bolniki morajo biti pri vožnji in upravljanju strojev previdni. **Neželeni učinki:** Zelo pogosti: okužbe, nevtropenija, levkopenija, anemija, trombocitopenija, pomanjkanje teka, stomatitis, navzea, diareja, bruhanje, izpuščaj, alopecija, utrujenost. **Način in režim izdaje:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, Velika Britanija. **Datum zadnje revizije besedila:** 28.03.2017
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

*Na podlagi rezultatov randomiziranega nadzorovanega preskušanja III. faze.
†mPFS = mediano preživetje brez napredovanja bolezni.

Literatura: 1. Povzetek glavnih značilnosti zdravila Ibrance, 28.3.2017. **2.** Finn RS, et al. PALOMA-2: Primary results from a phase 3 trial of palbociclib plus letrozole compared with placebo plus letrozole in postmenopausal women with ER+/HER2– advanced breast cancer. Kongres ASCO 2016, oralna predstavitev. **3.** Cristofanilli M, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425-439.

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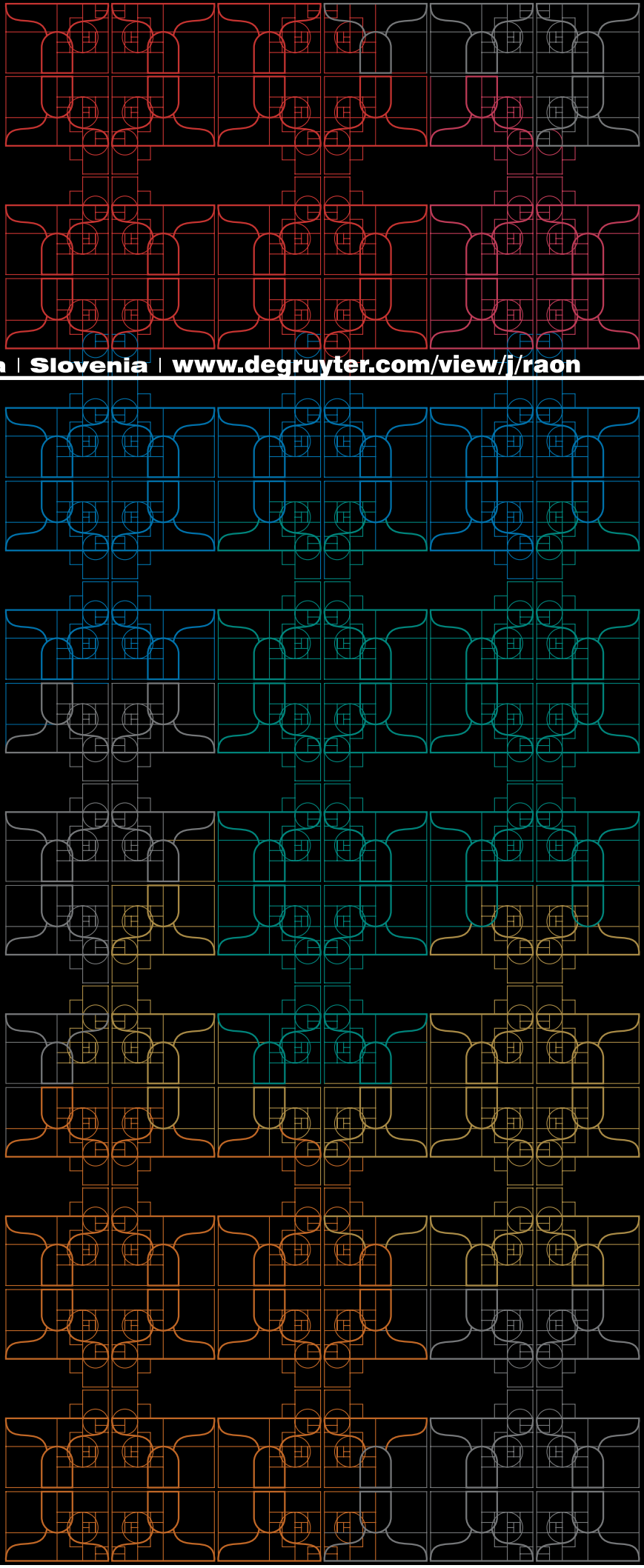

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