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ALIMTA®
pemetreksed

Edina histološko usmerjena citostatična terapija

Pravi **Izbor**
Pravi **Bolnik**
Pravi **Čas**

ALIMTA/Cisplatin:

Zdravljenje prvega reda pri bolnikih z nedrobnoceličnim pljučnim karcinomom, ki nimajo pretežno luskaste histologije

Edina kombinirana terapija z signifikantno izboljšanim preživetjem:
12,6 meseca pri bolnikih z adenokarcinomom pljuč[1]

*vs. Gemcitabin/Cisplatin

1. Scagliotti GV et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3543-51.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Ime zdravila ALIMTA 100 mg prašek za koncentrat za raztopino za infundiranje in ALIMTA 500 mg prašek za koncentrat za raztopino za infundiranje **Kakovostna in količinska sestava** ALIMTA 100 mg: vsaka viala vsebuje 100 mg pemetrekseda (v obliki dinatrijevega pemetrekseda), ALIMTA 500 mg: vsaka viala vsebuje 500 mg pemetrekseda (v obliki dinatrijevega pemetrekseda). **Pomožne snovi:** manitol, klorovodikova kislina, natrijev hidroksid, **Terapevtske indikacije** ALIMTA je v kombinaciji s cisplatinom indicirana za zdravljenje bolnikov z neresektabilnim malignim plevralnim mezoteliomom, ki jih še nismo zdravili s kemoterapijo. ALIMTA je v kombinaciji s cisplatinom indicirana kot zdravljenje prvega izbora za bolnike z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom, ki nima pretežno luskaste histologije. ALIMTA je indicirana kot monoterapija za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom, ki nima pretežno luskaste histologije. **Odmerjanje in način uporabe:** ALIMTO smemo dajati le pod nadzorom zdravnika, usposobljenega za uporabo kemoterapije za zdravljenje raka, ALIMTA v kombinaciji s cisplatinom: Priporočeni odmerek ALIMTE je 500 mg/m2 telesne površine (TP), dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21-dnevnega ciklusa, Priporočeni odmerek cisplatina je 75 mg/m2 TP, infundiran v dveh urah približno 30 minut po zaključku infuzije pemetrekseda prvi dan vsakega 21 dnevnega ciklusa. Priporočeni odmerek cisplatina je 75 mg/m2 TP, infundiran v dveh urah približno 30 minut po zaključku infuzije pemetrekseda prvi dan vsakega 21 dnevnega ciklusa. Bolniki morajo prejeti zadostno antiemetičnoo zdravljenje, pred in/ali po prejemanju cisplatina jih moramo tudi ustrezno hidrirati. ALIMTA kot monoterapija: Priporočeni odmerek ALIMTE je 500 mg/m2 TP, dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21 dnevnega ciklusa, Režim premedikacije: da zmanjšamo incidenco in resnost kožnih reakcij, dajemo kortikosteroid dan pred dajanjem pemetrekseda, na dan dajanja pemetrekseda in naslednji dan. Kortikosteroid naj ustreza 4 mg deksametazona, danega peroralno dvakrat dnevno. Za zmanjšanje toksičnosti morajo bolniki dnevno jemati tudi peroralno folno kislino ali multivitaminski pripravek, ki jo vsebuje (350 do 1000 mikrogramov). V sedmih dneh pred prvim odmerkom pemetrekseda morajo vzeti vsaj pet odmerkov folne kisline, odmerjanje pa morajo nadaljevati ves čas zdravljenja in še 21 dni po zadnjem odmerku pemetrekseda, Bolniki morajo prejeti tudi intramuskularno injekcijo vitamina B12 (1000 mikrogramov) v tednu pred prvim odmerkom pemetrekseda in enkrat vsake tri cikluse zatem, Kasnejše injekcije vitamina B12 lahko dajemo isti dan kot pemetreksed. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Med zdravljenjem s pemetreksedom je treba dojenje prekiniti. Sočasno cepljenje proti rumeni mrzlici. **Posebna opozorila in previdnostni ukrepi:** Pemetreksed lahko zavre delovanje kostnega mozga, kar se kaže kot nevtropenija, trombocitopenija in anemija (ali pancitopenija), Pri bolnikih, ki pred zdravljenjem niso prejemali kortikosteroidov, so poročali o kožnih reakcijah, Uporabe pemetrekseda pri bolnikih z očistkom kreatinina < 45 ml/min ne priporočamo. Bolniki z blagim do zmernim popuščanjem delovanja ledvic naj se izogibajo jemanju nesteroidnih protivnetnih zdravil (NSAID), denimo, ibuprofena in acetilsalicilne kisline 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Vsi bolniki, ki jih lahko zdravimo s pemetreksedom, naj se izogibajo jemanju NSAID-ov z dolgimi razpolovnimi časi izločanja vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Poročali so o resnih ledvičnih primerih, vključno z akutno ledvično odpovedjo, s pemetreksedom samim ali v povezavi z drugimi kemoterapevtiki, Pri bolnikih s klinično pomembno tekočino tretjega prostora moramo razmisliti o drenaži izliva pred dajanjem pemetrekseda, Kot posledico toksičnosti pemetrekseda v kombinaciji s cisplatinom za prebavila so opažali hudo dehidracijo, zato moramo bolnike pred prejemanjem terapije in/ali po njej ustrezno hidrirati, prejeti morajo zadostno antiemetično zdravljenje, Občasno so v kliničnih študijah pemetrekseda, običajno ob sočasnem dajanju z drugo citotoksično učinkovino, poročali o resnih srčnožilnih dogodkih, vključno z miokardnim infarktom in možganskožilnimi dogodki. Odsvetujemo uporabo živih oslabljenih cepiv. Spolno zrelim moškim odsvetujemo zapkoditev otroka v času zdravljenja in še 6 mesecev zatem. Priporočamo ukrepe proti zanositvi ali vzdržnost. Zaradi možnosti, da zdravljenje s pemetreksedom povzroči trajno neplodnost, naj se moški pred začetkom zdravljenja posvetujejo o shranjevanju semena, Ženske v rodni dobi morajo v času zdravljenja s pemetreksedom uporabljati učinkovito kontracepcijo, Poročali so o primerih radiacijske pljučnice pri bolnikih, ki so jih zdravili z radiacijo pred, med ali po zdravljenju s pemetreksedom. Poročali so o radiacijskem izpuščaju pri bolnikih, ki so se zdravili z radioterapijo pred tedni ali leti. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno dajanje nefrotokšičnih zdravil (denimo, aminoglikozidov, diuretikov zanke, spojin platine, ciklosporina) lahko potencialno povzroči zakasnjeni očistek pemetrekseda, Sočasno dajanje snovi, ki se tudi izločajo s tubulno sekrecijo (denimo, probenecid, penicilin), lahko potencialno povzroči zakasnjeni očistek pemetrekseda, Pri bolnikih z normalnim delovanjem ledvic lahko visoki odmerki nesteroidnih protivnetnih zdravil (NSAID-i, denimo, ibuprofen) in acetilsalicilna kislina v visokih odmerkih zmanjšajo eliminacijo pemetrekseda in tako lahko povečajo pojavnost neželenih učinkov pemetrekseda. Pri bolnikih z blagim do zmernim popuščanjem delovanja ledvic se moramo izogibati sočasnemu dajanju pemetrekseda z NSAID-i (denimo, ibuprofenom) ali acetilsalicilne kisline v visokih odmerkih 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda, Sočasnemu dajanju NSAID-ov z daljšimi razpolovnimi časi s pemetreksedom se moramo izogibati vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda,Velika različnost med posamezniki v koagulacijskem statusu v času bolezni ter možnost medsebojnega delovanja med peroralnimi antikoagulacijskimi učinkovinami ter kemoterapijo proti raku zahtevata povečano pogostnost spremljanja INR, Kontraindicirana sočasna uporaba: Cepivo proti rumeni mrzlici: tveganje za smrtno generaliziranо bolezen po cepljenju, Odsvetovana sočasna uporaba: Živa oslabljena cepiva (razen proti rumeni mrzlici): tveganje za sistemsko, potencialno smrtno bolezen, **Neželeni učinki** Klinične študije malignega plevralnega mezotelioma Zelo pogosto: znižani nevtrofili/granulociti, znižani levkociti, znižan hemoglobin, znižani trombociti, slabost, bruhanje, stomatitis/faringitis, anoreksija, diareja, zaprtje, utrujenost, nevropatija- senzorična, povišan kreatinin, znižan očistek kreatinina, izpuščaj, alopecija. Pogosti: konjuktivitis, dispepsija, dehidracija, motnje okusa. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA monoterapija: Zelo pogosti: znižan hemoglobin, znižani levkociti, znižani nevtrofili/granulociti, slabost, bruhanje, anoreksija, stomatitis/faringitis, diareja, utrujenost, izpuščaj/luščenje. Pogosti: znižani trombociti, zaprtje, povišana telesna temperatura, povišanje SQPT (ALT), povišanje SGOT (AST), srbenje, alopecija, Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA v kombinaciji s cisplatinom Zelo pogosti: znižan hemoglobin, znižani levkocitit, znižani nevtrofili/granulociti, znižani trombociti, slabost, bruhanje, anoreksija, zaprtje, stomatitis/faringitis, diareja brez kolostomije, utrujenost, povišan kreatinin, alopecija, izpuščaj/luščenje. Pogosti: dispepsija/zgaga, nevropatija-senzorična, motnje okusa. Občasno so v kliničnih študijah pemetrekseda poročali o primerih resnih srčnožilnih in možganskožilnih dogodkov, vključno z miokardnim infarktom, angino pektoris, cerebrovaskularnim insultom in prehodnimi ishemičnimi atakami; primerih kolitisa ter o primerih interstricijske pljučnice z respiratorno insuficienco in primerih edema. Redkeje pa o primerih potencialno resnega hepatitisa in pancitopenije. Po uvedbi zdravila na trg so poročali o primerih akutne odpovedi ledvic s pemetreksedom samim ali v povezavi z drugimi kemoterapevtiki, primerih radiacijske pljučnice pri bolnikih, ki so jih zdravili z radiacijo pred, med ali po njihovem zdravljenju s pemetreksedom, primerih radiacijskega izpuščaja pri bolnikih, ki so se v preteklosti zdravili z radioterapijo in o primerih periferne ishemije, ki je včasih vodila v nekrozo okončin. **Imetnik dovoljenja za promet** Eli Lilly Nederland B.V., Grootslag 1 5, NL 3991 RA, Houten, Nizozemska, **Datum zadnje revizije besedila** 06.01.2009
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review

Advances in the treatment of metastatic colorectal carcinoma

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Background. *In most cases, metastatic colorectal cancer is incurable; however, the prognosis and survival of these patients have significantly improved in the last 6 years. A few years back, the only efficient drug for colorectal carcinoma, 5-fluoruracil, yielded the mean survival of 10 months, whereas today, the survival rates of 20 months or more may be obtained by using new cytostatics. In the last six years, five new drugs were registered for the treatment of metastatic colorectal cancer. These are three cytostatics (capecitabine, irinotecan, oxaliplatin) and two target drugs (cetuximab and bevacizumab).*

Conclusions. *A combined treatment assures a better quality of life, and longer remissions and overall survival. The combination of cytostatics and target drugs improves particularly the mean survival rate, which may be longer than 30 months. These combinations of drugs used together with surgical treatment of lung and liver metastases may result in complete remission. An important research achievement of this year is the determination of KRAS mutations. The KRAS gene is the first biomarker that predicts how well patients will respond to certain combination of treatment.*

Key words: metastatic colorectal cancer; chemotherapy; targeted therapy; KRAS

Introduction

Only seven years ago, the treatment of metastatic colorectal cancer was based on a single agent, *i.e.* 5-fluorouracil (5-FU). This agent yielded a response rate of 20%, time to disease progression of four months, and mean survival of 10-11 months. From 2000 onwards, these values have doubled by applying new cytostatics and, by adding target drugs, they have trebled. Currently, the response rate in the first-line treatment of metastatic disease is >45%, the time to progression around 8 months, the survival around 20 months, and by adding the target drugs, it may be longer, often more than 3 years. With successful surgery of liver metastases, a 50% five-year survival may be obtained, while some authors have reported about 30% ten-year survival.

Given these new achievements, a new concept of the second- and third-line treatment of the patients with the metastatic colorectal cancer could be adopted; the real-

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ity we are witnessing today, only five years back appeared to be almost inaccessible. The second-line chemotherapy yields response rates of ~20%, time to progression of 4 months and mean survival of ~10 moths.

Taking into account the new biomarker, *i.e.* the determination of KRAS gene mutation, 60%-80% response rates may be achieved in the patients with non-mutated KRAS gene if chemotherapy is applied in combination with cetuximab. Several research studies have confirmed that better response rates improve the chances of the liver surgery for colorectal metastases.

In stage IV patients, treatment plans are made separately for each individual patient because the treatment mainly depends upon the size and location of the primary, the number and location of metastases, the performance status of a patient, and the liver and renal function.

In the treatment of these patients, we follow the basic treatment guidelines. In the patients with large tumours, obstructing the lumen and thus posing a serious risk for ileus, we recommend the resection of the primary tumour of the colon or rectum, or the preoperative irradiation of the rectal tumour before the resection.[1] If solitary metastases are detected in the lung or liver, they should be excised in the first place; in the patients with multiple metastases in one or more organs, the systemic treatment with chemotherapy is recommended if the patient's physical condition allows it.

Resectable metastatic disease

In the patients with the metastatic disease invading only the liver or the lung, surgery as the treatment option should be carefully considered. If radical resection of metastases is performed immediately after they have been detected, the disease recurs in ~80% of cases; this speaks in favour of the systemic treatment which could reduce the risk of the disease recurrence. It, however, appears that the best treatment approach would be to apply at first the systemic treatment which would indicate whether the disease is chemosensitive; if so, surgery would follow after the response to treatment was obtained. The results of the Phase III EORTC Trial on GI Group, published in 2008, confirm the benefits of such an approach.[2] In this trial, the patients preoperatively and postoperatively received 6 cycles of chemotherapy. This treatment scheme may pose a risk for the potentially curable patients who may experience early progression of the disease due to the systemic treatment. However, since in the patients receiving standard treatment in combination with chemotherapy, the percentage of early disease progressions is rather low, estimated at ~10%, the potential benefit of this treatment scheme outweighs the risk of early disease progression.[2,3]

Unresectable metastatic disease potentially put in remission

The patients who fall into this group have the metastatic disease so severely spread in the liver or the lung that it is unresectable. The primary aim of the systemic treatment of these patients is to reduce the size of the metastases in order to facilitate the radical resection. In selecting the systemic therapy, it should be noted that, after the radical resection, the survival rates of these patients may be the same as those of the patients with resectable disease, *i.e.* 30-50%. The neoadjuvant systemic treatment can downstage the disease to the extent allowing radical resection. This approach is effective in 15% of patients. As the neoadjuvant treatment aims at reducing the tumour mass as much as possible, the most effective combinations of cytostatics are selected,

e.g. FOLFIRI (irinotecan / 5-fluorouracil / Calcium folinate) and FOLFOX (oxaliplatin / 5-fluorouracil / Calcium folinate). The two combinations are equally effective. Several research studies have proved that better response to treatment increases the chances for liver surgery.[4] In order to improve the response rate, the combinations with target drugs are also used. The addition of cetuximab to standard chemotherapy significantly improves the response to chemotherapy, thereby doubling the number of liver metastases resections in comparison to the use of standard neoadjuvant chemotherapy alone.[5] Recently published research studies on KRAS gene mutations have proved that, by determining the mutations of the KRAS gene, it is possible to identify the patients who can most benefit from the use of cetuximab; these are the patients with KRAS wt (wild type / non-mutated) gene. In these studies, the absence of KRAS mutation proved to be a prognostic factor for the response to treatment, time to disease progression, and survival.[6] The response rates of this group of patients were higher by 40-60% than of the group of patients treated with standard chemotherapy. The patients in whom higher resectability rates of liver metastases are obtained by neoadjuvant chemotherapy, have a significantly longer survival. The five- and ten-year survivals of 40% and 25%, respectively, are comparable with the survivals of the patients with primary resectable liver metastases, which is indeed an important achievement in the treatment of metastatic colorectal cancer.[7] At ESMO 2008, a randomized multicentric trial was presented which was performed on the use of the combination of cetuximab with FOLFOX or FOLFIRI applied in the patients with the wild type KRAS gene and with primary unresectable liver metastases. The results of this trial are most encouraging; with the obtained response rate of 80%, R0 resection was possible in 34% of patients.[8] With the addition of bevacizumab, an agent that belongs to the group of the inhibitors of angiogenesis, to the irinoitecan-based chemotherapy (IFL treatment scheme), the response to treatment was obtained in 48% of patients, whereas the addition of bevacizumab to the FOLFOX or XELOX regimens did not improve the response rate.[9-11]

Unresectable metastatic disease

In the majority of patients with stage IV colorectal metastatic cancer, the disease is unresectable and metastasizing in more than one organ, thus not allowing the radical surgical treatment. The standard treatment for these patients is systemic chemotherapy or chemotherapy in combination with target drugs. From the last ten years of practicing the treatment of stage IV patients, a number of important conclusions were drawn:

- Chemotherapy with fluoropyrimidines is better than the best supportive care because it yields a longer survival and better quality of life.
- The sooner the treatment is started, the better the outcome for the patients.
- The combination of calcium folinate and 5-FU is more effective than 5-FU alone.
- The infused 5-FU infusion is better than bolus.
- Chemotherapy combining two agents is more effective in the first-line treatment than monotherapy, but it also has more toxic effects.
- Treatment with polychemotherapy with the addition of target drugs is more effective than polychemotherapy alone; moreover, it also yields a longer survival.
- The second-line systemic treatment is more effective than the best supportive care;[12,13] the same applies also to the third-line treatment.

The application of these new issues in clinical practice cannot always be a clear-cut practice because it should bear in mind that the most effective treatment modality is not always the best option for a particular patient. Therefore, in selecting the treatment modality, the following factors should be considered:
– age
– performance status
– tumour-associated symptoms
– size and invasion of metastases
– treatment line
– associated diseases.

Metastatic disease: which systemic treatment is most appropriate?

So far, no definite suggestion has been made which of the twin therapies to select, FOLFIRI or FOLFOX. Several randomized trials which compared the two treatment regimens confirmed that they were equally effective and also showed that the survivals were comparable. Thus, either of the twin therapies can be recommended as the first- or second-line treatment. Also the toxicity of the two treatment regimens is comparable, except that the specter of toxicity is different; the most typical toxic effect of FOLFOX is neurotoxicity, while FOLFIRI typically causes diarrhoea and alopecia. The FOLFOX-associated neurotoxicity may be severe; it is cumulative and occurs in late treatment cycle, the FOLFIRI-associated toxicities develop in the earliest treatment cycles, already after the first completed cycle.[14-18]

As the FOLFOX regimen has been designated as the adjuvant treatment of the patients with the stage III colorectal cancer, medical oncologists will in no time start receiving the patients with the disease progression after the completed chemotherapy. It is, therefore, obvious why the FOLFIRI scheme in combination with biological drugs will become a treatment of choice in the first-line treatment of metastatic colorectal cancer.

New target drugs

In Europe, and consequently in Slovenia, two new anticancer target drugs were registered in recent years; these are cetuximab which was approved in June 2004, and bevacizumab, approved in January 2005.

Cetuximab is a chimeric monoclonal antibody that targets the extracellular domain of the epidermal growth factor receptor (EGFR).[19] EGFR is overexpressed in 60%-80% of colorectal tumours. Several preclinical and clinical trials have confirmed the efficiency of cetuximab applied as monotherapy or, in the FOLFIRI non-responsive patients, in combination with FOLFIRI regimen. In a clinical phase III trial on cetuximab, the improvement of the disease-free survival, but no increase in the toxicity of chemotherapy, was observed in the FOLFIRI non-responsive patients treated with cetuximab plus FOLFIRI regimen. The adverse effects of treatment with cetuximab are allergic and skin reactions that can be managed.[19] It was also proved that the patients with grade II skin reactions are more likely to respond to treatment.[19,20] The efficiency and safety of cetuximab applied in combination with irinotecan in the patients refractory to chemotherapy was demonstrated also in the multicentric studies MABEL[21] and LABEL.[22] Most valuable data were provided also by the recent studies that were followed by phase II trials, which all support the comparability and consistency of the obtained results. A phase III randomised study on cetuximab NCIC CO.17 proved that cetuximab is the only biological drug which assures efficiency, safety and better quality of life of the

patients in whom all other treatment potentials have been exhausted. The patients who were treated with weekly doses of cetuximab (monotherapy) had significantly longer survival and better quality of life than the patients who were receiving the best supportive care.[23] The results of the EPIC phase III clinical trial are noteworthy, too. In this trial, the patients in whom oxaliplatin-based chemotherapy failed were receiving either the irinotecan-based chemotherapy or a combination of irinotecan and cetuximab. In the patients who had received cetuximab, a fourfold improvement of response rate, a significantly longer time to disease progression and improved quality of life were observed.[24] The results of two randomized studies (CRYSTAL and OPUS), in which the patients treated for metastatic colorectal cancer were receiving cetuximab in the first-line treatment, revealed that the mutations on the KRAS gene have a predictive value for prognosticating the efficiency of treatment with target agents targeting EGFR. Hence, these mutations are the first biomarkers that will be of great help in selecting a proper treatment that will assure a better response to treatment, longer survival and better quality of life to each individual colorectal cancer patient.[5,6]

The overexpression of vascular endothelial growth factor (VEGF) is an important mediator of angiogenesis in colorectal cancer as well as in a number of other cancers. Bevacizumab is a recombinant human antibody against VEGF. A combined treatment of the patients with colorectal cancer has proved to be most effective. By adding bevacizumab to chemotherapy, the response rate to treatment has increased by 10% and the survival by 5 months. On account of these favorable results, bevacizumab in combination with chemotherapy has become a treatment doctrine in the USA as well as in Europe. The most frequent adverse effects of the treatment with bevacizumab are proteinuria, hypertension, and thromboembolic disorders.[9]

The efficiency of bevacizumab was tested on 923 patients with metastatic colorectal cancer included in the randomized phase III AVF2107 clinical study. The study compared a placebo in combination with irinotecn plus 5-FU/LV (IFL regimen) versus bevacizumab and IFL regimen versus bevacizumab plus 5-FU/LV. The primary aim of the study was to evaluate the overall survival. The secondary aims were to evaluate the disease-free survival, overall response rate and duration of the response.[9] As soon as the safety and efficiency of the combination of IFL regimen plus bevacizumab was confirmed and approved, the recruitment of patients for the third group was closed. Altogether 813 patients were included in the study groups 1 and 2; the group that received bevacizumab in combination with chemotherapy had longer overall survival (20.3 months) than the group treated with chemotherapy alone (15.5 months). The combination of bevacizumab and irinotecan plus 5-FU/LV prolonged the time to disease progression by 4.4 months.

In the second-line treatment, bevacizumab was tested in two large international phase III studies, NO16966 and E3200. The NO16966 study showed a significantly longer time to disease progression in the patients who were receiving bevacizumab in addition to chemotherapy (XELOX or FOLFOX regimen). The patients who were receiving bevacizumab until the disease progression particularly benefited from this therapy.[25]

In the E3200 study, J. Giantonio *et al*. assessed the efficiency of bevacizumab (10 mg/kg) in combination with the FOLFOX4 regimen in 829 patients with advanced colorectal cancer who underwent prior therapies. The patients were randomized into three study groups by the following

treatment regimens: FOLFOX 4 plus bevacizumab, FOLFOX 4 alone, bevacizumab alone. The agents were applied in two-week treatment schedules. Bevacizumab in combination with FOLFOX 4 statistically significantly improved the disease-free survival (7.3 months vs. 4.7 months, $p<0.0001$) and objective response to treatment (22.7% vs. 8.6%). The results of the study also showed that the overall survival of the patients treated with the combination of bevacizumab and the FOLFOX 4 regimen was by 2.1 months longer than that of the patients treated with the FOLFOX 4 regimen alone. The time to disease progression was also longer, while the death risk was reduced by 24%.[25,26]

In October 2008 the results of the BriTE study, an American research study performed on a large cohort of patients with metastatic colorectal cancer treated with bevacizumab plus chemotherapy in the first-line treatments, were presented. The study included 1,953 patients from 49 countries. The aim of the study was to assess the efficiency of bevacizumab after the disease progression in the patients in whom the bevacizumab therapy was not discontinued after the disease progression. The patients with the disease progression were randomized in three study groups: the patients with no further therapy, the patients receiving further therapies without bevacizumab, and the patients treated with bevacizumab plus chemotherapy. The median overall survival was 25.1 months and the mean time to disease progression was 10 months. One of the most important conclusion of this study was that the patients treated after the disease progression with bevacizumab plus chemotherapy had the longest median survival (31.8 months, $p<0.001$).[27]

Conclusions

In the most recent years, five new agents, capecitabine, irinotecan, oxaliplatin, cetuximab and bevacizumab were registered. Their different combinations in the treatment of patients with metastatic colorectal cancer improved the efficiency of treatment, quality of life of patients, and survival rates. Before the use of these agents in clinical practice, the mean survival of colorectal cancer patients was 11 months; with the introduction of the new agents, the survival may be longer than three years or even five years if the treatment with new agents is combined with careful surgical excision of colorectal cancer liver metastases. Among the important advances in the study of a cancer cell was the determination of the KRAS gene mutation which appeared to be the first biomarker to predict the response to treatment with target drugs. We believe that the further development of this area will play a fundamental role in selecting the appropriate treatment regimen for each individual patient.

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review

Presence and role of Simian Virus 40 (SV40) in malignant pleural mesothelioma

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Background. *Evidence of a possible role of viruses in cancer first emerged in the early 1900s and was confirmed after the discovery of Epstein-Barr virus (EBV) in Burkitt's lymphoma cells. Thereafter, several oncogenic viruses and retroviruses were characterised. It is estimated that 15% of human malignancies are of viral aetiology. Oncogenic viruses use different proteins to interfere dramatically with the cellular cell cycle and affect many signalling pathways and checkpoints, causing genomic instability, immunoresistance and immortality.*

Conclusions. *Simian virus 40 (SV40) is a small DNA virus from the genus polyomavirus, closely related to human polyomaviruses John Cunningham virus (JCV) and BK virus (BKV) and is highly oncogenic for rodents. The virus accidentally entered the human population through contaminated early batches of polio vaccine in the 1960s. After the discovery of SV40-like DNA sequences in mesothelioma samples in 1994, a new wave of research started, focusing on the role of SV40 in malignant pleural mesothelioma and human cancer in general. Although the virus is not considered a cancer causing agent for humans, it is thought to have a (not yet defined) role in the development of the malignancy. Further research to better understand the interactions between the virus and the mesothelial cell is still ongoing.*

Key words: viral carcinogenesis; simian virus 40; mesothelioma; T antigen

Introduction

Evidence of a possible role of viruses in cancer first emerged in the early 1900s, but because malignancies were considered to be non-contagious, the findings were received with scepticism. The debate was finalised in 1964, when Epstein-Barr virus (EBV) was discovered in Burkitt lymphoma malignant cells. Further studies identified several other cancer–inducing human viruses and, in 1990, it was estimated that viruses and other infecting agents are associated with about 15% of all human cancer cases worldwide.[1] In addition to EBV, the most prominent human oncogenic DNA viruses are hepatitis B virus (HBV), human papilloma virus (HPV) and Kaposi sarcoma herpes virus (KSHV). Oncogenic retroviruses exist, too, and their role in human cancers has been discussed elsewhere.[3]

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Oncogenic viruses dramatically interfere with the cell cycle and affect many signalling pathways and checkpoints.[2] Different viruses use specific products to induce a progressive transition to the malignant phenotype. They may cause genetic instability of the infected cell, resistance to the immune system and cellular immortality.

Oncogenic DNA viruses adopt several different mechanisms to trigger host cell malignant transformation; a common feature of all oncogenic viruses is the ability to use multiple strategies. HPV oncoproteins, for example, induce genomic instability by inducing centrosome duplication errors and formation of abnormal centrioles, leading to a dysfunctional mitotic spindle and chromosomal imbalancies in daughter cells and, at the same time, prevent apoptosis. KSHV and EBV oncoproteins induce cell immortalization by modulating telomerase activity and promoting the alternative lengthening of telomeres (ALT) pathway. These mechanisms help cells bypass crisis and grant a dramatically prolonged lifespan. Other viral proteins destabilize p53, allowing cells to ignore cell cycle checkpoints and undergo undisturbed proliferation. Viral proteins interfere with the cellular microenvironment and impair communication with adjacent cells, ensuring a stable malignant phenotype and invasiveness of the host cell.[1]

Other DNA viruses can cause malignant transformations *in vitro*, but their definite role in human cancer is not determined. This group includes several adenoviruses and polyomaviruses. Very recently, a new polyomavirus has been identified and isolated from human Merkel cell carcinoma and could be the main causative agent for this skin malignancy.[3] Another polyomavirus, Simian virus 40 (SV40), is being extensively studied for its possible role as a human carcinogen, since it is highly oncogenic for rodents. The virus can also transform human cells *in vitro* and the first successful attempt to convert normal human cells to a stable malignant phenotype with a defined set of genetic elements actually used a combination of SV40, hRAS and hTERT sequences.[4]

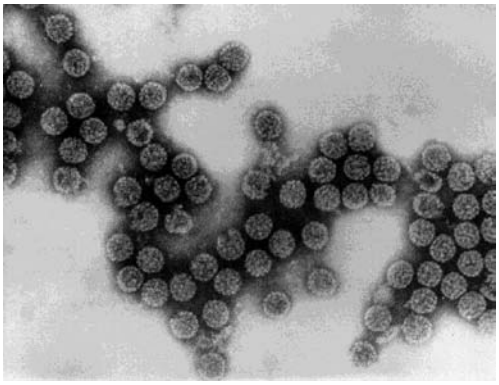

Figure 1. Transmission electron micrograph of polyomavirus SV40 (photo by Dr. E. Palmer, Center for Disease Control (CDC), GA, USA; no copyright restrictions under Public Domain – Property of the United States federal government (PD-USGov)).

SV40 in cancer

SV40, also known as Simian vacuolating virus 40, is a small (approximately 40 nm in diameter) icosahedral non-enveloped DNA virus from the genus polyomavirus (Figure 1). It is closely related to, and shares approximately 70% sequence similarity with, the human polyomaviruses John Cunningham virus (JCV) and BK virus (BKV; named after the initials B.K. of a renal transplant patient; viral particles were found in his urine). Its genome consists of a single circular double stranded DNA molecule and can be divided into three distinct regions – early, late and regulatory. The early region is expressed soon after entrance into the host cell, while the late region is expressed efficiently only after successful viral DNA replication has begun and it encodes for the capsid proteins (Figure 2).[5]

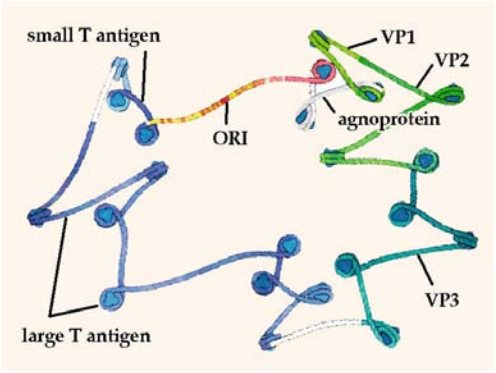

Figure 2. Structural view of the 5243 nucleotide SV40 genome with its characteristic nucleosomes. Blue highlights the early region, while the late region is green. Yellow and red denote the regulatory region of the viral genome (modified from D.S. Goodsell. Simian Virus 40 – November 2003 Molecule of the Month. Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank; no copyright restrictions under PD-USGov).

Its primary hosts are rhesus macaque (*Macaca mulatta*) monkeys. The virus is capable of causing tumours when injected into rodents.[6] Low antibody titters in human sera show that, compared to monkeys, replication of SV40 in humans is inefficient and that the virus is poorly adapted to the alternative host.[5]

Since the accidental contamination of large early batches of polio vaccine in the 1950s and 1960s, the previously unknown virus has spread in the human population and has become seen as an emerging human pathogen.[7] Both oral and intravenous vaccines were initially produced using rhesus monkey primary cell lines, some of which were naturally contaminated with SV40. The virus was discovered several years after the start of the mass polio immunization programme.[8] An unknown proportion of the vaccine was contaminated, presumably with small amounts of SV40.[9] The number of patients given the contaminated vaccine is also unknown, but estimates exist of more than 98 million people exposed to the contaminated vaccine in the United States alone.[10] Batches of intravenous polio vaccine (IPV – intravenous inactivated (Salk's) polio vaccine) produced after 1963 were SV40-free, while the virus remained present in the oral vaccine (OPV – oral live attenuated (Sabin's) polio vaccine) until the 1970s. Contaminated OPV and IPV were inadvertently used in many countries other than the United States, including the former Soviet Union, Japan, the United Kingdom, Italy, Mexico and several Central American and European countries.[5] No official records are available for Slovenia, but it is thought that no contaminated vaccine was used. It is presumed that SV40 has a tumour inducing or promoting role in humans.[10] Possible effects on human health, including the development of cancer, have been extensively researched in the past fifty years and many studies are still ongoing.

The virus triggers malignant transformations of both animal and human cells *in vitro* and is oncogenic for rodents when injected intraperitoneally or pericardially. Malignant transformation occurs if SV40 DNA becomes integrated in the host cell genome or remains in stable episomal form in the cytosol.[5] In mice, latent infection with SV40 can cause malignancy, mediated by two early viral proteins: large T antigen (Tag) and small t antigen (tag). Labelled one of the most potent oncogenic proteins, Tag has multiple functions in the host cell. It mainly acts as a transcriptional suppressor of tumour suppressor genes, while tag inhibits protein phosphatase 2A and thus serves as a modulator of Tag. Other important roles of Tag are direct binding and inactivation of expressed p53 and Rb and induction of insuline-like growth factor-1 (I-LGF 1) and its receptor[11] and, as recently discovered, p53-Tag complexes act as transcription factors acting as an inductor of I-LGF 1 promoter.[12]

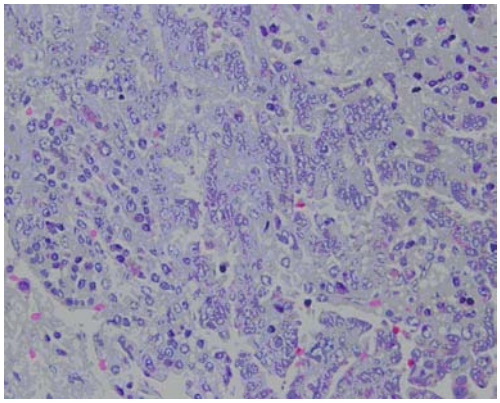

Figure 3. Classic HE stain of malignant pleural mesothelioma.

Large T antigen alone can initiate and maintain malignancy in hamster cells, but it is presumed that other events on the cellular level are required for *in vitro* malignant transformation of human cells.[13] Experimental data has shown that co-expression of SV40 early genes (Tag and tag genes), telomerase activity and oncogenic hRAS are sufficient for stable malignant transformation of human cells *in vitro*. This is mediated by perturbation of several intracellular signalling and metabolic pathways.[5]

The possible role of SV40 in human malignancies has been intensively debated. It is presumed that SV40 has either a tumour inducing or promoting role in humans.[10] Some human tumours (bone sarcomas, non-Hodgkin's lymphomas, brain tumours and mesothelioma in particular) frequently contain proviral DNA, usually in episomal form.

The strongest association between SV40 and human malignancies has been shown for malignant pleural mesothelioma.[14]

SV40 in malignant mesothelioma

Malignant pleural mesothelioma (MPM) is a rare but highly invasive tumour that is very rarely curable.[15,16] It arises from the malignant transformation of mesothelial cells, a uniform layer of non-differentiated serosal epithelial cells lining the pleura, the peritoneum and the pericardium (Figure 3).[11,15]

Among mesothelial malignancies, MPM is the most common, accounting for about 90% of all mesothelioma cases. It causes on average one death per million inhabitants worldwide, with very significant geographical variability,[16,17] since the incidence in Europe and Australia is considerably higher than in the Americas.[18]

There is no doubt that the vast majority of MPM are caused by asbestos fibres, since only 20% of mesothelioma cases occur without previous exposure to asbestos.[14,16] The data of patients with mesothelioma who had not been exposed to asbestos has varied.[15,19]

However, since only a small fraction of subjects exposed to asbestos fibres develop MPM, it has been suggested that additional factors may be involved in mesothelial malignant transformations. Other causes, in addition to asbestos, including non-asbestos fibres (erionite, in Cappadocia, Turkey), therapeutic radiation and intense pleural scarring (caused by prior plombage therapy for tuberculosis) have been reported to cause mesothelioma in rare cases.[18] Detection of Simian virus 40 DNA in several MPM tissue samples suggests that the virus itself could be the factor that renders some asbestos exposed individuals more susceptible to MPM.[20]

The discovery of SV40-like sequences in the genome of several MPM patients by Carbone *et al*.[21] in 1994 caused much controversy. Several studies of the presence of specific anti SV40 antibodies in patients' sera were mostly negative or detected extremely low antibody levels. Engels *et al*.[22] stated that these results mean that the antibody titter declined over the years, probably due to a lack of virus replication, indicating

a latent infection. Only the discovery of viral proteins within tumour tissues has confirmed the actual presence of the virus.[23]

Traces of either viral DNA or proteins have been repeatedly found in various independent studies. It is now accepted that mesothelial cells are unusually susceptible to SV40 mediated transformation,[5] but there is no indisputable epidemiological proof that contamination with SV40 increases the risk of developing MPM or cancer mortality.[10]

In vitro testing has shown that SV40 infects only about 20% of human fibroblasts and epithelial cells and becomes integrated in the cellular genome in only a small fraction ($1/10^7$) of infected cells. This results in cell lysis and thus prevents malignant transformation. Mesothelial cells, on the other hand, behave very differently compared to fibroblasts and epithelial cells. They seem to be more permissive for SV40 infection, but about 80% of infected mesothelial cells survive infection and undergo latent, rather than lytic, infection. Infected mesothelial cells actively express Tag, but do not produce viral particles. A very high rate, approximately $1/10^3$ cells, undergo malignant transformation.[11]

One of the easiest and most sensitive techniques for SV40 DNA detection in tissue and cell culture samples is polymerase chain reaction (PCR). The vast majority of researchers who have published scientific papers on the presence of SV40 in mesothelioma have used this technique. However, wide discordance in the results, poor reproducibility and episodes of positive results in no-template negative controls, has led to a questioning of the specificity and sensitivity of PCR assays.[11] Other viral detection techniques, such as Southern blotting, DNA sequencing, mRNA *in situ* hybridization, Tag immunoprecipitation, electron microscopy, immunohistochemistry and immunofluorescence, have been used to confirm the positiveness of PCR results.[5]

It is surprising that immunostaining of Tag in tissue samples revealed that viral expression is present in MPM cells, but not in the adjacent stromal and lung tissue.[11] This observation, together with low viral DNA copy numbers and the virtual absence of anti-SV40 antibodies in patients' sera, suggests that SV40 might be the factor that initiates carcinogenesis and becomes redundant and lost at a later stage, allowing the cancerous cells to evade the immune response, survive and grow.[5] This behaviour is consistent with the »hit and run« hypothesis in viral carcinogenesis. According to this hypothesis, infected cells evade the innate immune system response in early phases of viral infection and malignant transformation. In later phases, the cells become stably malignant and some lose the viral genome before specific antibodies are formed. Malignant cells that do not express viral proteins are less immunogenic, which gives them a selective advantage compared to malignant cells with an active viral infection. There are no conclusive data on its credibility yet, but the »hit and run« hypothesis is a possible explanation for the lack of specific antibodies in the sera of patients with putative virus-associated cancers.[1]

Asbestos and SV40 co-carcinogenity

Recent studies have shown a strong co-carcinogenic effect of crocidolite asbestos fibres and SV40 on hamster and human mesothelial cells. Asbestos exposure complements SV40 infected cells in malignant transformation.[11] Moreover, the same effect has been observed and extensively studied in experimental animals.[20] Human mesothelial cells are particularly sensitive to both asbestos genotoxicity and SV40 transformation. It is assumed that the latter may have the pivotal malignancy inducing role

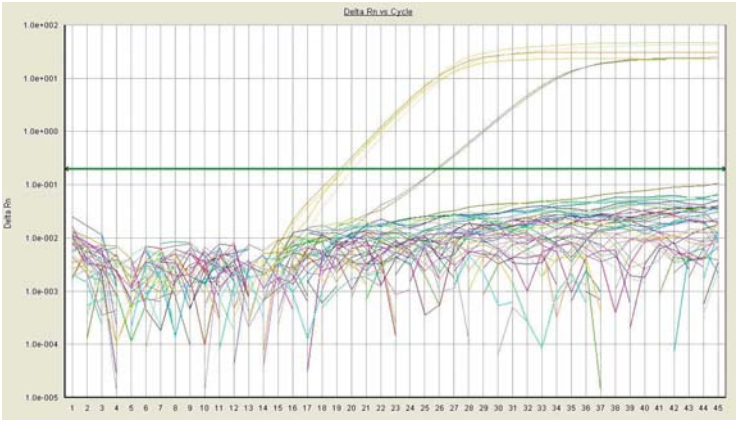

Figure 4. Amplification curve of a quantitative (real-time) polymerase chain reaction (qPCR) assay performed on DNA from mesothelioma tissue samples and DNA from SV40-transformed Wi-38 cells (ATCC acc. no. CCL-75.1) using a primer set for SV40 large T antigen (SV.for3 and SV.rev primers)[27] and two custom-made primer sets for SV40 small t antigen. Positive results were obtained only for the Wi-38 derived DNA, while mesothelioma samples were SV40 free.

in the mesothelium, especially in cells with asbestos damaged DNA.[24]

Asbestos fibres easily penetrate inside a cell, where they induce extensive DNA damage. The fibres generate genotoxic reactive oxygen and nitrogen species, cathalyse the synthesis of nitrotyrosine and induce DNA strand breaks. The presence of SV40 in asbestos exposed mesothelial cells affects the cell cycle, DNA repair and signalling pathways, especially through the interaction of some viral proteins (Tag and tag) with p53. The strong affinity of Tag for binding and inactivating p53 results in the cell avoiding key cell cycle checkpoints, thus surviving the otherwise fatal DNA damage and undergoing mitosis.[24,25] By escaping apoptosis and surviving, asbestos-damaged SV40 infected mesothelial cells pave the way to malignant transformation. It is very likely that asbestos fibres and viral Tag and tag interact and synergistically activate cellular signalling pathways, especially the ERK/AP-1 pathway, that lead to cell proliferation, malignant transformation and invasion.[20]

Conclusions and future aspects

Dilemmas and controversies about the role of SV40 as a human carcinogen are still strong, despite the ongoing extensive research. There is no powerful evidence of the exact role of SV40 in human cancers and MPM in particular. Some studies have suggested that the virus does not have a major implication in the development of MPM,[9,24] but several others claim the opposite.[20]

Researchers are still not able to find consensus, mainly because of flaws attributed to different SV40 detection techniques. The lack of appropriate, standardized approaches and quality control measures further adds to the controversy.[26] There is a high risk of false positive results, especially when using sensitive DNA detection techniques such as PCR. Some recent studies have proved that many previously published results of SV40 positive tumour specimens were not reproducible. The authors suggested contamination with laboratory plasmids and, for serological assays, cross-reactivity with antibodies to the SV40-related human polyomaviruses BKV and JCV.[9] The viral DNA sequences are common in many engineered plasmids and several immortalized cell lines, including the extensively used Wi-38 (ATCC acc. no. CCL-75.1). SV40 sequences containing DNA from these sources can easily contaminate PCR reaction mixes and laboratory equipment.

Extremely careful experiment design for every single step in the process is thus a must for reliable results, especially to avoid sample contamination and cross-contamination. Choosing multiple and appropriate primer sets for PCR can also avoid false-positive results and increase reproducibility (Figure 4).

Better understanding of viral carcinogenesis in general could provide new insights in our understanding of cancer biology and treatment.[1] Further studies, aimed not only at confirming the presence of the virus, but also at elucidating its role, will provide answers to open questions about a possible causal link.

Ongoing extensive research on the topic proves that elucidating the link between SV40 and MPM is of major interest to the scientific community. What seemed like a complex jigsaw puzzle even a few years ago is now being assembled and clarified and we will probably be able to tell the whole story very soon.

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research article

Deep dorsal vein embolization with N-butyl-2-cyanoacrylate and lipiodol mixture in venogenic erectile dysfunction: early and late results

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Background. *The aim of the study was to perform and evaluate pelvic venoablation with N-butyl-2-cyanoacrilate (NBCA) and lipiodol injection into the deep dorsal vein for the treatment of 32 patients with venogenic erectile dysfunction.*

Methods. *A total of 32 patients with the confirmed diagnosis of venogenic erectile dysfunction, with (n=15) or without (n=17) associated comorbidities were included. Deep dorsal veins were embolized with NBCA and lipiodol mixture. All patients were evaluated using the erectile function domain of the International Index of Erectile Function questionnaire (IIEF) before, at 3 months and 1 year after embolization.*

Results. *While the post-operative 3rd month scores were increased significantly in all groups ($p<0.001$), there was a significant decrease at 12th month when compared to that of 3rd month ($p<0.001$). But this decrease was significantly higher than those of preoperative values ($p<0.001$). In patients without comorbidities post-operative 3rd and 12th month scores were significantly higher than that of patients with comorbidities ($p<0.04$ and $p<0.02$, respectively). Although scores at 12th month were significantly higher compared to preoperative values, patients with comorbidities were dissatisfied with the quality of erection.*

Conclusions. *Our pelvic venoablation technique was effective short-term. A limitation of this technique is that some patients are not candidates for this procedure due to comorbidites.*

Key words: n-Butyl-2-cyanoacrylate; lipiodol; venous impotence; deep dorsal vein; embolization

Introduction

Erectile dysfunction (ED) is a complex phenomenon which could be related to physiologic, hormonal, neurologic, and vascular factors.[1,2] Vascular impotence is defined as the inability to maintain an erection because of the inability to maintain a sufficient volume of blood within the penis to engorge the *corpora cavernosa*.[3] This could occur due to either arterial or venous causes.[4] Although the exact cause of veno-occlusive dysfunction is not known, several pathophysiologic processes like the presence of large venous channels draining

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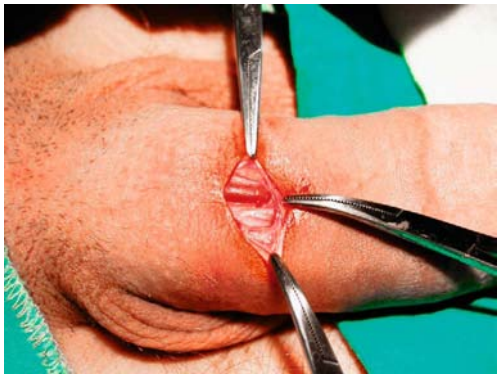


Figure 1a. After local anaesthesia, a small incision was made at the mid penile level and isolated.

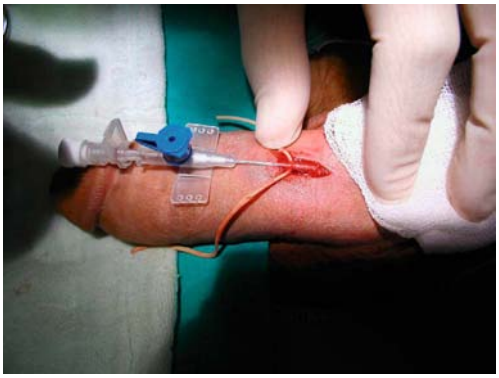


Figure 1b. It was catheterized with angiocath.

the *corpora cavernosa*, Peyronie's disease, diabetes and structural alterations in the fibroelastic components of the trabeculae, cavernous smooth muscle and endothelium have been mentioned in the literature.[5]

Even though the results of deep dorsal vein embolization (DDVE) are reported to be encouraging, the longer follow-up of these patients is needed.[6] In this study, we are reporting on early and late follow-up results of our patients that were treated with DDVE using N-butyl-2-cyanoacrilate (NBCA) and lipiodol injection. Patients suffered from the venogenic erectile dysfunction.

Patients and methods

A total of 32 patients with the confirmed diagnosis of venogenic erectile dysfunction by penile Doppler ultrasound and cavernosography gave informed consents after the detailed explanation of results, advantages, disadvantages and possible complications of available treatment options (surgical ligation, vacuum device, penile prosthesis implantation, oral and intracavernosal medications and embolization) for DDVE with NBCA and lipiodol mixture. All patients completed a brief self-administered questionnaire, the erectile function domain of the International Index of Erectile Function questionnaire (IIEF-EF). The severity of ED based on IIEF-EF domain score was classified as normal (≥26), mild (22-25), mild to moderate (17-21), moderate (11-16) and severe (6-10).

The embolization procedure was performed in the angiography suite. After the patient prepared and draped in the supine position, penile block with prilocain was

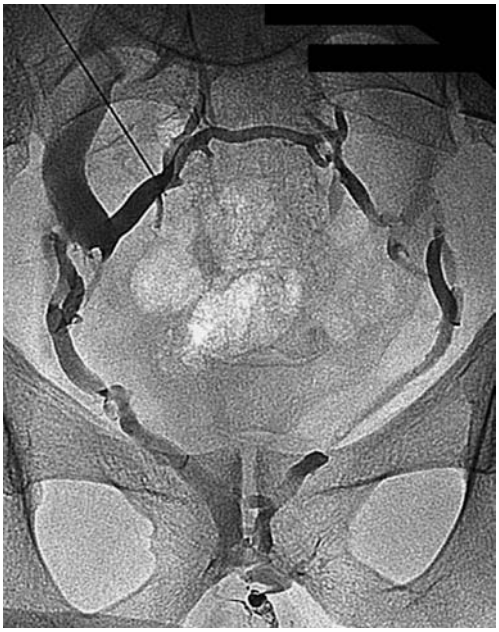


Figure 2a. Initial venogram after catheterization of deep dorsal vein showed significant venous leakage.

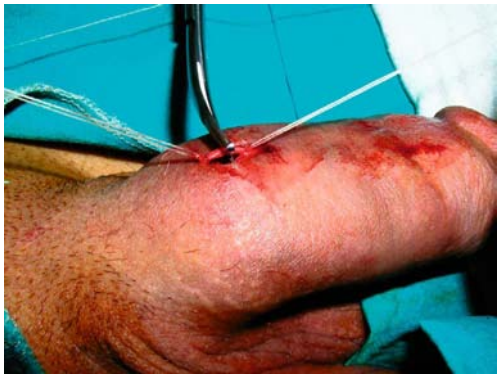


Figure 1c. After embolization incision was anatomically closed with absorbable suture material.

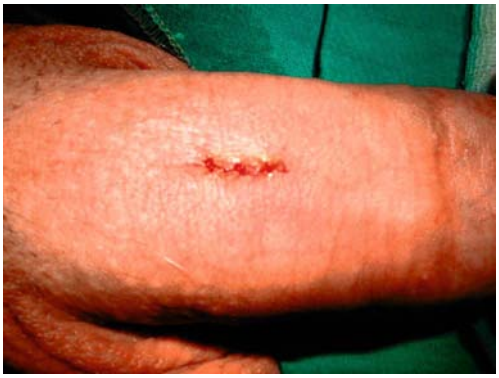


Figure 1d. The penile incision was anatomically closed with absorbable suture material.

performed and papaverine was administered intracavernosally. A 2 cm penile dorsal midline incision was made at the mid penile level. The deep dorsal vein was isolated under Buck's fascia and catheterized with 21G angiocath (Figures 1a, b). Venography was performed to confirm the intravenous location and to demonstrate retropubic venous plexus and draining veins (Figure 2a). Residual contrast material in the venous structures and angiocath was washed with 5% dextrose solution. A mixture of NBCA (Histoacryl; Braun-Melsungen, Germany) and lipiodol (Lipiodol; Guerbet, France) was prepared in 1:5 ratio as reported by Peskircioglu *et al*.[6] But based on the rate of venous filling on the initial venogram, the amount of lipiodol was increased or decreased in 4 and 3 cases, respectively. A volume of 5 ml was injected antegrade into

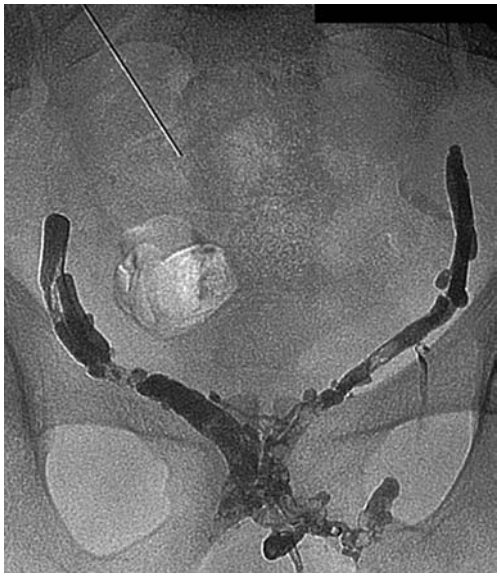


Figure 2b. N-butyl-2-cyanoacrilate (NBCA) and lipiodol mixture was administered under continuous fluoroscopic control. Occluded leaking veins were seen.

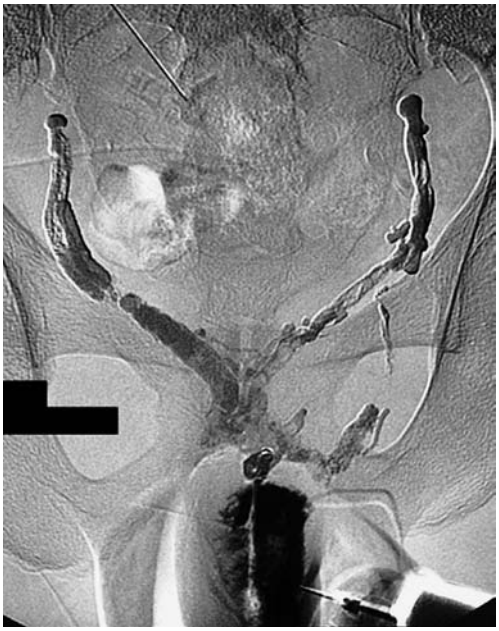


Figure 2c. Control cavernosography after embolization showed absence of venous leakage.

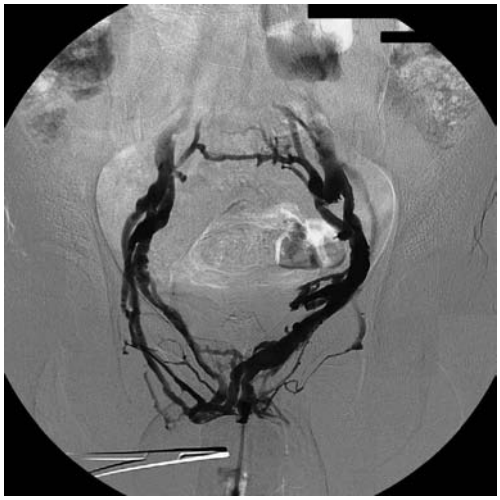


Figure 3a. Venogram showed significant and rapid venous leak to iliac veins.

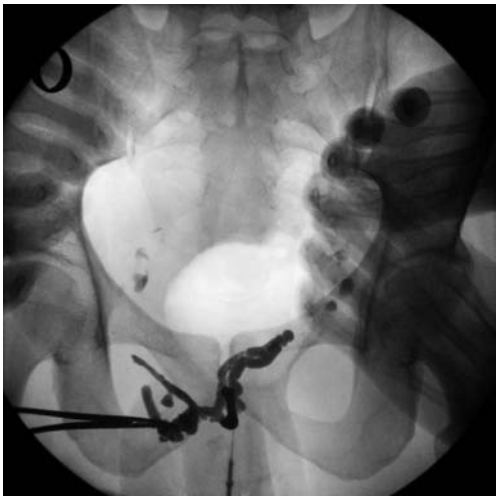


Figure 3b. During the embolization both groins were manually compressed to prevent reflux of the mixture into the larger veins and avoid complications.

the previously catheterized dorsal vein under the continuous fluoroscopic control. The occluded dorsal vein and its collaterals were visualized (Figures 2b,c). If the mixture preferentially occluded the veins on one side, a repeat injection was performed for the remaining veins on the other side after the injection of a small bolus of 5% dextrose. If the venous leak to iliac veins was significant and rapid, the manual compression was applied on both groins (Figures 3a,b,c). The penile incision was anatomically closed with absorbable suture material (Figures 1c,d) and an elastic bandage was applied to the penis. Compressive dressings were removed after 24 hours. Patients were reevaluated with IIEF-EF at 3 months and 1 year. No invasive examinations (cavernosography or cavernosometry) were performed during the follow-up period.

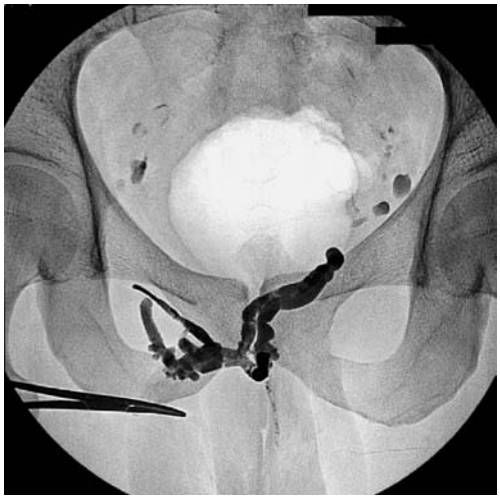


Figure 3c. Digital roentgenogram showed occluded leaking veins after embolization.

The preoperative, post-operative 3rd and 12th month IIEF-EF domain scores were compared with Wilcoxon's test and a p value of less than 0.05 was regarded as statistically significant. These scores were also compared between patients with and without comorbidities using Mann-Whitney U test and a p value of less than 0.05 was regarded as statistically significant.

Results

The patients, mean age 48.3 (± 12.2) years, were evaluated in three groups as total, with associated comorbidities (diabetes

Table 1. The mean preoperative, post-operative 3rd and 12th month International Index of Erectile Function questionnaire (IIEF-EF) domain scores in all groups (±SD)

IIEF-EF domain score	pre-op	post-op 3rd month	post-op 12th month
Total [n:32]	11.4 ± 1,9	20.1 ± 3,4	15.9 ± 3,2
Comorbidity (+)[n:15]	11.1 ± 1,9	18.9 ± 3,8	14.6 ± 2,5
Comorbidity (-)[n:17]	11.8 ± 1,6	21.5 ± 2,2	17.4 ± 3,2

mellitus, coronary heart disease, hypertension, and smoking) and without associated comorbidites. The mean preoperative, post-operative 3rd and 12th month IIEF-EF domain scores in all groups were presented in Table 1.

Post-operative 3rd month IIEF-EF scores were increased significantly in all groups ($p<0.001$). But, there was a significant decrease in IIEF-EF scores at 12th month when compared to that of 3rd month ($p<0.001$). In spite of this decrease at 12th month, IIEF-EF scores were significantly higher than those of preoperative values ($p<0.001$). In patients without comorbidities post-operative 3rd and 12th month IIEF-EF domain scores were significantly higher than those of patients with comorbidities ($p<0.04$ and $p<0.02$, respectively) (Figure 4).

Although in patients with comorbidities, IIEF-EF domain scores, at 12th month were significantly higher compared to preoperative values; these patients were dissatisfied with the quality of erection. A penile prosthesis was implanted in a diabetic patient. Although the satisfaction at 3rd month was decreased at 12th month in patients without

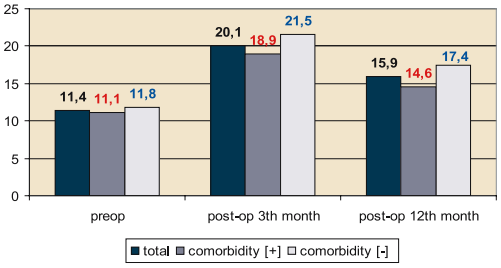


Figure 4. International Index of Erectile Function (IIEF) domain scores in all groups.

comorbidities, enough erection to have intercourse with the help of PDE5 inhibitors was possible in 7 patients.

No complaints or complications were noted during the exposure of the deep dorsal penile vein in any patient. The 21G angiocath was inserted into the deep dorsal penile vein and successfully advanced in all patients. In two cases, a symptomatic pulmonary embolism complication occurred but that we treated conservatively (Figures 5a,b,c,d).

Pelvic radiograms at 1 year follow-up were negative for contrast material.

Discussion

Erectile dysfunction could occur due to either arterial (inadequate inflow to meet the volume expansion of the dilated penile sinusoids) or venous (insufficient restriction of venous outflow to allow the retention of penile perfusion and to produce rigidity) causes.[4] Venogenic erectile dysfunction is an important problem leading to impotence that could result from several pathophysiologic processes (large venous channels, degenerative changes or traumatic injury to the *tunica albuginea*, structural alterations in the fibroelastic components, insufficient trabecular smooth muscle relaxation, and acquired venous shunts).[7] In order for a successful intercourse tonically contracted, flaccid penis needs some threshold amount of smooth muscle relaxation for conversion to the fully erect state with sufficient rigidity.[6] If there is corporeal smooth mus-

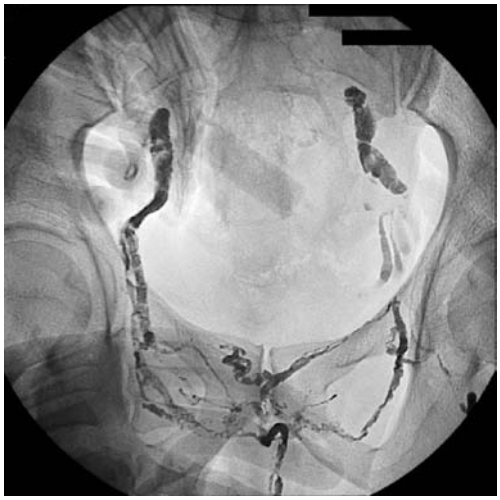


Figure 5a. In a patient with a significant venous leakage, mixture extended to both iliac veins despite the manual compression.

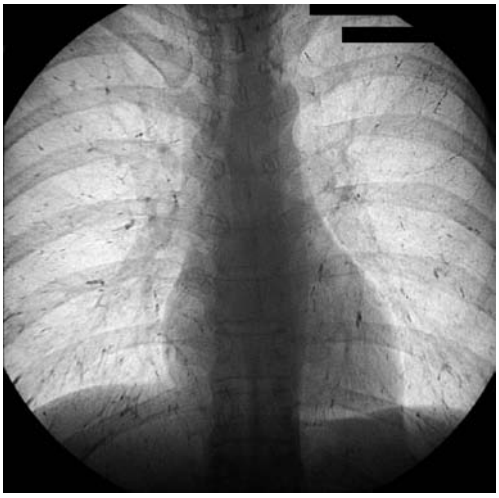
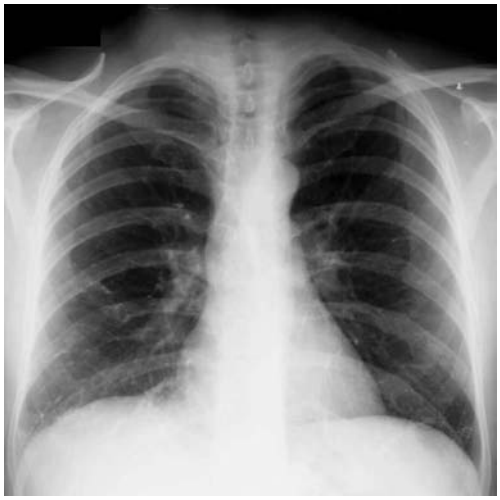


Figure 5b. Digital roentgenogram obtained immediately after the development of respiratory symptoms shows multiple tubular and round opacities alongside the pulmonary arteries in both lung zones.

cle dysfunction preventing relaxation, it will result in the incomplete resistance to outflow of blood from the *corpora*, venous leakage and incomplete erection.[6,8] Venous leakage is either due to functional causes like incomplete relaxation of trabecular smooth muscle or due to structural changes like fibrosis of the trabecular tissue, and less frequently venous leakage is originated by the presence of anomalous drainage through venous channels or through malfunctioning or ectopic veins which could be repaired.[8]

The penis is drained by three groups of veins: (1) superficial which primarily drains penile skin, but it could have anastomoses with the deep dorsal vein, (2) intermediate which consists of deep dorsal and circumflex veins and (3) deep which drains the deep cavernous tissue and consists of cavernosal and crural veins that are extensions of the emissary veins.[9,10] The superficial dorsal vein runs superficially to the deep (Buck) fascia and these veins do not participate in erection.[11] The venous drainage of the *corpora cavernosa* is mainly dependent on the deep dorsal vein that courses under the fascia penis, and it runs through the intracavernous sulcus to the prostatic plexus.[12] The trabeculae of the *corpus cavernosum* drain into a system of subtunical venules that coalesce just beneath the *tunica albuginea* and form a number of veins transversing the tunica called emissary veins. Emissary veins usually drain into the circumflex veins on the outer surface of the *tunica albuginea*, and these circumflex veins in turn drain into the deep dorsal vein of the penis shaft between the dorsal arteries.[9] The blood flowing from the circumflex veins to the deep dorsal veins is unidirectional.[8]

Currently, surgical ligation, radiological embolization, penile implants, self-injection therapy and pharmacotherapy are among the treatment options for venogenic ED.[13] The main goal of the treatment in patients with veno-occlusive dysfunction is to occlude the venous outflow to provide a long-term improvement of erectile function.[6,14] Several types of venous ligation surgery have been proposed for ED. Although the



Figures 5c. One month later, after the conservative treatment of the patient, control chest roentgenogram showed clearance of opacities.

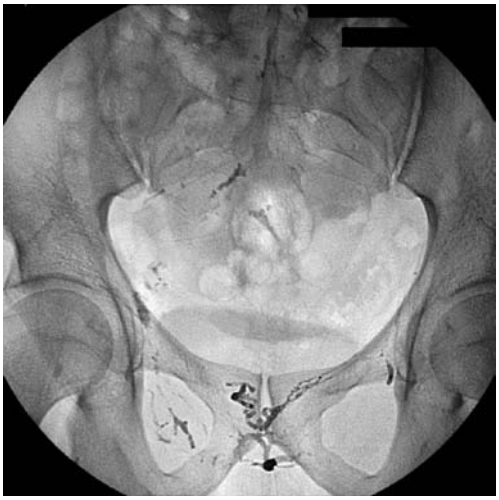


Figure 5d. Digital roentgenogram at 6th month control showed still occluded periprostatic plexuses.

ligation of penile veins to cure impotence has a long history, beginning in early 1900, recently renewed interest in venous surgery has increased due to the low acceptance rate of penile implants as the first line therapy, difficulties and expense of mixed pharmacotherapy, and high dropout rate (more than 50%) for self-injection therapy in longitudinal studies.[13] The surgical procedure has been expanded from the simple deep dorsal vein ligation to the extensive surgical exposure and vein ligation, excision, crural plication and spongiolysis performed alone or in combination.[8] The dissection of the superficial dorsal vein and ligation or the dissection of the deep dorsal vein, with the occlusion of the circumflex veins, is reported to be the least invasive type of surgery.[15] However, other more invasive procedures also require the ligation of the crural veins by means of perineal incision and dissection of the ischiocavernous muscles or the ligation of the crural portions of the *corpora cavernosa*.[15] Due to the early development of collateral veins of the *corpora cavernosa*, the long-term success rate of such surgical treatments is approximately 25%.[7] The inability to ligate all of the defective veins because of tiny collaterals which cannot be seen intraoperatively and also the inability to ligate proximal veins like the retropubic venous plexus due to exposure problems are among the reasons for the failure of surgical ligation.[7]

In addition to various surgical and medical treatment options, radiological embolizations have been used for the treatment of venogenic erectile dysfunction with variable success rates.[2,6,7,12,16,17] Various endovascular interventional procedures were developed for the treatment of venous erectile incompetence like embolization with surgical ligation, bilateral occlusion of crural veins with coils, percutaneous penile venous ablation with sclerosing agents.[7,8] Multiple veins can be embolized by an intraluminal procedure at once.[7] DDVE with NBCA has been reported with encouraging results as a safe and effective procedure.[6] NBCA is a tissue adhesive material that has been used for various vascular embolizations without any systemic side effects.[7,8] It has high adhesive force, instantly polymerizes upon contact with water and

proteins in blood, and also its degradation rate is quite low which makes the occlusion long-lasting.[18] Since it is non-opaque it is mixed with a radiopaque contrast media to observe during intervention under fluoroscopy. Lipiodol is used for this purpose due to its high hydrophobic feature which makes the hydrophilic ion species difficult to interact with NBCA monomers.[17] Lipiodol also prolongs the polymerization time of NBCA. The embolization with NBCA and lipiodol is less expensive than a surgical procedure; the procedure is short and requires no hospitalisation.[6] In all of our patients, it was possible to embolize all leaking veins responsible for anomalous venous drainage. Since embolic mixture is in a liquid form, even the tiny collaterals were embolized easily. Polymerization time can be controlled by the amount of lipiodol. Although we routinely mixed the NBCA with lipiodol in a ratio of 1:5, based on the rate of venous filling on the initial venogram, in four cases we decreased the amount of lipiodol in order to embolize most of the draining veins. Our pulmonary complications were among the ones where we decreased the lipiodol amount. In one of the pulmonary complication cases, a repeat injection had also been performed. Although our intention was to embolize most of the leaking veins, increasing polymerization time and in repeat injection cases increased risk of fragmentation and distal migration of NBCA and lipiodol mixture after the administration of dextrose bolus, leaded to the reflux of the mixture into the main and larger veins. The embolization of non-target organs or structures, like pulmonary arteries as in our cases, is a possible risk. If pulmonary embolism occurs, embolized NBCA causes an acute and chronic foreign body reaction in lungs. Lipiodol might produce lung damage due to breakdown into free fatty acids.[17] The treatment of symptomatic pulmonary complications of glue embolization is primarily conservative as in our cases.

Since cavernosometry and cavernosography are invasive procedures, we did not perform them. For the further evaluation of our early and late results the validated IIEF was used. IIEF is a self-administered sexual function questionnaire that has demonstrated high specificity and sensitivity for detecting changes in erectile function associated with the treatment.[19] It is reported to discriminate well between men with and without ED and has been used to assess the therapeutic efficacy and outcomes in patients with ED.[19] The erectile function domain of IIEF pertains to sexual experience within the last 4 weeks consists of 6 questions designed to address sensitively and specifically relevant aspects of erectile function[14,19] IIEF-EF domain could be used in clinical and research settings as a diagnostic aid for assigning degrees of ED severity.[19]

Statistically IIEF-EF domain scores in all of our patients were significantly increased at post-operative 3rd month. There was a significant decrease in IIEF-EF domain scores in all groups at one year when compared to 3rd month values. However, IIEF-EF domain scores were significantly higher than those of preoperative values. Despite this statistical significance, patients with comorbidities were dissatisfied with their quality of erection. Therefore, taking into consideration inherent possible complications and risks, we believe that DDVE should not be performed in patients with comorbidities despite the early good results. In venous surgery improved erections could be interpreted as converting a non-responder to oral or vasoactive injection therapy or a reduction in dose required for a successful intercourse.[8] Even though the satisfaction level was decreased at one year in our patients without comorbidities, 7 of them had enough erection to have intercourse with the

help of PDE5 inhibitors. Therefore, DDVE could be regarded as a procedure causing the improvement in erections in patients without comorbidities. Also, the synergism of penile venous surgery and oral sildenafil in treating patients with erectile dysfunction has been reported.[20]

In conclusion, our pelvic venoablation technique was effective and promising short-term. A limitation of this technique is that some patients are not candidates for this procedure due to comorbidites.

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case report

Retroperitoneal perforation of the rectum during double-contrast barium-enema examination: a life-threatening complication

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Background. *Rectal injuries during barium-enema are rare but life-threatening complications.*
Case report. *We present a case of an 82-year-old man in whom extensive retroperitoneal perforation of the rectum occurred during double-contrast barium-enema examination. The patient was revealed acute abdomen, difficulty in breathing and diffuse subcutaneous crepitus at the chest and neck area. The patient underwent a surgery because signs of peritonitis developed. We performed a Hartmann's procedure. The patient died 20 hours after the surgery due to a septic shock.*
Conclusions. *Prompt recognition and management of retroperitoneal perforation of the rectum are sine qua non in decreasing mortality.*

Key words: rectal perforation; barium-enema

Introduction

Rectal perforation is a rare complication of the barium-enema examination. The clinical presentation varies according to the anatomic location and degree of the rectal injury. Extensive retroperitoneal emphysema and barium may cause acute abdomen and respiratory distress. The diagnosis is based on the clinical and imaging studies.[1] The radiographic findings depend upon the volume of extravased air and barium. Perforative rectal injuries have been categorized by Ault.[2] Injuries of Category 1 and 2 are mild injuries that meaning patients can be treated with conservative methods. Category 3 and up are accompanied by septic infection and high mortality rate. In this article, we report about a case of retroperitoneal rectum perforation due to barium-enema examination.

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Case report

An 82-year-old man was admitted to Izmir Bozyaka Teaching and Research Hospital, Department of Surgery with a history of diffuse abdominal pain, swallowing and dyspnoea of 3 hours duration.

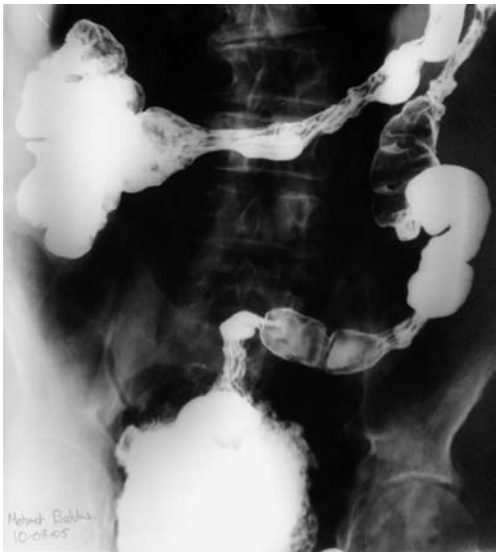

Figure 1. Presence of perirectal extravasation of barium in double-contrast barium-enema examination.

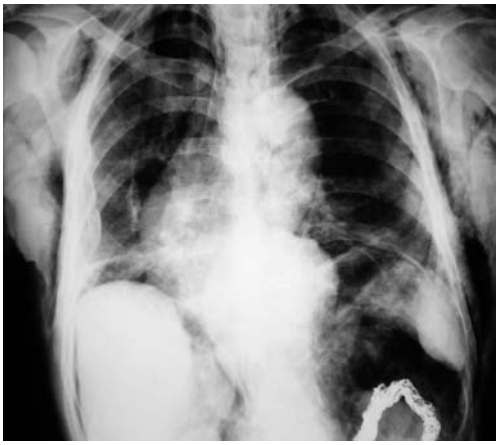

Figure 2. Erect chest X-ray at presentation demonstrates air under the diaphragm, in mediastinum and subcutaneous emphysema.

He was presented with a history of two-month's constipation and weakness. For differential diagnosis, barium-enema with additional air-contrast study was performed 4 hours before in Radiology Department. Later on, on the same day, the patient developed abdominal complaints associated with breathing difficulties. When admitted, his temperature was 38°C, blood pressure was 110/70 mm Hg, pulse rate 90 bpm and breath rate 24 bpm. The double-contrast barium-enema examination showed the perirectal extravasation of barium (Figure 1).

On examination he had generalised abdominal tenderness with guarding, rebound tenderness, swallowing and diffuse subcutaneous *crepitus* in the chest and neck area. Rectal examination showed that blood passed per-rectum. Laboratory studies showed a WBC count of 14 x 10^9L and 20 x 10^9L. A roentgenogram of the chest showed free air in the peritoneal cavity, in the retroperitoneal space in the mediastinum and subcutaneous emphysema (Figure 2). Computerized tomography showed perirectal barium and subcutaneous emphysema (Figure 3). Based upon these clinical and radiological findings we suspected that a perforation of the rectum occurred.

After the initial resuscitation in our clinic, the patient underwent a midline transperitoneal laparotomy during which was found out that he suffered to an extraperitoneal perforation in the posterior wall of the rectum. The perirectal tissues were of emphysematous nature and soiled with barium. In the retroperitoneum and anterior abdominal wall a large amount of barium and oedema, involving the muscle, fascia and subcutanous tissues was found extraperitoneally. The mesenterium of sigmoid colon was widened with the large amount of barium. The perforation wasn't suitable for suture repair and the Hartmann's procedure was done. Large irrigation tubes were inserted into the *rectovesical fossa*. At the intensive care unit postoperatively, he was in a shock with temperature of 36.5°C, blood pressure of 70/40 mmHg, a pulse of 130 bpm, and a respiratory rate of 30 bpm. Later he developed to multiple organ dysfunction syndrome and systemic inflammatory response syndrome and he died 20 hours after operation.

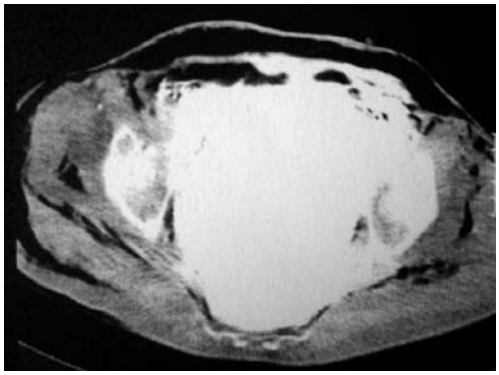

Figure 3. CT showed perirectal migration of barium in pelvic cavity and subcutaneous emphysema.

Discussion

Rectal perforation following double-contrast barium-enema examination is uncommon. Terranova *et al.*[3] reported that this complication occurred in 1% of all barium studies. In the study of Fry *et al.*[4] rectum or sigmoid colon perforations were found in 5 cases among the 2200 barium-enema examinations performed during a 4-year period.

The most frequent causes of rectal perforations are traumatic injury of the tip of the enema catheter or presumably the excessive hydrostatic pressure. In some studies, intraluminal lesions such as cancer, *diverticulum* or rectal biopsies were reported pre-existing factors.[1] Rectal perforations may be either intraperitoneal or extraperitoneal. Five types of perforations have been described based upon anatomic boundaries. Category 1 includes perforations of the anal canal below the *levator ani* muscle. Category 2 is incomplete perforations with only perforation of rectal mucosa. These perforations involve lower or/and middle third of rectum extraperitoneally. They present rectal pain and bleeding. Surgery is not always required for Category 1 and 2 perforations. These perforations can be treated conservatively with broad- spectrum antibiotics. Surgery is required only in cases of large perforations and when the extravasation of large amount of barium occurs. Category 3 includes rectal perforation above the *levator* muscle but below the peritoneal reflection. Retroperitoneal injury may cause difficulty in breathing, cyanosis, abdominal discomfort, and shoulder pain. Category 4 covers transmural perforation into the adjacent organs and Category 5 the intraperitoneal perforation. Half of surgically confirmed rectal injuries in Category 2 are painless or they occur with delayed pain.

In our case Category 3 perforation with extensive retroperitoneal and subcutaneous emphysema was determined. Subcutaneous emphysema in the chest, neck and scrotal areas were identified by physical examination. Clinically signs of difficulty in breathing, swallowing in the cervical area and subcutaneous *crepitus* were found in our patient. After few hours leucocytosis (20 x 10^9L), tachycardia and fever developed.

The radiological findings in each case depend upon the amount and nature of extravaseted material. In most radiological reports extravasation of air was found more frequent than barium leakage.[2] The perirectal air may dissect tissue plans extending into the retroperitoneal area gathering under the diaphragm. In our case extension of large volume air into the mediastinum and soft tissue of the neck resulted difficulty in breathing.

The retroperitoneal emphysema generally resolves within 1-2 weeks without sequelae.[5] In contrast as in our case spillage of dense barium and air produced progressive, fatal septic shock.

The treatment of retroperitoneal perforations depends on the clinical status and severity of perforations. Intraperitoneal or large retroperitoneal perforations must be treated by prompt laparotomy with removal of barium and drainage of abdominal cavity. During laparotomy a careful search for

injury of adjacent organs must be conducted. Primary repair of rectal perforations should be performed in appropriate cases. An end colostomy (Hartmann's procedure, colostomy of Devine, end colostomy with mucus fistula) must be performed to provide a defunctioning stoma.[6]

The studies suggests that the incidence of rectal perforation during barium-enema can be reduced by performing anoscopy prior to barium enema, avoiding the use of rectal balloon in rectal lesions, using a lower pressure and concentration of barium.[3]

Conclusions

Retroperitoneal perforations of rectum need immediate aggressive critical care because of the high mortality. Radiologist and surgeons must be able to communicate closely to achieve a better result.

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research article

MRI-based texture analysis: a potential technique to assess protectors against induced-liver fibrosis in rats

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Background. *In this study, the protective effect of extract of Moringa oleifera against carbon tetrachloride (CCl_4)-induced liver fibrosis in rats was evaluated using Magnetic Resonance Imaging-Texture Analysis (MRI-TA) and the results were compared to liver function tests and histopathology.*

Methods. *Twenty-eight male Wistar rats were randomly divided into 4 groups: a) the normal control group (C) received an intra-gastric administration of vehicle for eight weeks; b) the fibrosis group (F) received an intra-peritoneal administration of CCl_4 twice a week for eight weeks; c) the silymarin group (S) received 0.2 g/kg orally once a day for eight weeks along with CCl_4; d) the M. oleifera protected group (M), received an intra-gastric dose at 0.5 g/kg for 8 weeks concomitantly with CCl_4. Histopathology and liver function were performed and both confirmed protection against CCl_4-induced liver fibrosis.*

Results. *The fibrosis index showed a remarkable increase in collagen-I contents in the CCl_4 – injured animals (12.73±2.37%) while fibrotic indices were significantly less in liver tissues of Moringa-treated and silymarin-treated animals (5.23±0.13% and 1.23±1.01%, respectively). MRI-TA results were consistent with previous histopathological findings. Classification of MRI-TA parameters for the C, F, and M groups showed that the F group was separated from both M and C groups on the MDF-1 axis (Most Discriminating Parameters-1) whereby this group always had negative values. The C and M groups clustered closely on the same axis with positive values. Very similar results were obtained from classification of the C, F and S groups. The texture parameters used in this study measure the coarseness of the imaged tissue, which is influenced by the collagen contents and distribution, that are known to be increased in fibrosis and inhibited by antifibrotic drugs thus affecting image classification.*

Conclusions. *Based on our findings, MRI-TA can be established as a potential tool for assessing the protective or therapeutic effects of tested antifibrotic drug/s. M. oleifera exhibits a partial hepatoprotective effect on rats treated with CCl_4 which was proven by histopathology and liver function tests and indicated by MRI-TA performed on liver samples. We recommend MRI-TA as a potential tool for a simpler, easier, and faster way of indicating the therapeutic effect of antifibrotic drugs.*

Key words: MRI; liver fibrosis; Moringa oleifera; texture analysis

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Introduction

Hepatic fibrosis is a dynamic and complicated pathological condition that occurs in response to chronic hepatocellular injury. Liver fibrosis takes place as a result of many chronic liver diseases, such as hepatitis viral infection, including hepatitis B and hepatitis C. It is characterized by altered hepatic function and an excessive accumulation of extracellular matrix proteins, including collagen, which occurs in most types of chronic liver diseases. The progression of liver fibrosis often develops into irreversible cirrhosis and is associated with liver cancer.[1-3] It is therefore imperative to reduce the damage to the liver and to slow down the progress of liver injury into fibrosis and cancer. Oxidative stress may be a common factor in chronic liver diseases of different etiologies.[4] Many agents have been proposed for the prevention and treatment of fibrosis. New clinical approaches need to be developed to improve the efficiency of current treatments, which require continuous trials on new drugs with a therapeutic or protective effect against live fibrosis. However, the gold standard diagnostic method of any therapeutic follow-up of liver damage remains biopsy analysis. Biopsy requires expensive and complicated biochemical and histopathological procedures that are irreproducible and unsuitable for large population screening.[5] New techniques, which are less expensive and more reproducible, are continuously being investigated to provide a reliable preliminary evaluation of antifibrotic effects of novel tested drugs. Magnetic Resonance Imaging (MRI) has been successful in evaluating liver condition by using different acquisition sequences.[6,7] Automated image analysis methods, particularly texture analysis, when applied to different imaging modalities, are capable of providing quantitative data on a liver pathological condition, and therefore provide a powerful tool of automated characterization.[8-10] Previous studies have also demonstrated that TA of MR images can characterize tissue condition during degeneration and regeneration processes, as well as in relation to collagen contents.[11,12] MRI analysis is reproducible and can be rapidly applied. It can also be repeated many times over the same site without any hazardous or destructive effects to the tissue. Most importantly, MRI can be applied *in-vivo* and *ex-vivo*.[11,12] Taken together, MRI-TA offers a promising tool for monitoring the histopathological status of liver tissues and throughout therapeutic or preventive testing against fibrosis.

MRI-TA is studied in this work as a new approach applied on liver in order to predict the protective effect of a local plant, *Moringa oleifera*, suggested to have an antifibrotic effect; and compare the results to those of silymarin as a standard treatment of fibrosis. Conventional histopathological and liver function tests were performed and compared to MRI-TA results. To our knowledge, MRI-TA has not been previously applied to assess the therapeutic effects of antifibrotic drugs on liver.

Various parts of the *M. oleifera* Lam tree have been studied for several pharmacological applications. The plant extract has been shown to possess antioxidant activity[13], hypocholesterolemic, anti-inflammatory and antimicrobial effects. Moringa seeds are known as a rich source of oil, protein and many bioactive compounds.[14-18] Seeds extracts have also been shown to be potent anti-microbial, antigenotoxic, anti-inflammatory and anti-tumour remedies.[19-21] A recent study reported that Moringa seed oil had the strongest anti-fungal activity against a zoophilic dermatophyte that is known to cause severe inflammatory reactions in humans.[22]

The antioxidant potential of *M. oleifera* might allow it to succeed where other anti-

oxidants have failed in preventing hepatic fibrosis.[23] Taken together, these findings support the suggestion that *M. oleifera* is a promising herbal remedy for the treatment of hepatic fibrosis. Investigations are currently underway to unravel the biochemical basis of Moringa's protection against CCl_4-induced liver fibrosis.

Materials and methods

Plant extraction

Mature seeds of *M. oleifera* were collected in Al-Ain city, U.A.E. The plant was authenticated and specimen identification numbers are kept in the Biology's herbarium for future reference. A hundred grams of dried *Moringa oleifera* were mixed in 1000 ml of 70% ethanol. Every 10 gm of ground *M. oleifera* (Lam.) seeds were mixed with 100 ml of 70% ethanol in 250-ml conical flask. The mixture was then irradiated by microwave for two minutes.[24] The extracts were finally filtered through gauze and evaporated under vacuum at 40°C using a rotary evaporator. The dried extract was dissolved in distilled water before administration.

Animals

Adult Wistar male rats having with the weight ranging from 180-220 g were obtained from the Animal House, UAE University Al-Ain, U.A.E. They were maintained on a standard pellet diet and tap water *ad libitum* and were kept in polycarbonate cages with wood chip bedding under a 12 h light/dark cycle and room temperature of 22-24°C. The rats were acclimatized to the environment for two week prior to experimental use. This study was conducted following the guidelines of the Animal Research Ethics Committee of U.A.E University.

Experimental design

The rats were randomly divided into four groups: a) the normal control group (C; n=7) received an intra-gastric administration of vehicle only for eight weeks; b) the fibrosis group (F; n=7) received an intraperitoneal administration of CCl_4 twice a week for eight weeks; c) the silymarin group (S, n=7) received 0.2 g/kg orally once a day for eight weeks along with CCl_4; d) *M. oleifera* protected group (M; n=7), received an intra-gastric dose of 0.5 g/kg for 8 weeks concomitantly with CCl_4. At the end of eight weeks, one day after the last administration and after induction of ether anesthesia, blood samples were drawn from the eye retro-orbital plexus from all the rats prior to the excision of organ tissues. The serum was stored at -80°C after separation until it was assayed as described below. Liver was excised and specimens were placed in plastic containers with 10% buffered formaldehyde solution and kept overnight for following MRI.

Detection of serum markers

The activities of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assayed by spectrophotometric analysis (Bio-Merieux, RCS Lyon, France) according to the manufacturer's instructions.

Histochemistry

Liver tissue samples from all animals were processed for light microscopy and embedded in paraffin blocks, which were cut to obtain 5 μm thick sections and were mounted on slides. Sections were immunostained with anti-collagen I antibodies (Santa Cruz, CA, USA). Sections were examined using a Leica DMRB/E light microscope (Heerbrugg, Switzerland).

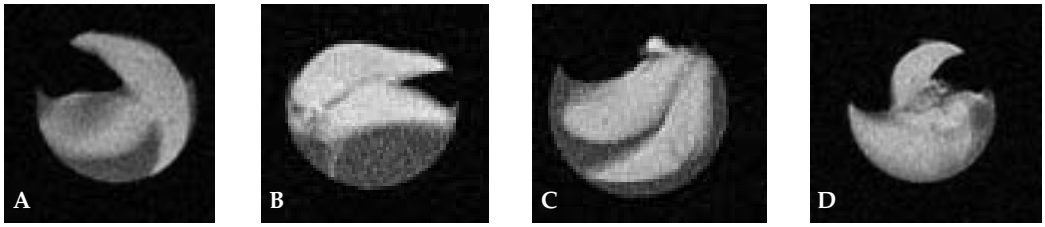


Figure 1. MRI image of liver specimens from: a) control, b) fibrotic, c) Moringa-treated and d) silymarin-treated rat groups. Images were acquired on the excised liver samples using the 1.5-T MRI system and T1-weighted Spin Echo sequence.

Statistical Analysis

SPSS (version 10) (SPSS Inc., Chicago, IL, USA) was used to carry out a one-way analysis of variance (ANOVA) on the histochemistry results. When significant differences were detected by ANOVA, analyses of differences between the means of the treated and control groups were performed using Dunnett's t-test.

Fibrosis index calculation

Microscopic images of 100x magnification were acquired for collage-I immunostained liver slides giving a resolution of 2.6 μm^2. Images were initially encoded on 24-bits per pixel three channels (Red, Green, and Blue). The percentage of fibrosis in the liver tissue was determined using a computer assisted automated image analysis program made by the authors using Matlab© (version 7.00, © 1984-2004, The MathWorks Inc). It gives the fibrosis index by calculating the ratio of type I collagen fibers (immunostained areas) to the whole liver area on a slide.[25,26] Histopathological evaluation was performed in four different sites per section for each treatment (n=7). The average value was then calculated for each experimental group to give the fibrosis index for each group.

MRI and regions of interest

The specimens were imaged on a 1.5-T MR scanner (General Electric Medical Systems, Milwaukee). The plastic containers containing liver specimens were attached on a standard MR phantom. Specimens were imaged within a standard quadrature head coil. A Spin Echo T1-weighted sequence was used to image all specimens (TE = 14 ms, TR= 500 ms, flip angle = 90°), with a field of view of 12 cm, matrix size 256x256, slice thickness of 5 mm, and NEX= 1. DICOM images were converted to 8 bits-per-pixel bitmap images, and one region of interest (ROI), covering the largest possible homogenous area of liver was selected for texture analysis (about 250 pixels) (Figure 1).

Texture analysis and image processing

Microscopic images were converted to grey-levels bitmap images suitable for texture analysis, and ROIs of about 30000 pixels were selected on each image.-

Texture analysis of microscopic and MR images was performed using Runlength Matrix and Gradient Matrix methods.[27,28] These two matrices were chosen since they are sensitive to texture coarseness and can therefore characterize collagen accumulation.[12] Collagen accumulations produce a coarse image texture, while the absence of collagen gives fine texture, which is used as a base for discrimination between groups. The Runlength Matrix method was proposed by Galloway.[27] It calculates the number of runs $p(i, j)$ of greylevel i and length d in the direction of angle θ from one or more of the

Table 1. Effect of Moringa oleifera (M) and silymarin (S) on serum markers of liver damage in CCL_4-induced fibrotic (F) and control (C) groups. Values are expressed as mean ± SEM (n = 7). ***P<0.001 vs. control group; ♦♦♦P<0.001 vs. fibrotic group.

	C (n=7)	F (n=7)	M (n=7)	S (n=7)
AST (IU/L)	43.68 ± 3.53♦♦♦	112.60 ± 25.90***	58.22 ± 10.26♦♦♦	65.83 ± 7.66♦♦♦
ALT (IU/L)	46.71 ± 1.86♦♦♦	128.88 ± 19.74***	60.46±8.55♦♦♦	71.98 ± 9.73♦♦♦

values (*0°*, *45°*, *90°*, *135°*). In coarse textures, relatively long greylevel runs would be more common, while fine textures should primarily comprise short runs. Some of the parameters extracted from this method are: long-run emphasis, short-run emphasis, runlength nonuniformity, and greylevel nonuniformity. The Gradient Matrix (GrM) characterises the distribution of greylevel differences around a pixel *g(x, y)*, located at row *x* and column *y*, within a "mask" of neighbouring pixels (usually 3x3 or 5x5). The mask is applied pixel by pixel over the whole image or ROI.[28] Some of the GrM parameters are: mean, variance, skewness and kurtosis.

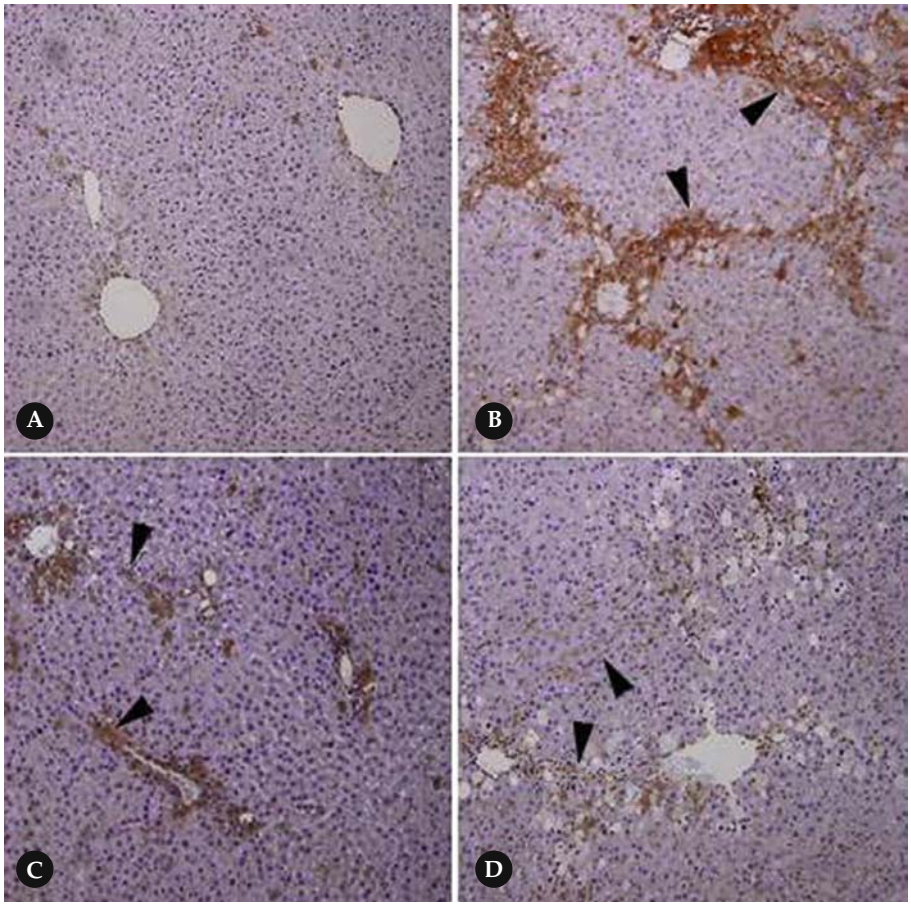
Features selection and classification

Features selection aims to identify the most discriminating parameters from each matrix that separate the different classes most efficiently. The Fisher-coefficient (*F*-coefficient) was calculated for this purpose, giving the ratio of *between class variance* to *within class variance* for each parameter. The ten parameters of the highest *F*-coefficient were entered into Linear Discriminant Analysis (LDA) for classification. LDA aims to find a linear transformation matrix so that the ratio of the within-class scatter matrix to between-class scatter matrix is maximized. Such a transformation is composed of eigenvectors corresponding to the largest eigenvalues of this ratio of matrices; more details about the classification method can be found elsewhere.[29] The classification results of LDA are represented graphically as the relationship between the most discriminating features (MDF). The number of MDF axes is less than the number of the output classes by one. In this study, we have three output classes for each classification attempt, thus classes would be represented on two axes, MDF1 and MDF2. Texture analysis, features selection, and classification were performed using MaZda-B11 software (version 4.5, ©1999-2006 by Piotr Szczypinski) which were initially developed under the auspices of the COST action B11 European project. More details about the software can be found in.[30]

Results

Effect of M. oleifera on liver function

The activity of serums AST and ALT are useful indicators of the extent of liver injury following CCl_4 treatment. Table 1 shows AST and ALT activities at the end of the experiment. Increases of 2.6- and 2.8-fold in the activity of AST and ALT, respectively, were observed in the CCl_4 group compared to the control group ($p<0.001$). Treatment with Moringa decreased the CCl_4-induced levels of AST and ALT by 47% and 52% ($p<0.001$), respectively. Similarly, treatment with silymarin in CCl_4 treated rats reduced the AST level by 40% ($p<0.001$). It is worth mentioning here that both biochemical and histopathological results confirmed that Moringa alone did not have any toxic effects on rat liver tissues (data not shown).



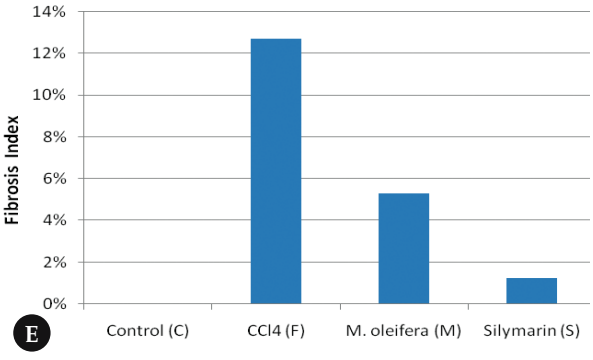


Figure 2. Histological sections of liver showing Collagen-I. A) control, B) fibrotic, C) Moringa, and D) silymarin. (A) Section of liver tissue of control rat showing normal architecture with central veins and radiating cords of hepatocytes. (B) Section of liver tissue of rats treated with CCl_4 showing macrovesicular fatty change around central vein and large areas of necrosis fatty degeneration, necrosis, infiltration of inflammatory cells and apparent formation of fibrotic septa. (C) Section of liver tissue of rats treated with Moringa oleifera extract (0.5 g/kg b.wt) and CCl_4 showing the presence of normal hepatic cords, absence of necrosis and macrovesicular fatty change. The degree of liver damage and fibrosis were significantly reduced in the M. oleifera (0.5 g/kg b. wt.) treated rats. (D) Section of liver tissue of rats treated with silymarin (0.2 g/kg b.wt.) and CCl_4 showing normal hepatic architecture, which was nearly similar to that of the healthy control. Collagen deposition (arrowheads) is indicated as brown-stained fibers in panel B-D. All sections were immunostained with anti-collagen I antibody, 100×. (E) Histogram representing the calculated fibrotic indices for all groups. The fibrosis index was calculated as the ratio between the connective tissue (immunostained area) and the whole liver area in the slide.

Pathological histology

Collagen-I immunostaining of liver specimen examination showed no histological abnormalities and the absence of collagen strands in the extracellular hepatic matrix in normal control liver (Figure 2a). Liver tissue in CCl_4-injured rats presented a gross nodular appearance as well as steatosis, cell necrosis and inflammatory infiltration compared to control rats. Histological abnormality in fibrotic model rat was characterized by the deposit of bundles of collagen in pericentral and midzonal areas of liver tissues (Figure 2b), which gave a fibrosis index of 12.73±2.37% (Figure 2e). Co-administration of *M. oleifera* (0.5 g/kg) or silymarin (0.2 g/kg) markedly alleviated the degree of liver fibrosis and significantly lowered collagen deposited (Figure 2c, d). Treatment with *M. oleifera* decreased in the fibrosis index by 5.23±0.13%, while reduction with silymarin was by 1.23±1.01% (Figure 2e).

Texture analysis and classification

Texture analysis of microscopic images followed by LDA was always able to cluster samples belonging to the F group as a homogenous class separate and distant from other classes (Figure 3a,b) and always separable on the MDF1 axis with positive values. On the other hand, class S tended to cluster with class C (Figure 3a); as did class M (Figure 3b). Classes C, S and M always had negative values on MDF1 (Figures 3a,b). MRI-TA classification results were similar to those of microscopic images. F was always classified as a separate class distant from other classes (Figure 4), while M and S classes clustered close to or even mixed with class C (Figure 4a,b). Class F was separable on MDF1, on which it had always negative values, unlike the classes C, S or M, which that had positive values on the same axis. In all classification attempts, class F (true positive) did not show any classification errors with other classes and no sample that belonged to other classes (true negative) was classified as F. This gives a sensitivity and specificity of 100% for that test. This result in particular highlights the uniqueness of textural features of fibrotic liver tissue. In contrast, C, M and S groups were occasionally *misclassified* with each other (Figures 3, 4), indicating the presence of similar textural features.

Discussion

This study measured the consistency of results among MRI-TA, TA on microscopic images, histopathology and biochemical analysis, of the effect of crude extract of *M. oleifera* seeds on CCl_4-induced liver fibrosis.

CCl_4 is a well-known hepatotoxin.[31,32] Continuous exposure to this toxin produces progressive liver injury and fibrosis, eventually causing cirrhosis, portal hypertension and death.[33,34] The main cause of acute liver injury by CCl_4 is free radicals of its metabolites. Activation of CCl_4 by liver cytochrome P-450 generates methyltrichloride radicals (CCl_3). These radicals cause lipid peroxidation, which produces hepatocellular damage and enhanced production of fibrotic tissue.[35] The results of this study demonstrate that treatment of rats with *M. oleifera* had a markedly protective effect against CCl_4-induced hepatotoxicity in rats, as evidenced by decreased serum AST and ALT activities. Similarly, total flavonoids of *Bidens pilosa* L. has been shown to decrease the elevated level of ALT and AST in a CCl_4-induced liver fibrosis model.[36] It was evident from the histopatholgy and biochemical analysis that co-administration of *M. oleifera* seed extract with CCl_4 provided significant protection against liver fibrosis.

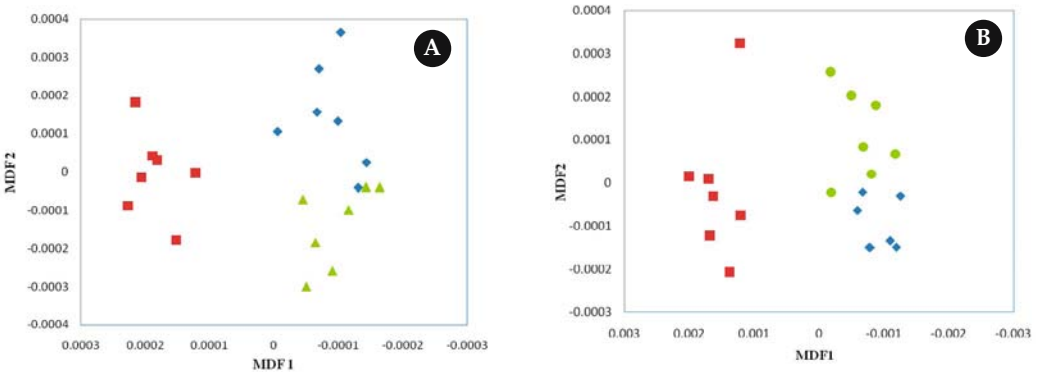


Figure 3. Linear Discriminant Analysis (LDA) of microscopic image texture showing: **a)** control class (C) (♦), fibrotic class (F) (■), against silymarin class (S) (▲). **b)** control class (C) (♦), fibrotic class (F) (■), against Moringa class (M) (●). MDF1 and MDF2 are the most discriminating features axes that are used in LDA to represent the classification graphically.

Immunostaining of liver specimens showed a remarkable difference in collagen-I contents, as a fibrosis index (FI), in the experimental groups (Figure 2e). Control rats showed an absence of collagen strands in the extracellular hepatic matrix (Figure 2a) and this was set as zero FI. The fibrotic group showed a clear formation of collagen networks in the liver (Figure 2b); and therefore gave the highest FI (Figure 2e). The Moringa treated group, as well as silymarin-treated group, showed much less collagen accumulation (Figure 2c, d) and accordingly a lower FI (Figure 2e).

MRI-TA reveals textural changes related to minor or major pathological modifications that take place in tissue. These textural changes are basically alterations in the physical-chemical properties of the underlying tissue that affect the relaxation times (T1 and T2) in MRI, and, consequently, appear in the image as alterations in greylevel intensities (taking the healthy tissue as reference). These altered intensities are impercentible to the human eye and can only be measured using a texture analysis method. In this respect, texture analysis followed by automatic classification provides a powerful quantification tool of liver pathology, which offers a wide range of applications. One of these fields of application is antifibrotic pharmaceutics research, which requires recurring essays. Collagen is particularly influential on texture. It has been demonstrated in the literature that collagen contents and distribution have a direct effect on texture discrimination on MR images.[12] This is due to the collagen extracellular network, which gives a coarse texture for thicker networks and fine texture for thinner ones.[12] Coarse texture gives longer runs using the Runlength method of texture analysis[27]; the Runlength matrix therefore seems to be a suitable method of texture analysis of fibrotic liver. LDA on both MRI- and microscopic image TA, showed that class S always clustered closely or even mixed with class C. This indicates that the S experimental group has textural properties, which are themselves dependent on tissue composition, close to those of C group. This was confirmed by liver function tests (ALT and AST) and collagen-I contents indicated as FI. Similarly, the clustering of group M in close proximity to group C can be attributed to the closely related textural properties of those groups, which may also be related to their collagen contents.

MRI-TA correlated well with fibrosis histopathological results and showed a clear

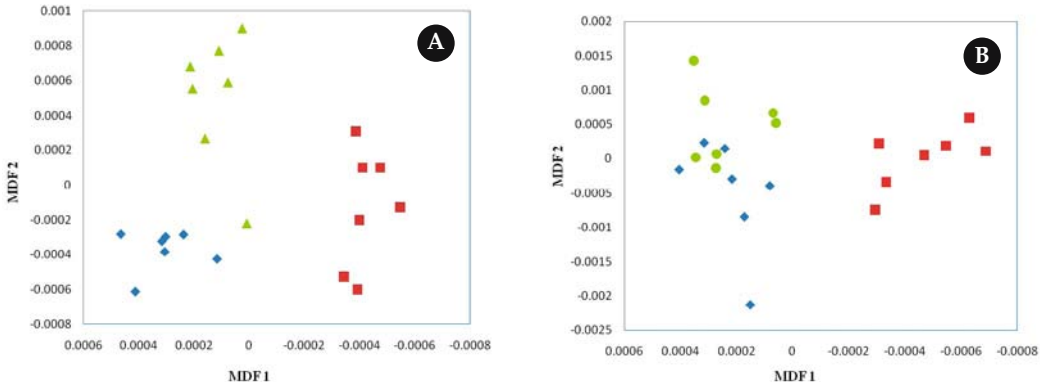


Figure 4. Linear Discriminant Analysis (LDA) of MRI-TA (Texture Analysis on MRI) showing: **a)** control class (C) (♦), fibrotic class (F) (■), against silymarin class (S) (▲). **b)** control class (C) (♦), fibrotic class (F) (■), against Moringa class (M) (●). MDF1 and MDF2 are the most discriminating features axes that are used in LDA to represents classification graphically.

discrimination between group F on the one hand and other (C, M and S) groups on the other, with 100% sensitivity and specificity. MRI-TA results were also consistent with texture analysis of microscopic images, which suggests that the former method can be used as a reliable evaluation tool of liver condition during different treatments. Therefore, using an appropriate standard drug as a positive control, and with minimal biochemical and/or histopathological diagnostic procedures, the MRI-TA protocol can now provide a reliable diagnostic and monitory tool for testing new antifibrotic drugs. Further investigations are currently underway to identify and characterize Moringa's bioactive ingredients and to gain more molecular insights into its potent antifibrotic property.

Conclusions

MRI-based texture analysis provides a reliable alternative tool for primary evaluation of therapeutic effects. This technique would open a new door for drug assessment, since it is a rapid, less expensive and nondestructive tool. *Moringa oleifera* has shown a protective effect against liver fibrosis. This protection was confirmed by liver function tests and histopathological analysis and found to be measurable using MRI-TA.

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research article

Irradiation of regionally advanced carcinoma of the penis

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Background. *Penile cancer patients with inoperable groin metastases as well as patients with residual or recurrent groin tumours after inguinal lymphadenectomy are frequently considered for radiation treatment.*

Methods. *A retrospective study of 12 patients with regionally advanced penile carcinoma treated with radiotherapy in the period 1995-2003 was done. Acute and chronic treatment-related complications were observed.*

Results. *All patients (8/8) with the tumours palpable at the beginning of radiotherapy and two patients (2/4) with microscopic post-lymphadenectomy tumour residue died from the disease. The death occurred 4–24 months after starting radiotherapy. Median survival was 8 months. Locoregional control could only be achieved in patients irradiated for microscopic post-lymphadenectomy tumour residue (4/4).*

Conclusions. *A timely and accurate diagnosis of regional disease spread and immediate lymphadenectomy are of vital importance. Radiotherapy should be applied soon after surgery as postoperative treatment of regional metastases that are at risk to recur – recurrences following lymphadenectomy could not be salvaged by radiotherapy.*

Key words: penile cancer; advanced disease; radiotherapy

Introduction

Penile cancer is a rare disease. According to the data collected by Cancer Registry of Slovenia, the annual incidence of penile cancer is 0.4-1 per 100,000 males.[1]

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The standard treatment modality in penile cancer is surgery, which involves partial or total penectomy, depending upon the stage of primary tumour.[2] In case of enlarged inguinal nodes or the nodes that are not palpable, but at risk to develop metastases due to the nature of primary tumour, penectomy is often followed by inguinal lymphadenectomy.[2]

Radiotherapy is usually indicated when patients do not wish to have their penis removed.[3-5] However, it is also considered in the patients who have the disease in regionally advanced stage and in whom, ac-

Table 1. Characteristics of 12 patients with regionally advanced carcinoma of the penis at the beginning of treatment/beginning of radiotherapy

Patient No.	Initial stage			Lymphadenectomy	Groin status at the beginning of RT†
	T-stage	Grade	N-stage		
1	2	1	0	yes*	microscopic residual
2	2	2-3	0	yes*	microscopic residual
3	2	1	0	yes*	microscopic residual
4	3	2	2	yes	microscopic residual
5	2	2-3	0	yes*	palpable tumour
6	2	2	2	yes	palpable tumour
7	1	1-2	2	yes	palpable tumour
8		3	3	no	palpable tumour
9		3	3	no	palpable tumour
10	2	2	0	no	palpable tumour
11	2	2	0	no	palpable tumour
12	2	2	3	no	palpable tumour

Legend: * - lymphadenectomy was performed after regional progress of the disease; † - RT=radiotherapy

cording to the urologist's estimates, the tumour is inoperable, or the resection of the enlarged lymph nodes was not radical, or post-lymphadenectomy recurrence is diagnosed. The data on what treatment results can be expected in these patients are very scarce.

In order to assess the efficiency of the radiotherapy of penile cancer in Slovenia we started the study in patients with advanced metastases in inguinal region, who were referred to the radiotherapy at the Institute of Oncology Ljubljana.

Patients and methods

This is a retrospective study of 12 patients with cytologically or histologically confirmed squamous cell carcinoma of the penis treated with radiotherapy in the period 1995-2003. The patients did not have distant metastases, but rather extensive metastatic involvement was observed in the inguinal lymph nodes. The patients' data on the primary stage and histology grade of the disease are shown in Table 1. T-stage of the patients 8 and 9 was not determined because, in these patients, penectomy was not performed.

In 6 patients, enlarged inguinal nodes were observed immediately at diagnosis. In others, the enlargement was observed later on; in 4 patients (patients 1, 2, 10, and 11), the nodes were enlarged due to post-penectomy recurrence and surveillance policy, in one (patient 5), the enlargement was observed after prophylactic lymphadenectomy, and in one (patient 3), after sentinel lymph node dissection. In 8 patients (Table 1), radiotherapy was indicated because of palpable inguinal tumours which were diagnosed either as inoperable infiltrations in the nodes in 5 patients (patients 8-12) or as inoperable post-lymphadenectomy locoregional recurrence in 3 (patients 5-7). Microscopic tumour residue detected after lymphadenectomy in 4 patients was also an indication to apply radiotherapy. The microscopic residue was defined as extran-

Table 2. Radiotherapy treatment characteristics of 12 patients with regionally advanced carcinoma of the penis

Patient No.	TD bioequivalent doses for $\alpha/\beta = 10$ (Gy)		
	Inguinal region	Pelvic region	Pubic region
1	50	50	50
2	52		52
3	50	50	50
4	50	50	50
5	58	41	46
6	66	46	50
7	68	47	60
8	52		52
9	44		44
10	25		
11	44		26
12	24	24	24

odal tumour involvement that was, in all 4 patients, accompanied with metastases in several nodes.

In 9 patients, radiotherapy was planned as radical treatment, whereas in 3 patients (patients 10, 11, and 12), radiotherapy was planned to have palliative effect because of the extensiveness of groin tumours. All patients who received palliative radiotherapy and 3 patients who were treated with radical radiotherapy were irradiated by Co^{60} unit, using a single anterior field technique, with a dose determined at a depth of 4-5 cm and the field covering both inguinal regions and pubic area. The remaining 6 patients treated with radical radiotherapy were irradiated by two opposite field technique, with the larger anterior field covering also the lateral part, smaller posterior field limited to pelvic region, and two additional electron fields to boost the irradiation dose to the inguinal region. In all cases, 2-D treatment planning and standard dose fractionations were used – radical radiotherapy was performed at a dose range of 2–2.5 Gy and palliative at 2.5–5 Gy per fraction. Bioequivalent total doses for $\alpha/\beta = 10$ are given in Table 2. Patient 9 was concomitantly treated with chemotherapy and received 2 cycles with cisplatin (100 mg/m^2), methotrexate (40 mg/m^2) and bleomycin-C (10 mg/m^2).

Considering the nature of the present study, acute treatment-related complications were evaluated on the basis of most pronounced problems, while the evaluation of chronic complications was limited to the patients in whom locoregional control of the disease was obtained.

Results

All patients (8/8) with the tumours that were palpable at the beginning of radiotherapy died from the advanced disease, and so did also the two patients (2/4) with microscopic post-lymphadenectomy tumour residue who were referred to radiotherapy (Table 3). The death occurred 4–24

Table 3. Results of treatment of 12 patients with regionally advanced carcinoma of the penis

Patient No.	Local complete remission	Months of follow-up	Status
1	yes	10	dead of disease
2	yes	24	dead of disease
3	yes	43	dead without disease
4	yes	55	no evidence of disease
5	no	17	dead of disease
6	no	16	dead of disease
7	no	8	dead of disease
8	no	8	dead of disease
9	no	10	dead of disease
10	no	6	dead of disease
11	no	4	dead of disease
12	no	4	dead of disease

months after starting radiotherapy. Median survival of these patients was 8 months. Distant metastases were detected in 7/12 patients; in 6/7 patients, the first symptom of disease spread were enlarged retroperitoneal and mediastinal lymph nodes. In patient 3, who died 43 months after starting radiotherapy, the cause of death was carcinoma of the sigmoid colon. Patient 4 was alive and with no evidence of disease 55 months after radiotherapy.

In none of 8 patients who had palpable tumours in the inguinal region at the beginning of radiotherapy, complete locoregional control was obtained. Of these 8 patients, 5 were treated with radical radiotherapy.

In 3 patients with post-lymphadenectomy recurrence, deep ulcerations with cytologically confirmed tumour residue in necrotic margins developed after radiotherapy on the sites of inguinal tumours. Further progress of the disease in the field margins was observed in 2 patients who both developed lymphangitis carcinomatosa prior to irradiation – patient 6 on the skin of partly shielded penis residue and patient 5 on the skin of the scrotum and of the thigh. In the patients in whom radiotherapy was indicated for the treatment of microscopic post-lymphadenectomy tumour residue, locoregional progress of the disease was not assessed.

Pronounced acute toxicity was limited to confluent radiodermatitis that developed in the patients irradiated with the doses over 50 Gy. In patient 9, who was treated with concurrent chemoradiotherapy, radiodermatitis was so severe that irradiation had to be discontinued.

In the patients in whom locoregional control of the disease was obtained, the only chronic treatment-related complications were edematous penis and scrotum and atrophic skin in the inguinal folds.

Discussion

In the patients with penile carcinoma, the regional lymph node status proved to be an

independent prognostic factor.[4] Prognosis of the patients with the regional disease depends upon the extensiveness of metastases. If metastatic spread in an early stage is detected immediately upon prophylactic or therapeutic lymphadenectomy, more than three quarters of patients can survive,[6-8] whereas in case of the metastatic spread in an advanced stage with bilateral nodal infiltration as well as extranodal tumour extension, less than 12% of patients may survive.[9] A similar observation was pursued in our study in which only 2/12 patients survived with regionally advanced disease after radiotherapy. Bilateral or clinically fixed nodes with extranodal extension at lymphadenectomy (when it was applied) were present in all our patients. A quick systemic progress of the disease observed only a few months after the completed irradiation in 7/12 patients from our study may speak in favour of the presence of distant metastases that remained undetected at the regional disease stage.

Upon the disease spread in the inguinal region (groin tumours), it is hard to obtain and keep local control of the disease.[4,10] The patients with recurrence or palpable post-lymphadenectomy tumour residue may be as problematic as the patients with inoperable metastases. In any of these patients from our study, local control was not achieved, and they all developed deep ulcerations after the completed radiotherapy; in one of them, even the perforation of femoral artery occurred. This may further support the view that the limited tolerance of healthy tissue following the inguinal lymphadenectomy does not allow the application of doses that would assure local control. Therefore, an inguinal tumour that is still palpable after inguinal lymphadenectomy or detected as a recurrence is not only an indication of extremely bad prognosis, but also of very poor quality of the patient's life due to further local complications.

On the other hand, radiotherapy may be most effective in microscopic disease control, at least in terms of local control.[6] However, the results seem to be somehow conflicting. Mazeron reported uncontrolled metastatic nodes in 4/5 patients after selective dissection of enlarged nodes (2 patients) or groin dissection (3 patients) and postoperative inguinal irradiation with Co^{60} and electrons applied in 4/5 patients.[5] Four patients from our study may well be a proof of the efficiency and of acceptable chronic toxicity of postoperative irradiation. All four, though they were treated with macroscopic radical lymphadenectomy, were also irradiated postoperatively because of extranodal tumour extension and numerous positive nodes. In all 4 patients, a stable local control was obtained. Radiotherapy proved to be successful also in terms of treatment-related complications which were, in all patients, within the limits of somewhat more pronounced fibrosis of the inguinal region. The efficiency of postoperative radiotherapy is an important aspect that needs particular consideration because the incidence of locoregional recurrences following radical therapeutic lymphadenectomy seem to be rather high; in the study by D'Ancona, it was reported to be 37%.[11]

In conclusion, a timely and accurate diagnosis of regional disease spread and immediate lymphadenectomy are both of vital importance for the patients with penile cancer.[7,12] In order to assure the patients a proper quality of life and survival, particular care should be taken that the regional control of the disease is obtained by primary treatment. Due to limited number of patients it would be invalid to draw firm conclusions; nevertheless, we believe that radiotherapy should be applied soon after surgery as postoperative treatment of regional metastases that are at risk to recur. Recurrences following lymphadenectomy could not be salvaged by radiotherapy.

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research article

Is there any progress in routine management of lung cancer patients? A comparative analysis of an institution in 1996 and 2006.

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Background. *The aim of the study was to establish eventual progress in routine management of lung cancer patients over a ten-year period at University Clinic for Respiratory and Allergic Diseases Golnik, Slovenia, comparing the results of analysis of 345 patients, diagnosed in 1996 (with analysis performed in 2002), and 405 patients, diagnosed in 2006 (with analysis performed in 2008).*

Patients and methods. *The patients of both analysed groups were of comparable age and number of patients in stage I and II, but there were relatively more females, patients with better performance status, more precise clinical staging and tumour histology in the 2006 group. The parameters used for assessing the progress of management were as follows: time period from admittance to diagnosis and to surgery; precision of staging; accordance of clinical and pathological staging in resected patients; percentage of exploratory thoracotomy; and use of new treatment modalities. The proportion of patients in selected/actual primary treatment modality and survival rate could also be used for assessing the progress.*

Results. *Although unessential longer time from admittance to microscopic confirmed diagnosis increased from a mean 7.4 to 8.6 days in 2006 progress was established by the following: more precise clinical staging (stage I and II also A and B stage, TNM staging also in small-cell lung cancer patients); improved accordance with clinical and pathological staging in resected patients (46% against 58%); decreased percentage of exploratory thoracotomy (13% against 4%); increased use of multimodality therapy as primary treatment modality (radiotherapy/chemotherapy, neoadjuvant chemotherapy); newly performed radio frequency tumour ablation. The proportion in selected/actual surgery increased from 76% to 93% and median survival rate of all patients from 6.2 to 10.6 months. One-year survival increased from 33.6% to 45.8% and two-year survival from 17.4% to 23%.*

Conclusions. *Progress in routine lung cancer management was proved by better staging, lower percentage of exploratory thoracotomy, use of new treatment modalities, minor discordance between selected and actual therapy, and improved short-term survival rate.*

Key words: lung cancer; diagnostics; therapy; survival

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Introduction

Much new information on epidemiology, pathogenesis, early detection, better diagnostics, accurate staging, and different treatment options is presented at the lung cancer conferences and published in literature, resulting in better outcomes: improved survival rates and sometimes better quality of life, as supported by some clinical studies. From the clinician's point of view the most important concrete progress in routine management of patients has been achieved through wide use of multi-slice CT scanning and MRI, CT and US-guided sampling, FDG-PET and PET/CT, videothoracoscopy and videothorascopic surgery, new multidrug chemotherapy, more accurate radiation therapy, bronchoscopic interventional therapy (cauterisation, laser, cryo-ablation, argon plasma coagulation, stenting) and endobronchial brachytherapy, radio frequency tumour ablation, target therapies, and better palliative care. Key questions are which of the new findings are implemented into routine management of lung cancer patients at a particular institution, how they are implemented, and how much they influence survival.

The aim of the study was to establish eventual progress in routine management of all lung cancer patients over a ten-year period at the University Clinic for Respiratory and Allergic Diseases Golnik (Clinic Golnik), Slovenia, comparing the results of analysis of 345 patients diagnosed in 1996 (with analysis performed in 2002)[1], and 405 patients diagnosed in 2006 (with analysis performed in 2008).

Patients and methods

All patients, hospitalised or ambulatory, firstly diagnosed for lung cancer from January 1st to December 31st, 1996 and 2006 were included in the analysis. Patients from abroad were excluded due to lost of follow-up and unavailable survival data. The characteristics of patients and tumours are presented on Table 1. The patients of both analysed groups were of comparable age and number of patients in stage I and II, but there were relatively more females, patients with better performance status, more precise clinical staging, tumour histology and also estimated comorbidity in the 2006 group.

The parameters used for assessing the progress of management were:

- time period from admittance to diagnosis and to surgery;
- precision of staging;
- accordance of clinical and pathological staging in resected patients;
- percentage of patients undergoing exploratory thoracotomy;
- use of new treatment modalities.

The proportion of patients in selected/actual primary treatment modality and median survival time in each group of patients could also be used for assessing progress.

Staging was made according to TNM classification[2], while the staging of small cell lung cancer (SCLC) was carried out, in 1996, with classification into limited disease (LD) and extended disease (ED). The zero time for the calculation of the survival was the date of admittance to the institution until death or until the end of the follow-up period, on 31 December 2001 for patients of 1996, and 30 April 2008 for patients of 2006. Only the date of death due to any reason was available. All living patients were confirmed in the Cancer Registry of Slovenia and by comparison with the Registry of Death of Slovenia to have been alive at this date. So the minimum follow-up time for patients of 1996 was 5 years, and for patients of 2006 was 16 months. The survival rate was calculated according to Kaplan-Meier's method,

Table 1. Characteristics of patients and tumours of 1996 and 2006

		1996	2006
No. of patients		**345**	**405**
Gender	Male	285 (83%)	301 (74%)
	Female	60 (17%)	104 (26%)
Age (years)	mean	65	67
	range	37-90	41-89
Performance status (ECOG*)			
	0 and 1	171 (49%)	300 (74%)
	2	130 (38%)	79 (20%)
	3 and 4	44 (13%)	26 (6%)
Clinical stage		NSCLC	NSCLC&SCLC
		I: 64	IA: 34
			IB: 40
		II: 32	IIA: 6
			IIB: 28
		IIIA: 48	IIIA: 56
		IIIB: 62	IIIB: 85
		IV: 85	IV: 155
		SCLC	
		LD**: 24	
		ED***: 27	
Undeterminable stage		3	1
Microscopically	confirmed	334 (97%)	399 (98.5%)
	not confirmed	11 (3%)	6 (1.5%)
Histology			
	squamous cell	131 (39%)	162 (41%)
	adenocarcinoma	86 (26%)	120 (30%)
	large cell	63 (19%)	18 (5%)
	non-small cell	1 (0.3%)	22 (5%)
	small cel	51 (15%)	73 (18%)
	adenosquamous		1 (0.25%)
	sarcomatoid		2 (0.5%)
	LCNEC****		1 (0.25%)
	unclassified	2 (0.7%)	
Charlson comorbidity index (CI)			CI 0: 158 (39%)
			CI 1: 154 (38%)
			CI 2: 52 (12.8%)
			CI 3: 29 (7.2%)
			CI 4: 9 (2.2%)
			CI≥5: 3 (0.8%)

* Eastern Cooperative Oncology Group

** Limited Disease

*** Extended Disease

**** Large Cell Neuro-Endocrine Carcinoma

Table 2. Selected primary treatment modality of patients diagnosed in 1996 and 2006

	1996	2006
Surgery	93 (27%)	92 (23%)
Radiotherapy	110 (32%)	54(13%)
Chemotherapy	50 (15%)	121 (30%)
Supportive care	84 (24%)	49 (12%)
Radio and chemotherapy		75 (19%)
Neoadjuvant chemotherapy		9 (2%)
Radio frequency tumour ablation		2 (0.5%)
Death before treatment selection	8 (2%)	3 (0.5%)

and the survival differences were confirmed by the log-rank test using SPSS version 13.0 for statistical analysis.

Results

Duration of diagnostic procedure

The mean time period from admittance to microscopic verification of tumour was 7.4 (range 1-75) days in 1996, and 8.6 (range 1-74) days in 2006. The mean time period from microscopic confirmation of lung cancer to surgery was 27 (range 14-99) days in 2006, but in 1996 was only assessed as about one month.

Precision of clinical staging

All patients in 2006 were staged according to the cTNM classification considering A and B in stage I and II, though without A and B in non-small cell lung cancer (NSCLC) stage I and II, and only LD and ED in SCLC in 1996. In 1996, a thorax CT scan was performed consistently only in candidates for surgery and in some of the remaining patients, while in 2006 it was performed in all but 15 patients. This change enabled more accurate staging.

Accordance of staging in resected patients

In resected patients in 1996 clinical *vs.* pathological staging was correct in 46%, underestimated in 44%, overestimated in 10%. For 2006, respective figures were 58%, 25%, and 17%.

Percentage of patients undergoing exploratory thoracotomy

The rate of exploratory thoracotomy (thoracotomy without resection due to various causes) among patients was 12.7% in 1996 and 4.3% in 2006.

Use of new treatment modalities

The selected primary treatment modality is presented on Table 2. In 2006, there were more patients underwent primary treatment by chemotherapy and by combined therapy (radiotherapy/chemotherapy and chemotherapy/surgery), and radiotherapy of primary tumour and/or metastases with curative and palliative intent. In two patients, the new therapy by radio frequency tumour ablation was performed. Neoadjuvant (preoperative) chemotherapy was performed in nine patients, potential candidates for surgery. Six of them were radically resected, while three patients were irradiated due to the progress assessed after the chemotherapy. In one patient with microscopically confirmed intrabronchial squamous carcinoma and subcarinal lymph node metastasis after three cycles of cisplatin/gemcitabin, the histology of the resected lobe and all lymph nodes was without cancer. In both groups

Table 3. Resection and exploratory thoracotomy in patients diagnosed in 1996 and 2006

	1996	2006
Selected for surgery	93	101
Realised surgery	71 (76%)	94 (93%)
Lobectomy	35	68
Bilobectomy	5	6
Pneumonectomy	22	16
Exploratory thoracotomy	9 (12.7%)	4 (4.3%)

of patients, various bronchial interventional therapies were performed. In 2006, targeted therapy was also performed, but of course not as a primary treatment modality.

Proportion in selected/actual primary treatment

Actual surgery in both groups of patients is shown in Table 3. The percentage of realised surgery including neoadjuvant chemotherapy increased and the number of pneumonectomies decreased in 2006.

Survival rate

The overall survival of both patients group is presented in Figure 1. The median survival was 6.2 months in 1996, and 10.6 months (p<0.000) in 2006. One-year observed survival was 33.6% and two-year 17.4% in 1996. In 2006 one-year survival was 45.8%, calculated two-year survival was 23%.

The median survival for NSCLC for stage I, II, IIIA, IIIB, and IV was 30.1, 11.0, 8.6, 4.3 and 3.3 months, respectively in 1996. In 2006, median survival in stage I has not yet been reached, in stage II it was 14.8 (p=0.064), stage IIIA 12.3 (p=0.077), stage IIIB 8.13 (p=0.002), and stage IV 3.8 (p=0.035) months. In SCLC patients, the median survival in LD was in 1996 11.0 months and in ED 3.3 months, and in 2006 13.3 (p=0.116) months and 8.5 (p=0.01) months respectively.

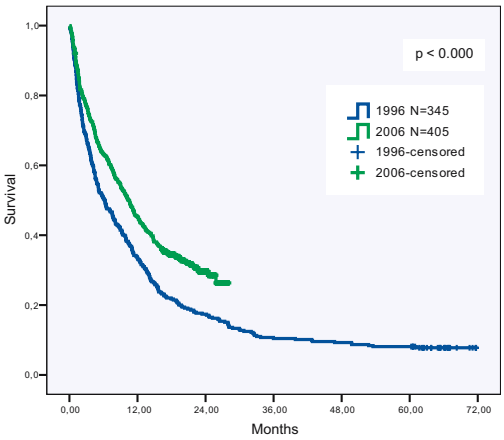

Figure 1. Overall survival of 1996 and 2006 patients.

Median survival according to performance status in 1996 was for patients in ECOG 0 and 1 10 months, ECOG 2 4.2 months, and ECOG 3 and 4 1.7 months, and in 2006 was 13 months (p=0.001), 4.3 months (p=0.175) and 1.9 months (p= 0.217), respectively.

Discussion

Lung cancer management is comprised of detection, diagnostics inclusive microscopic confirmation, staging, selection and performance of therapy, follow-up of patients, as well as evaluation of results. At an institution like Clinic Golnik, it is difficult to influence the detection of lung cancer. Some patients are diagnosed while being treated for another disease. The clinic certainly has a teaching role for residents, students and through patients' follow-up also for general practitioners and other referring physicians. However, it is routinely possible to expedite the diagnostic procedure, to improve the staging, the selection of optimal treatment modality by a multi-disciplinary team meeting, the performing of therapy within the institution, and partly also the follow-up. Since all diagnostic procedures

except PET-CT, MRI and radioisotope scanning are performed at Clinic Golnik, it is understandable that a complete diagnostic procedure including microscopic confirmation of a tumour takes about one week in the majority of patients. From 2007, PET-CT scanning has been available in Ljubljana, in 2006 we referred two patients for FDG-PET to Klagenfurt, Austria.

Of the therapy modalities chemotherapy is performed at the institution, but surgery also started in 2008. So, a shorter period from diagnosis to surgery can be expected in the future, at least for some of the patients. The Institute of Oncology Ljubljana is the only institution for radiotherapy in Slovenia where we can not influence the waiting time for radiotherapy and radiochemotherapy in both those hospitalised and out-patients. The realisation of the selected therapy modality depends on possibilities for achievement and on patients' compliance. From patients selected for surgery, 93% underwent thoracotomy in 2006, but only 76% in 1996. It is obviously that thoracotomy could be partly avoided through a more accurate preoperative staging procedure.[3]

Despite the many prognostic and predictive factors established[4,] in routine selection of treatment modality only stage, histology, performance status, technical and medical operability and age are still regarded.

The stage of lung cancer patients by the time of the diagnosis depends, beside symptomatology, also on awareness of lung cancer risk in smokers and ex-smokers, and the awareness of their physicians, especially those who treated their previous cancer. It is known that double cancers[5], mainly head and neck and lung cancer, are frequent. In 2006, we registered a previous malignant tumour in 59 of 405 (15%) patients, and 15 of these had head and neck cancer.

In the literature, there is a paucity of comparable data of outcomes in routinely treated lung cancer patients in a single institution. In our opinion, this is due to two reasons: 1. many journals seem reluctant to publish articles that report on testing management efficacy in an institution and do not directly contribute to new knowledge on disease; 2. researchers do not like to publish poor results in which they could hardly influence outcomes. In the only comparable study, of Free *et al.*[6] from Nottingham City Hospital, UK, over the period 1998-2001, there were similar results. In 835 lung cancer patients (87% histologically confirmed and 80% discussed at multidisciplinary team meetings) clinical stage I 25%, II 9%, IIIA 8%, IIIB 23%, IV 35% in NSCLC and, in SCLC, LD 34%, ED 50%, with 16% unknown due to missing data, surgery was undertaken in 10%, radiotherapy in 30%, chemotherapy in 16%, supportive care in 34%, and 10% unknown due to missing data. Median survival was 4.9 months (NSCLC 6.3, SCLC 4.0) and five-year survival 6.9%.

Fernandez *et al.*[7] reported in the period 2001-2006 a median survival time of 3 months in 124 lung cancer patients (mean age 68 years, 64% in stage IV!) in the internal medicine department in Pamplona, Spain. Otherwise, de Cos *et al.*[8] reported the one-year survival rate of 36.2% and three-year survival rate of 13.8% in 1,014 patients with lung cancer diagnosed in 2003 in 10 hospitals from across 8 different Spanish regions.

Erridge *et al.*[9] estimated improved treatment and survival for lung cancer patients in South–East Scotland, comparing data of 927 patients diagnosed in 1995 and 971 diagnosed in 2002. The median survival time increased from 4.1 to 5.2 months, and two-year overall survival from 11% to 15%. Reasons cited for the improvement in survival include greater access to CT scanning and development of scanners with improved image quality, more oncologists specialising in lung cancer, introduction of

multidisciplinary team meetings, increasing use of chemotherapy, and increased experience with 3D-conformal radiotherapy.

Leo *et al*.[10] studied discordance between the treatment planned by a multidisciplinary team of specialists and the administered treatment in 344 patients between July 2003 and June 2004. Discordance rate was 4.4% and median delay of treatment 20 days (surgery 22, chemotherapy 16, radiotherapy 27, chemo-radiotherapy 24).

In contrast to the modest observed survival rates cited above, cancer survival reports present the relative five-year survival rate, which was calculated according to age, sex and life tables from the population nationwide. The Cancer Registry of Slovenia reported a five-year relative survival for lung cancer in period 2000–2004 of 11% for male and 14% for female patients[11], which is comparable to EUROCARE-4 data for period 2000–2002 collected from 47 of the European cancer registries, amounting to 10.9 (10.5–11.4) months.[12]

In conclusion, progress in lung cancer management at Clinic Golnik was proved by better staging, a lower percentage of patients undergoing exploratory thoracotomy, use of new treatment modalities, a reduced discordance between selected and actual therapy, and improved short–time survival rate, not only because of patient characteristics (better performance status, more females), but also because of more suitable management.

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images in clinical medicine

Acrospiroma of the left temporal region

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An eighty-year-old patient was operated on for the tumour in the left temporal region. Surgery was performed at the University Department of Plastic Surgery and Burns of the University Medical Centre Ljubljana in December 2006. Before surgery, the tumour measured 6 x 4 cm. Histological examination of the excised tumour tissue confirmed acrospiroma (porocarcinoma).

The fine needle biopsy performed in April 2007 confirmed local recurrence of the disease (Figure 1).

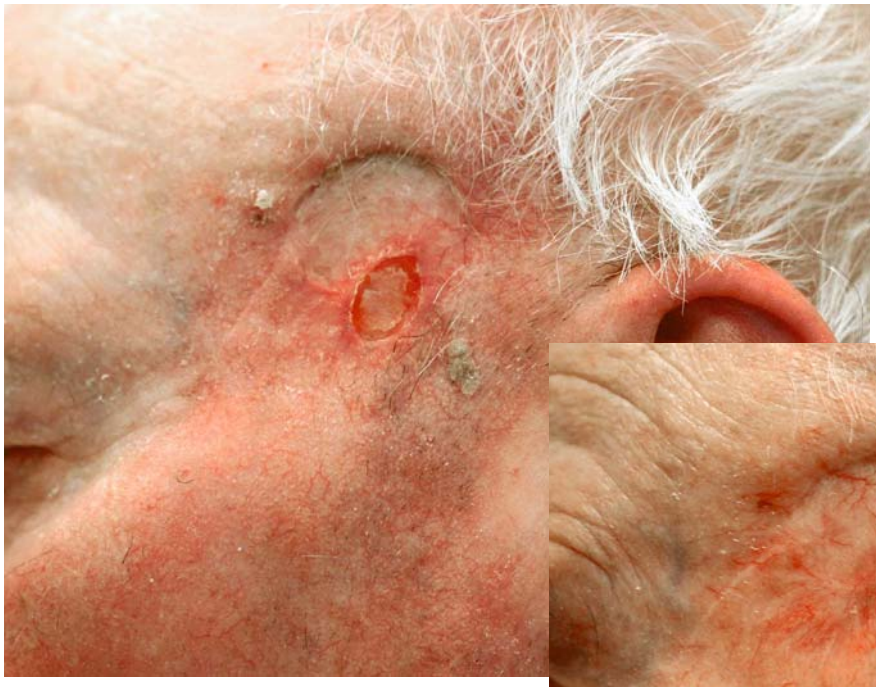

Figure 1. Local recurrence of the acrospiroma.

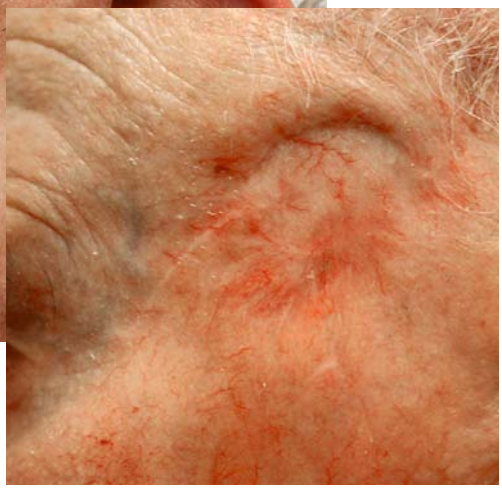

Figure 2. The tumour completely regressed after radiotherapy.

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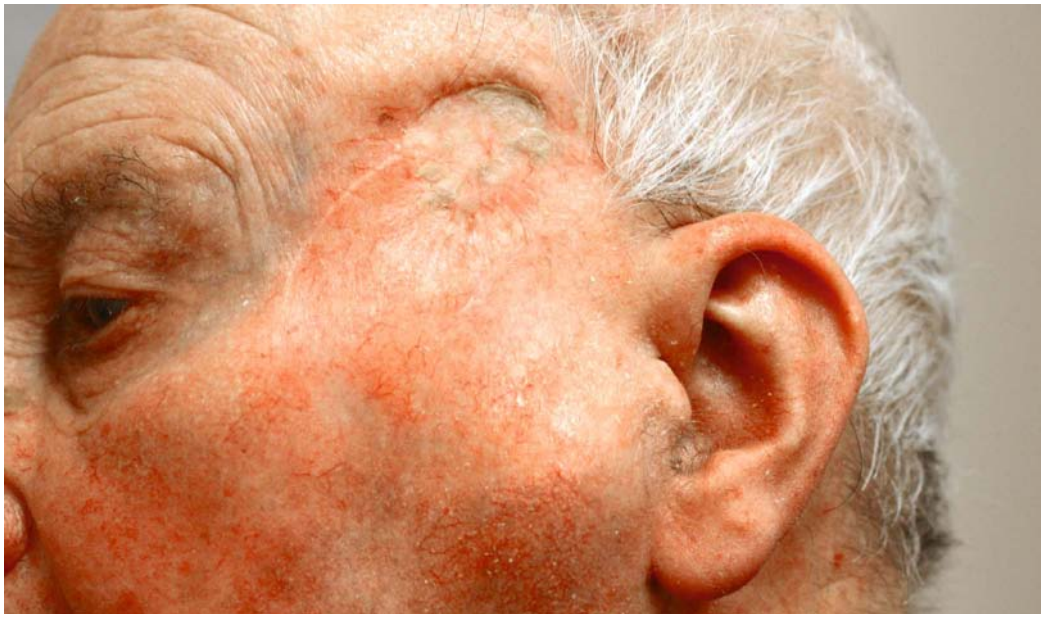

Figure 3. Metastasis in the parotid gland.

At that time, US examination of the neck did not detect any metastases. The skin lobe covering the section of the excised tumour and of the recurrence was irradiated by orthovoltage machine with a dose equivalent of 70 Gy. The tumour completely regressed (Figure 2).

The fine needle biopsy performed in September 2007 detected a metastasis in the parotid gland (Figure 3). The patient was treated by telecobalt and electrons with a total dose equivalentof 70 Gy.

Nine months after the completed radiotherapy, the patient's status was no evidence of disease (NED.), locally and regionally (Figure 4). At the last follow-up control 10 months after the completed radiotherapy, the patient again presented with NED.

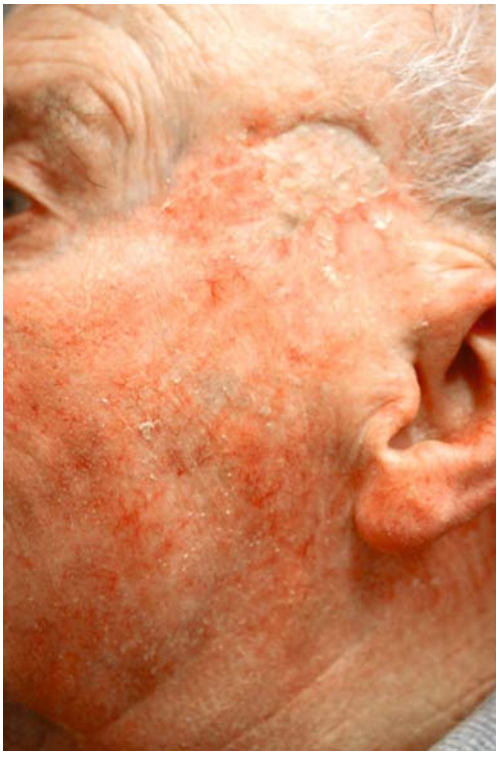

Figure 4. Nine months after the completed radiotherapy there was no evidence of disease.

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research article

The sigmoid colon and bladder shielding in whole pelvic irradiation at prostate cancer (forward planned IMRT from Institute of Oncology Ljubljana)

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Background. *The whole pelvic irradiation (WPI) is again gaining the important role in radiotherapy of prostate cancer. With the conformal irradiation of the large fields that are covering the pelvic nodes, the extra damage is done to sigmoid colon and urinary bladder. Sparing the region between the iliac nodes is necessary since the dose delivered to the organs at risk that are partly included in the mentioned area (the sigmoid colon and bladder) can be importantly reduced.*

Methods. *We are presenting a possible way of shielding the central region between iliac nodes that does not need to be irradiated. Dose volume histograms of standard box technique and technique with additional central shielding of sigmoid colon and urinary bladder in WPI are compared in 10 patients.*

Results. *Applying the described shielding technique 30 to 45 % or in some cases even up to 55% of the sigmoid colon that would with standard box technique be irradiated at doses from 30 to 50 Gy is spared, and also around 10% of the bladder that would receive 45-55 Gy is spared.*

Conclusions. *In the whole pelvic irradiation (WPI) in prostate radiotherapy the sparing of the region between the iliac nodes is crucial since it allows the dose delivered to the sigmoid colon to be reduced to the recommended restrictions. Since the sigmoid colon benefits most from described shielding, the technique is addressed as the Sigmoid Colon Shielding (SCS). The SCS technique is in use at our department at Institute of Oncology in Ljubljana.*

Key words: prostate radiotherapy; whole pelvic irradiation; sigmoid colon shielding; dose distribution; forward planned IMRT

Introduction

The whole pelvic irradiation (WPI) is again gaining the important role in radiotherapy of prostate cancer.[1,2] The radiotherapy for locally advanced and high risk localized prostate tumour at our department consists

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of the treatment of three planning target volumes (PTV1, PTV2 and PTV3) irradiated in 42 fractions (28 + 5 + 9) of 180 cGy.

PTV1 represents the WPI that is irradiated up to 50.4 Gy. PTV1 includes prostate, seminal vesicles and nodes with specific margins.

Gross target volume (GTV) = prostate

Clinical target volume 1 (CTV1) = GTV+ CTV seminal vesicles + CTV Nodes

PTV1= (GTV + Pmargin) + (CTV SV + SVmargin) + (CTV N + Nmargin)

Nodes that are included in CTV N are pelvic nodes in the region of iliacae communis, nodes around iliacae externe and interne in the length of 7 to 8 cm from iliac vessels bifurcation and nodes around aortic bifurcation. Perirectal nodes are not included in CTV N due to the otherwise unacceptable toxicity on rectum.[3,4] To lower the dose on rectum and sigmoid colon and due to the low incidence of the appearance in the area,[5] presacral nodes are not entirely included in CTV N. Margins of PTV1 are uniform 1cm, but are also reduced when necessary in order to attain the treatment plan that respects the restrictions on rectum.

PTV2 and PTV3 represent the boost on the seminal vesicles and prostate. PTV2 that includes prostate with seminal vesicles is irradiated up to 59.4 Gy and PTV3 which is boost on prostate alone and is finally irradiated up to 75.6 Gy. The boost treatment delivery is image guided. Prior to the treatment planning three golden markers are implanted in the patient's prostate, and the boost treatment fields of PTV2 and PTV3 are positioned according to the marker locations. Due to the image guiding the dorsal prostate margins (PBmargin) in PTV2 and PTV3 are shrunk to 7mm.

CTV2 = GTV + CTV SV

PTV2 = (GTV + PBmargin) + (CTV SV + SVmargin)

CTV3= GTV

PTV3= (GTV + PBmargin)

With treatment planning we are trying to spare organs at risk (OR) and tend to assure the restrictions on OR. With the restrictions we are applying the irradiation toxicity on OR are still acceptable:[3,4]

Rectum: V50<64%, V60<45%, V70<25%, Dmean<45 Gy,

Anus: V55<16%, V60<5%, Dmean< 40Gy.

In our experience, we found out that those restrictions could not be achieved when perirectal nodes were included in CTV N. Cost – benefit calculation lead us to the solution to exclude perirectal nodes from CTV N.

For sigmoid colon we aim to apply the same restrictions that are in use for rectum.[6,7]

We are also respecting that more than half of urinary bladder should not receive doses higher than 70 Gy (V70<50%). Since the stricter dose constraints on bladder, that prevent G1 and G2 toxicity,[8,9] cannot be respected, applying WPI, the chosen restrictions are set to prevent G3 toxicity.

We are checking also the dose on hips and penile bulb, but we are not altering the treatment due to the high doses on hips and penile bulb.

The planning target volumes PTV1, PTV2 and PTV3 are required to be enclosed in 95% isodose relative to the prescribed dose. The maximal dose should not exceed 107% of the prescribed dose.

The treatment plan

With the conformal irradiation with box technique (4 fields of gantries: 0°, 90°, 180°, 270°) and smaller fields of mentioned gantries (forward planned IMRT), the dose is delivered to the large volume PTV1. The smaller fields added in order to homogenize the delivered dose,[10] are usually applied in the region of prostate, where the dose delivered with the bigger fields

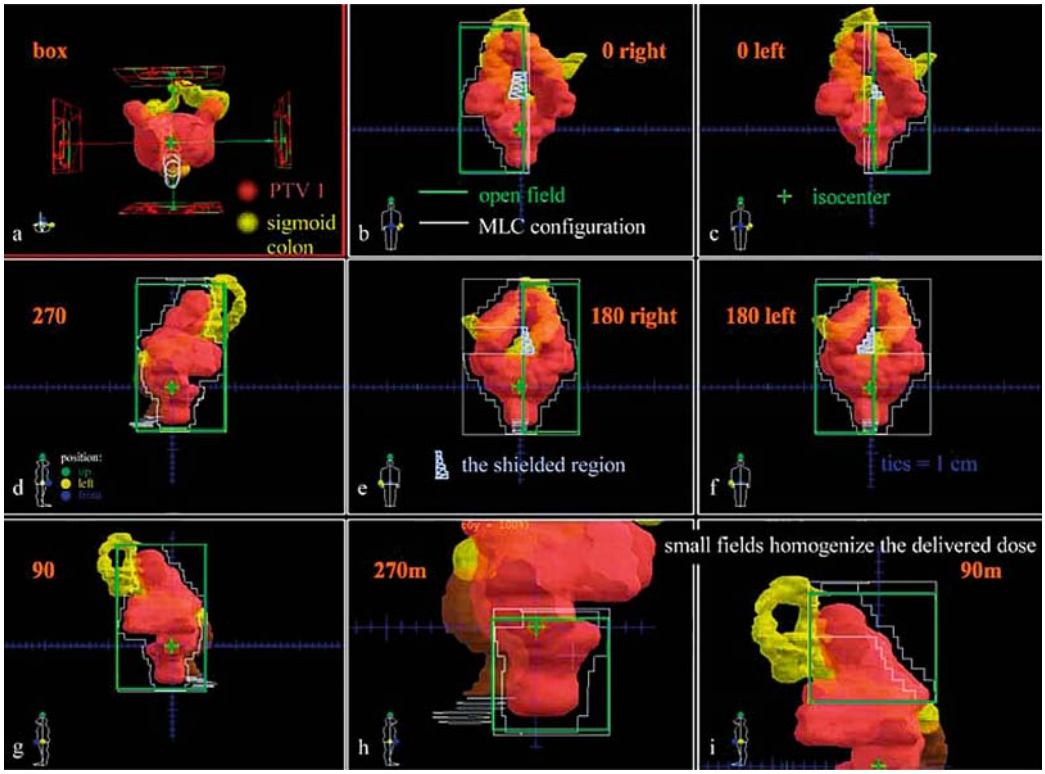

Figure 1. The sigmoid colon shielding (SCS) technique. The classical box technique consists of the four fields of gantries: 0°, 90°, 180° and 270°, shaped to the planning target volume (PTV) (a). The fields are named according their gantries. In SCS technique the box technique is altered so the central part that is not included in the PTV1 can be shielded. In SCS the irradiation gantries remain the same as with classical box technique. In order to shield the central part fields 0° and 180° have to be split through the region of shielding. Right and left contributions to the irradiation from 0° are presented on b and c, whereas e and f present the right and left contributions from 180°. Presented fields 0° and 180° are off centre split (0°: 0.5 cm to the left from the isocentre, 180°: 0.5cm to the right from the isocentre). The collimator is set to 0°, so the MLC can slide in the region that needs to be shielded. The outer margins of the fields remain the same as the ones the primary field. The part of sigmoid colon (yellow) in the shielded region is spared. Lateral irradiation remain intact, major fields 270° and 90° (d, g), as well as the small fields that homogenize the dose distribution 270°m and 90°m (h and i).

is not sufficient, due to the bony anatomy and due to the patient's shape. With the dose delivered to the large fields of PTV1, the dose is delivered also to the region between the iliac nodes that does not need to be irradiated. Keep at box technique, the dose delivered to the region between iliac nodes, that is not included in PTV1 could be reduced, by shielding pieces of the large fields from 0° and 180°.

Considering the uniform dose delivery from all four sides of the box, the dose to the shielded region can be lowered for 50%. Since, as we are describing later on, the sigmoid colon benefits most from such shielding, the described technique is addressed as the Sigmoid Colon Shielding (SCS). It is important to pay attention on sigmoid colon since it appears that dose on sigmoid colon is co-responsible for lower intestinal toxicity.[7] At our department we achieve the SCS in different ways: with individual shielding blocks or with the "off centre field splitting". All the changes required for SCS re-

Table 1. The average DVH parameters for sigmoid colon and bladder. The average DVH parameters with corresponding standard deviations are presented for sigmoid colon and bladder. For the every patient the DVH parameters were calculated for BOX and for SCS technique as well as for the difference between techniques (BOX – SCS). The average DVH parameters and corresponding standard deviations were calculated from 10 consecutive patients. Even though the number of patients is small the clear advantage of the SCS technique is visible from the comparison of the DVH parameters. The beneficial DVH parameters changes that are higher than the standard deviations are indicated with yellow.

Organ& technique	V30 [%]	V35 [%]	V40 [%]	V45 [%]	V50 [%]	V55 [%]	V60 [%]	Dmean [Gy]
sigmoid colon BOX	90.2 ± 16.67	86.36 ± 17.35	82.61 ± 17.51	78.61 ± 17.65	72.66 ± 17.91	9.54 ± 9.44	4.36 ± 4.97	47.97 ± 5.55
sigmoid colon SCS	78.23 ± 15.65	59.69 ± 17.62	48.49 ± 14.13	39.94 ± 14.20	27.23 ± 13.19	4.51 ± 4.72	1.94 ± 2.03	38.9 ± 4.09
sigmoid colon difference (BOX- SCS)	11,98 ± 10,62	26.67 ± 16.74	34.12 ± 15.91	38.67 ± 16.69	45.43 ± 17.32	5.03 ± 4.95	2.42 ± 3.20	9.08 ± 3.44
bladder BOX	98.90 ± 3.11	98.52 ± 4.18	98.22 ± 5.05	96.78 ± 5.59	94.92 ± 6.57	82.26 ± 15.33	64.89 ± 17.23	64.47 ± 4.74
bladder SCS	98.18 ± 4.06	94.74 ± 7.72	91.22 ± 9.48	86.36 ± 11.43	80.71 ± 12.83	72.17 ± 15.03	60.94 ± 17.28	61.67 ± 5.97
bladder difference (BOX- SCS)	0.72 ± 1.18	3.79 ± 6.06	7.00 ± 7.59	10.41 ± 8.93	14.21 ± 10.19	10.10 ± 5.64	3.95 ± 2.77	2.8 ± 1.98

fer to the big fields of gantries 0° and 180°, whereas, the small fields as well as fields from other directions remain unchanged.

Methods

The SCS with individual shielding blocks

The region between iliac nodes, not included in PTV1, can be shielded from 0° and 180° with individual shielding blocks. The shielding blocks for both fields are made according to the PTV1. Eight cm thick shielding blocks are made of Wood alloy. At our department we are using the individual shielding blocks at Elekta Synergy Platform linear accelerator.

The SCS with the off centre fields splitting

Shielding can be preformed also with multi-leaf collimator (MLC) as presented in the Figure 1. At our department the majority of the patients with locally advanced and high risk localized prostate tumour are scheduled to be treated at linear accelerator Varian 2100 CD, where individual shielding blocks are not in use, and, therefore, we need to perform SCS with multi-leaf collimator.

In order to shield the part in the middle of the field, the fields have to be split across the region of shielding. The collimator of the field should be turned so the MLC-s can slide perpendicular to the field cut. Pre-optimized conformly shaped 0° and 180° fields are duplicated and shaped in the left and the right part. The outer margins of the duplicated fields remain unchanged, but the margins at left - right junctions have to be shaped according to the PTV1 as presented in the Figure 1. After the shaping, the irradiation times of left and right parts are set to the same optimal irradiation time.

In case the fields are split in two parts through the centre (half beam blocks – HBB),

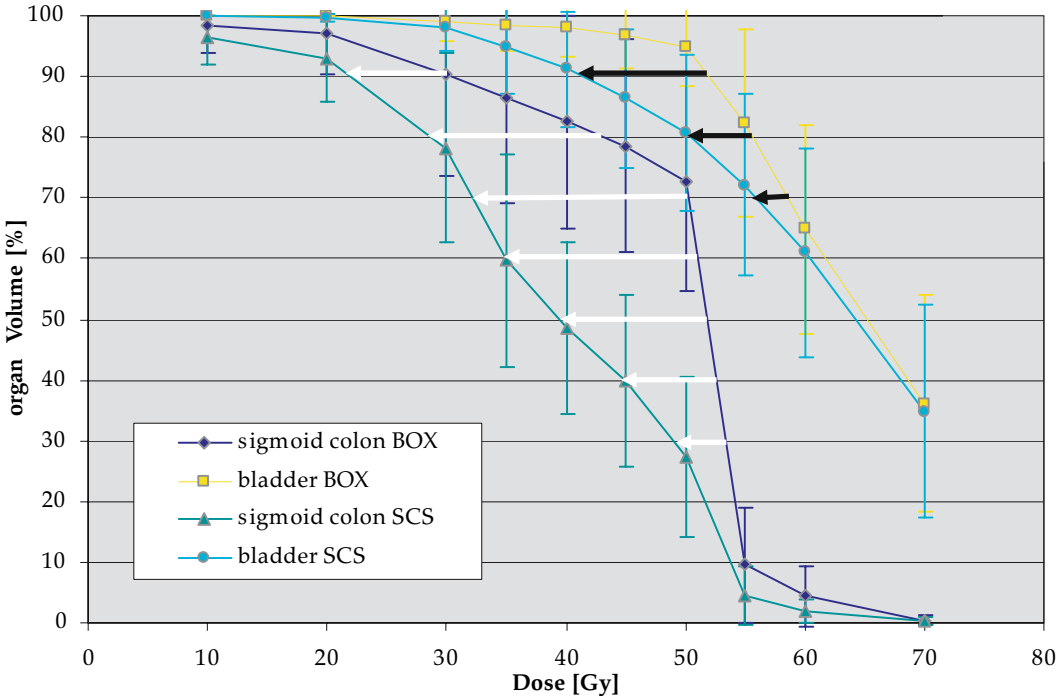

Figure 2. Cumulative dose volume histograms (DVH) for sigmoid colon and bladder for box alone and sigmoid colon shielding (SCS) technique. The dose on sigmoid colon and bladder in high risk prostate cancer irradiation were evaluated with the DVH. The cumulative DVH for box alone and for SCS technique were analyzed in 10 cases. In every single case, both sigmoid colon and bladder were spared with SCS. The figure presents the average DVH for sigmoid colon and bladder for both techniques. The arrows indicate the dose reduction on the parts of organs when applying SCS.

both beams 0° and 180° are split in the same central plane. In such case fields from both directions (0° and 180°) contribute to the potential cold or hot spots at the field junction plane. Therefore, we are proposing the "*off centre field splitting*". The experience shows that 0.5 cm off centre splitting can still support the appropriate shielding of the part not included in PTV1. The split for the two fields (0° and 180°) should be at left and right to the central line, so there is a 1 cm gap between the 0 and 180 split planes. With this kind of splitting the cold and hot spots are blurred compared to the splitting in the one plane since the contribution to the cold and hot spots at split planes arises from one side only. Therefore, the possible inaccuracy in delivered dose is lowered.

The evaluation of the SCS

The SCS technique was evaluated in group of 10 consecutive patients that received radical radiotherapy treatment for locally advanced and high risk localized prostate tumour. To plan the treatment, CT images were taken with Philips MX 8000 and used with CMS XIO planning system. In all patients both treatment techniques were planned: box alone and SCS. The techniques were evaluated with dose volume histograms (DVH) comparison. We were checking and comparing the PTV coverage and organs at risk exposure (rectum, anus, sigmoid colon, bladder, penile bulb, acetabulum, small intestine). The detailed analysis was carried out for sigmoid colon and bladder, since in all the cases the dif-

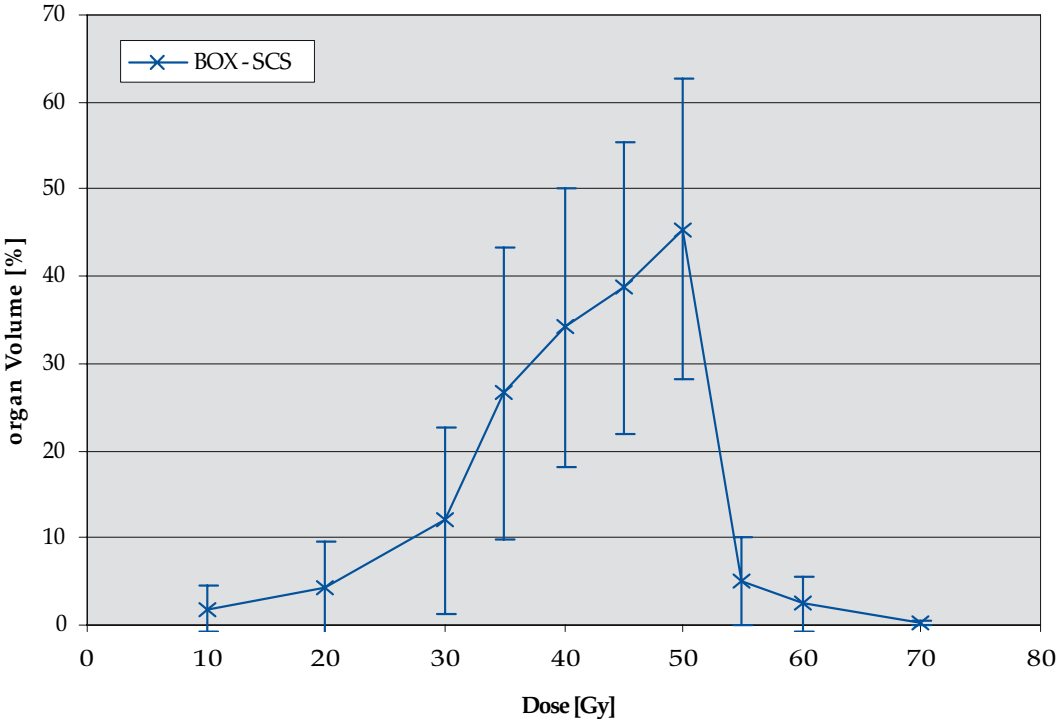

Figure 3. The average difference in cumulative DVH for sigmoid colon between box alone and SCS. Using the SCS technique at WPI of high risk prostate irradiation the inclusion of the sigmoid colon the irradiation region is reduced. Around 30-40% of the whole sigmoid colon that would be irradiated with 35 to 50 Gy with box technique is spared with sigmoid colon shielding.

ference in DVH was the greatest for the two organs. The differences in V10, V20, V30, V35, V40, V45, V50, V55, V60, V70 and in mean dose for sigmoid colon and for bladder were calculated for every patient for box alone and SCS technique. Since the number of patients is still small only the average difference in DVH parameters and their standard deviation is presented and commented.

Results

Applying the Sigmoid Colon Shielding (SCS) technique in the WPI the dose to sigmoid colon and bladder is importantly reduced, at the unchanged coverage of PTV. Since the WPI represents two thirds of the radiotherapy for locally advanced and high risk localized prostate tumour, any changes that are introduced in planning WPI express notably in the cumulative treatment plan. The comparison of the average DVH of box alone and SCS technique is presented in the Figure 2 and Table 1.

The general idea of the average DVH, presented in the Figure 2 and Table 1, holds also for every single case observed. As can be seen from DVH comparison, applying SCS a part of the sigmoid colon and bladder can be spared. The most obvious is saving of the part of the sigmoid colon that would receive 35Gy to 50Gy with box-alone, whereas there is almost no difference in the irradiation of the parts of sig-

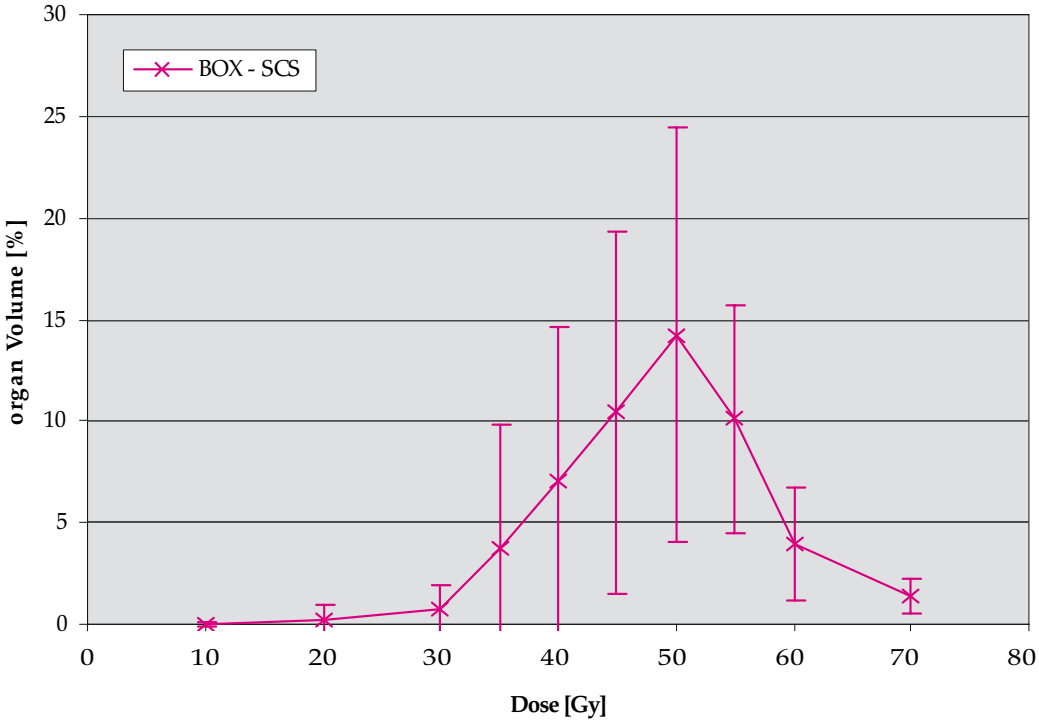

Figure 4. The average difference in cumulative DVH for bladder between box alone and SCS. Around 10% of the bladder that would be irradiated with 45 to 55 Gy with box alone is spared applying SCS technique. Although, compared to the sigmoid colon) the smaller part of the bladder is spared, the higher doses are lowered.

moid colon with smaller or higher doses. The bladder sparing is not as obviously expressed than the sigmoid colon sparing, but the proportion of the bladder that would receive higher doses is reduced.

Since the parts of the sigmoid colon and bladder that are not shielded are in SCS technique are irradiated the same way as with box alone, the shift of DVH curves holds also the relevant information of the dose reduction on sigmoid colon and bladder due to the shielded region sparing (indicated with arrows in Figure 2). The average dose reduction on the majority (70%) of the sigmoid colon reduction can be almost 20 Gy (from 50 Gy to almost 30 Gy). Applying SCS 90 % of the bladder can be irradiated with approximately 10 Gy smaller doses (dose is reduced from 55 Gy to 45 Gy), as can be seen following the black arrow.

Figure 3 presents the average difference in DVH of sigmoid colon between box alone and SCS technique. Form 30 to 45 % or in some cases even up to 55% of the sigmoid colon irradiated at doses from 35 to 50 Gy is spared applying SCS. The average sparing of the sigmoid colon is in spite of small patient number (10) significant, even 2.5 times as big as the standard deviation.

With SCS technique also bladder is spared. The benefit for the bladder can be seen in Figure 4, that presents the average difference in DVH for bladder between box alone and SCS technique, can be seen that around 10% of the bladder that receives 45-55 Gy with box alone can be spared with SCS technique.

It was also observed in DVH that small intestine does a bit better with SCS, but the detailed analysis was not preformed.

Discussion

Applying the SCS technique instead box alone in WPI the sigmoid colon and bladder can be spared at the unchanged PTV coverage. We assume that with the decreased dose on organs at risk also the toxicity of the irradiation is reduced.[7,9] We tend to prepare the report on lowered toxicity due to SCS implementation.

We have in mind that in order to compare dose volume histograms resulting from different applied techniques one has to be extremely careful, since completely different techniques can arise in same DVH. In our cases we are confident to compare DVH, since we keep in mind that most of the technique and therefore the dose delivered to the majority of the irradiated volume remained unchanged, and all the differences in DVH arise from the shielding part. We are presenting the average difference in DVH between the SCS technique and box alone, but also, in every single case, there was a beneficial difference observed in favour of SCS technique. The beneficial changes in DVH were, dependent on the patient anatomy, expressed in the different parts of the DVH. This was leading to the higher standard deviation of the average DVH difference. With higher number of patients, we expect that the difference between techniques would be more accurately expressed and therefore the presented benefit of applying the SCS technique would be greater than presented.

We also tend to improve the bladder sparing. Our current advices to the patients lead us to the bladders of volumes around 100 cm^3. We assume that with bladders filled up to 200 cm^3 the dose on bladder decrease.[8] Combined with SCS technique the dose decrease would be even more important. Therefore, we are preparing to change our current advice to patient to result in bladders of volumes around 200 cm^3.

Conclusions

Sparing the region between the iliac nodes is beneficial since the dose delivered to the organs at risk that are partly included in the mentioned area (the sigmoid colon, and bladder) can be importantly reduced. In our analysis we evaluated the reduction of the dose delivered to the sigmoid colon and bladder with the implementation of the SCS technique. Even with the small number of analysed cases, at the unchanged PTV coverage, the dose reduction on OR is evident. Due to the dose reduction on the organs at risk, the reduction of the irradiation toxicity is also expected. Therefore, the toxicity will be monitored and reported later on.

Acknowledgement

The improvement of the well established and common techniques can only be carried out with coordinate cooperation of all the workers involved in the process. Therefore I would like to thank to all the coworkers and the crew that are working hard in order to improve the treatment quality.

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Radiol Oncol 2009; 43(1): 1-8.

Zdravljenje metastatskega raka debelega črevesa in danke

Ocvirk J

Izhodišča. Metastatski rak debelega črevesa in danke je v večini primerov še vedno neozdravljiva bolezen, vendar pa sta se prognoza in preživetje teh bolnikov močno izboljšala v zadnjih šestih letih. Srednje desetmesečno preživetje smo dosegali z zdravljenjem s 5-fluorouracilom, ki je bilo do pred nekaj leti edino učinkovito zdravilo za zdravljenje teh bolnikov. Srednje preživetje smo povečali na 20 mesecev, kar so omogočila nova citostatska zdravila. V zadnjih šestih letih je bilo registriranih pet novih zdravil za zdravljenje matastatskega raka debelega črevesa in danke: citostatiki – kapecitabin, irinotekan in oksaliplatin ter tarčni zdravili – cetuksimab in bevacizumab.

Zaključki. Kombinirano zdravljenje omogoča boljšo kakovost življenja in daljše obdobje brez napredovanja bolezni, s tem pa tudi daljša celotna preživetja. Uporaba kombinacije citostatikov s tarčnimi zdravili vodi še v nadaljnje podaljšanje srednjega preživetja bolnikov. Pri tako zdravljenih bolnikih je srednje preživetje daljše od 30 mesecev. Tovrstno zdravljenje v kombinaciji z operacijo pljučnih ali jetrnih zasevkov pa omogoča tudi zazdravitve. Pomembna letošnja novost je določanje mutacij na genu KRAS. Pri raku debelega črevesa in danke je gen KRAS prvi biološki napovedni dejavnik (biomarker), ki napoveduje, kako se bodo bolniki odzvali na določena zdravljenja.

Radiol Oncol 2009; 43(1): 9-16.

Prisotnost in vloga Simian virusa 40 (SV40) pri malignem plevralnem mezoteliomu

Hmeljak J, Cör A

Izhodišča. Prvi dokazi o možni vlogi virusov pri razvoju rakavih obolenj segajo v začetek 20. stoletja, dokončna potrditev pa je prišla po odkritju virusa Epstein-Barr (EBV) v celicah Burkittovega limfoma. Kasneje so odkrili številne onkogene viruse in retroviruse in danes je široko sprejeta ocena, da virusi povzročijo 15% vseh rakavih obolenj pri ljudeh. Onkogeni virusi uporabljajo mnogo različnih beljakovin, s katerimi dramatično vplivajo na celični cikel, signalne poti in kontrolne točke. Vse to privede do destabilizacije genoma, odpornosti na imunski odziv in nesmrtnost.

Zaključki. Simian virus 40 je majhen virus DNA, ki tako kot človeška JCV in BKV sodi v rod *Polyomavirus*. Dokazano je, da je močno kancerogen za glodalce. V človeško populacijo je prišel preko okužene vakcine v 60. letih 20. stol., v začetku masovnega cepljenja proti otroški paralizi (poliomielitisu). Leta 1994 so odkrili virusno DNA v vzorcih človeških mezoteliomov, kar je sprožilo val raziskav o vlogi virusa pri razvoju te bolezni. Danes velja, da virus sam po sebi sicer ne povzroča raka pri ljudeh, vendar so si znanstveniki edini, da ima (še ne opredeljeno) vlogo pri razvoju bolezni. Boljše razumevanje delovanja virusa pri ljudeh je nujno in številne raziskave interakcij med beljakovinami virusa SV40 in človeškimi mezotelijskimi celicami še potekajo.

Radiol Oncol 2009; 43(1): 17-25.

Embolizacija globoke dorzalne vene z mešanico N-butyl-cianoakrilata in lipiodola pri venski erektilni disfunkciji: zgodnji in pozni rezultati

Kutlu R, Soylu A

Izhodišča. Namen raziskave je bil oceniti učinek venoablacije z injiciranjem N-butyl-cianoakrilata (NBCA) in lipiodola v globoko dorzalno veno pri zdravljenju venske erektilne disfunkcije.

Metode. V raziskavo smo vključili 32 bolnikov s potrjeno vensko erektilno disfunkcijo. 15 od 32 bolnikov je imelo še spremljajoče bolezni. Globoka dorzalna vena je bila embolizirana z mešanico NBCA in lipiodola. Uspeh zdravljena, to je izboljšanje erektilne funkcije, smo ocenjevali z vprašalnikom Mednarodni indeks erektilne funkcije (IIEF) pred posegom ter 3 mesece in eno leto po embolizaciji.

Rezultati. Tri mesece po posegu smo ugotovili izrazito povišanje vrednosti indeksa IIEF pri bolnikih s spremljajočimi boleznimi in bolnikih brez njih ($p<0.001$). Po enem letu pa je glede na vrednost pri treh mesecih indeks IIEF izrazito padel ($p<0.001$). Pri bolnikih brez spremljajočih bolezni so bili tri in dvanajstmesečni indeksi IIEF izrazito višji kot pri bolnikih s spremljajočimi boleznimi ($p<0.04$ in $p<0.02$). Čeprav so bile vrednosti indeksa IIEF pri bolnikih s spremljajočimi boleznimi po dvanajstih mesecih izrazito višje kot pred posegom, so bili ti bolniki nezadovoljni s kakovostjo erekcije.

Zaključki. Z našo tehniko pelvične venoablacije smo dosegli kratkoročno dobro izboljšanje erektilne funkcije. Nekateri bolniki zaradi spremljajočih bolezni niso primerni za takšen način zdravljenja.

Radiol Oncol 2009; 43(1): 26-9.

Retroperitonealna perforacija danke med klistriranjem z dvojnim barijevim kontrastom: življenjsko ogrožajoč zaplet

Yildirim M, Oztekin O, Bayam ME, Yagli E, Yakan S

Izhodišča. Poškodbe danke med klistriranje z barijevim kontrastom so redke, a življenjsko ogrožajoče.
Prikaz primera. Predstavljamo 82-letnega bolnika, pri katerem smo ugotovili obsežno retroperitonealno perforacijo danke, ki je nastala med klistriranjem z dvojnim barijevim kontrastom. Bolnik je kazal znake akutnega abdomna, težko je dihal, v predelu prsnega koša in vratu pa smo zaznali difuzne podkožne krepitacije. Zaradi znakov peritonitisa smo bolnika operirali. Naredili smo operacijo po Hartmannu, bolnik pa je 20 ur po posegu umrl v septičnem šoku.
Zaključki. Če retroperitonealno perforacijo danke takoj prepoznamo in pričnemo zdraviti, lahko zmanjšamo umrljivost.

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Magnetnoresonančna analiza teksture in njena uporabnost pri ugotavljanju protektorjev za indukcijo jetrne fibroze pri podganah

Mahmoud-Ghoneim D, Amin A, Corr P

Izhodišča. V raziskavi smo uporabili magnetno resonanco pri analizi teksture (MRI-TA) in preučevali zaščitno delovanje izvlečka *Moringa oleifera* proti jetrni fibrozi. To smo inducirali z ogljikovim tetrakloridom (CCl_4) pri podganah. Učinke smo primerjali glede na funkcionalne teste jetrnih funkcij in histopatološko.

Metode. 28 podgan smo naključno razdelili v 4 poskusne skupine: [1] kontrolna skupina (C), ki je prejela intragastrični nosilec v času štirih tednov, [2] skupina s fibrozo (F), ki je prejela intraperitonealno CCl_4 dvakrat tedensko 8 tednov, [3] sylmarin skupina (S), ki je prejela 0,2 g/kg dnevno oralno 8 tednov CCl_4, [4] z *Moringo oleifero* zaščitena skupina (M), ki je prejela intra-gastrično 0,5 g/kg *Moringe oleifere* sočasno z CCl_4. Pri vseh skupinah so bili izvedeni funkcionalni jetrni testi in histologija, ki so potrdili zaščitno delovanje *Moringe Oleifera* proti s CCl_4 inducirani jetrni fibrozi.

Rezultati. Indeks fibroze in količina kolagena I sta bila zelo povišana v jetrih živali, ki so dobivale CCl_4 (12,73% ± 2,37), v primerjavi z živalmi, ki so bile tretirane z Moringo (5.23±0.13%) ali silmarinom (1.23±1.01%). MRI-TA rezultati so se ujemali s histopatološkimi preiskavami. Razporeditev MRI-TA parametrov je pokazala ločbo med skupinami F in M in C na osi, kjer so nanešeni najbolj diskriminatorni parametri (MDF-1) in so vedno imeli negativne vrednosti. Skupini C in M sta bili skupaj na isti osi s pozitivnimi vrednostmi. Zelo podobni rezultati so bili dobljeni pri klasifikaciji skupin C, F in S. S parametri teksture smo merili grobost teksture na sliki, na kar so vplivali količina in razporeditev kolagena, kot kazalnika fibroze ter zaščitni dejavniki antifibrotičnih zdravil.

Zaključki. Na osnovi naših rezultatov lahko ugotovimo, da je MRI-TA metoda, ki jo lahko uporabimo pri preučevanju protektivnega in terapevtskega delovanja antifibrotičnih učinkovin. *Moringa oleifera* ima potencialni hepatoprotektivni učinek na podganah, ki so bile tretirane z CCl_4, kar smo dokazali z MRI-TA testom in histopatološkimi preiskavami. Priporočamo MRI-TA kot možno orodje za enostavnejše in hitro ocenjevanje učinka antifibrotičnih učinkovin.

Radiol Oncol 2009; 43(1): 41-6.

Obsevanje pri regionalno napredovalih karcinomih penisa

Kragelj B

Izhodišča. Inoperabilni zasevki karcinoma penisa v dimeljskih bezgavkah, ostanek ali ponovitev karcinoma po dimeljski limfadenektomiji so pogosti razlogi za zdravljenje bolnika z obsevanjem.
Metode. Opravili smo retrospektivni pregled 12 bolnikov z zasevki karcinoma penisa v dimelskih bezgavkah. Bolnike smo obsevali v obdobju od 1995-2003. Opredelili smo akutne, kot tudi kronične zaplete obsevanja.
Rezultati. Vsi bolniki (8/8) s tipnimi dimeljskimi zasevki ob pričetku obsevanja in tudi dva bolnika (2/4) bolnika z mikroskopskim ostankom karcinoma po dimeljski limfadenektomiji so umrli zaradi karcinoma v 4-24 mesecih po pričetku obsevanja. Mediano preživetje bolnikov je bilo 8 mesecev. Lokoregionalni nadzor nad boleznijo je bil dosežen le pri bolnikih z opravljeno dimeljsko limfadenektomijo in mikroskopskim ostankom karcinoma ob pričetku obsevanja.
Zaključki. Pravočasno odkritje razsoja v dimeljske bezgavke, kot tudi takojšnja dimeljska limfadenektomija sta ključni za preživetje bolnikov s karcinomi penisa. Obsevanje dimeljskih bezgavk je smiselno le neposredno po limfademnektomiji – ob domnevnem mikroskopskem ostanku karcinoma. Obsevanje je ob tipnih ostankih, ponovitvah karcinoma po dimeljski limfadenektomiji ali inoperabilnih dimelskih zasevkih neuspešno in spremljano s hudimi zapleti.

Radiol Oncol 2009; 43(1): 47-53.

Ali se rutinska obravnava bolnikov s pljučnim rakom izboljšuje? Primerjalna analiza ustanove v letih 1996 in 2006.

Debevec L, Jerič T, Kovač V, Bitenc M, Sok M

Izhodišča. Namen raziskave je ugotoviti morebitni napredek pri rutinski obravnavi bolnikov s pljučnim rakom v Bolnišnici Golnik. Primerjali smo rezultate analize 345 bolnikov, pri katerih smo ugotovili rak pljuč v letu 1996 (analizirali smo leta 2002) in 405 bolnikov v letu 2006 (analizirali smo leta 2008).

Bolniki in metode. Obe skupini sta primerljivi glede na starost in število bolnikov v stadiju I in II. V letu 2006 pa je bilo sorazmerno manj bolnic, več bolnikov z boljšo telesno zmogljivostjo, natančnejša je bila klinična zamejitev in histološka opredelitev tumorja. Parametri za oceno napredka so bili naslednji: časovno obdobje od sprejema do diagnoze in operacije, točnost zamejitve, ujemanje kliničnega in patološkega stadija pri operiranih bolnikih, odstotek eksplorativnih torakotomij in uporaba novih načinov zdravljenja. Tudi razmerje med izbranim in izvedenim primarnim načinom zdravljenja ter preživetje smo uporabili za oceno napredka.

Rezultati. Kljub nebistveno daljšem času od sprejema do mikroskopske potrditve tumorja, ki je porasel od povprečno 7,4 na 8,6 dni, smo v letu 2006 ugotovili izboljšanje ostalih parametrov. Natančnejša je bila klinična zamejitev (pri stadijih I in II smo opredelili tudi podstadije A in B, pri drobnoceličnem raku tudi TNM zamejitev), boljše ujemanje klinične in patološke zamejitve pri operiranih bolnikih (46% proti 58%), manjši odstotek eksplorativnih torakotomij (13% proti 4%), pogosteje uporabljeno kombinirano zdravljenje že kot primarno zdravljenje in uvedba radio- frekvenčne ablacije tumorja. Razmerje med izbranim in izvedenem zdravljenje se je izboljšalo (od 76% na 93%), srednje preživetje vseh bolnikov se je podaljšalo od 6,2 na 10,6 mesecev. Odstotek bolnikov, ki so preživelih eno leto, se je povečal od 33,6% na 45,8% in bolnikov, ki so preživeli dve leti od 17,4% na 23%.

Zaključki. Napredek pri rutinski obravnavi pljučnega raka se je pokazal v boljši zamejitvi bolezni, nižjem odstotku eksplorativnih torakotomij, uporabi novih načinov zdravljenja, manjši razliki med izbranim in izvedenim zdravljenjem ter daljšem kratkoročnem preživetju.

Radiol Oncol 2009; 43(1): 56-64.

Ščitenje sigmoidnega črevesa in mehurja ob obsevanju celotne medenice pri bolnikih z rakom prostate

Grabec D, Kragelj B

Izhodišča. Obsevanje območja celotne medenice (WPI) ponovno pridobiva na veljavi pri radioterapiji raka prostate. Ob konformnem obsevanju velikih polj, ki obsegajo območje iliakalnih bezgavk, je povzročena dodatna škoda na sigmoidnem črevesu, mehurju in tankem črevesu. Ščitenje osrednjega dela med iliakalnimi bezgavkami je potrebno, ker lahko na ta način pomembno znižamo dozo na kritične organe, ki delno posegajo v omenjeno področje (sigmoidno črevo in mehur).

Metode. Predstavljamo možen način ščitenja osrednjega dela med iliakalnimi bezgavkami, ki ga ni potrebno obsevati. V skupini 10 bolnikov smo primerjali dozni volumenski histogram (DVH) standardne škatelne tehnike s tehniko centralnega ščitenja sigmoidnega črevesa in mehurja.

Rezultati. Z uporabo predstavljene tehnike ščitenja zavarujemo od 30 do 45 %, v nekaterih primerih celo do 55% sigmoidnega črevesa, ki bi z uporabo standardne škatelne tehnike bilo obsevano z dozami med 30 in 50 Gy. Poleg tega s predstavljeno tehniko zavarujemo okoli 10% mehurja, ki bi sicer prejelo od 45 do 55 Gy.

Zaključki. Ob obsevanju celotne medenice (WPI) pri raku prostate je ščitenje osrednjega dela med iliakalnimi bezgavkami nujno, ker omogoča znižanje obsevalne doze na sigmoidno črevo na zadovoljivo raven. Omenjeno ščitenje najbolj koristi sigmoidnemu črevesu, zato opisano tehniko naslavljamo z imenom ščitenje sigmoidnega črevesa (SCS). Opisano in komentirano SCS tehniko uporabljamo na našem oddelku na Onkološkem inštitutu v Ljubljani.

Notices

*Notices submitted for publication should contain a mailing address, phone and/or fax number and/or e-mail of a **Contact** person or department.*

Targeted therapies

April 1-5, 2009
The "4th IASLC/ASCO/ESMO International Meeting on Targeted Therapies on Lung Cancer" will be offered in Saint Paul de Vence, France.
E-mail: pia.hirsch@uchsc.edu

Breast cancer

April 2-4, 2009
The ESTRO multidisciplinary teaching course on breast cancer will take place in Lisbon, Portugal.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org or http://www.estro-education.org/courses/Documents/Announcement_Lisbon2009.pdf

Molecular oncology

April 26-30, 2009
The ESTRO teaching course ''Molecular Oncology for the Radiation Oncologist'' will take be offered in Santorini, Greece.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Radiation oncology

April 27-29, 2009
The international IAEA's conference "Advances in Radiation Oncology (ICARO)" will be held in Vienna, Austria.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; see http://www/astro.org

Thoracic oncology

May 1-3, 2009
The European Multidisciplinary Conference in Thoracic Oncology (EMCTO) will take place from in Lugano, Switzerland.
Contact EMCTO Conference Secretariat, c/0 ESMO Congress Department, Via Luigi Taddei 4, CH-6962 Viganello-Lugano, Switzerland; or fax +41 (0)91 973 19 18, or see www.emcto.org

Rectal cancer

May 10-12, 2009
The ESTRO multidisciplinary teaching course on evidence and research in rectal cancer will take place in Rome, Italy.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Radiotherapy

May 10-14, 2009
The ESTRO teaching course on radiotherapy with protons and ions will be offered in Villingen, Switzerland.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Radiotherapy

May 17-21, 2009
The ESTRO teaching course on IMRT and other conformal techniques in practice will be held in Milan, Italy.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Thyroid cancer

May 27-31, 2009
The "World Congress on Thyroid Cancer'' will be held in Toronto, Canada.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; see http://www/astro.org

Clinical oncology

May 29 – June 2, 2009
The American Society of Clinical Oncology Conference (ASCO 2009) will be offered in Orlando, USA.
E mail enews@asco.org; or see http://www/asco.org

Clinical trial statistics

June 9-12, 2009
The EORTC course "Clinical Trial Statistics for Non Statisticians" will be held in Brussels, Belgium.
See http://www.eortc.be/Seminar/Educationpgm/Stats2009/Default.htm

Oncology

June 20-26, 2009
The ECCO-AACR-ASCO workshop "Methods in Clinical Cancer Research" will be offered in Flims, Switzerland.
Contact the Workshop Coordinator Mrs. Kaat Cumps at kaat.cumps@ecco-org.eu; or see http://www.ecco-org.eu (go to the section Eduction/Flims/Flims11)

Radiotherapy

June 21-25, 2009
The ESTRO teaching course ''Imaging for Target Volume Determination in Radiotherapy'' will be held in Tours, France.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Radiation oncology

June 25-27, 2009
The "MASCC/ISOO 2009 International Symposium of Supportive Care in Cancer: Multinational Association of Supportive Care of Cancer/International Society of Oral Oncology" will be held in Rome, Italy.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; see http://www/astro.org

Paediatric oncology

June 28-30, 2009
The ESTRO teaching course on paediatric oncology will be offered in Brussels, Belgium.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Prostate cancer

June 28-30, 2009
The ESTRO teaching course on brachytherapy for prostate cancer will take place in Istanbul, Turkey.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Radiotherapy

June 28 – July 2, 2009
The ESTRO teaching course on 2D-3D planning and imaging will be offered in St Petersburg, Russia.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Oncology

July 2-5, 2009
The Educational Cancer Convention (ECCLU) will be held in collaboration with European Society for Medical Oncology in Lugano, Switzerland.
E-mail www.cmelcher@eso.net; or see www.eso.net

Lung cancer

July 31 – August 4, 2009
The "13th World Conference on Lung Cancer" will be offered in San Francisco, USA.
Contact Conference Secretariat International Conference Services Ltd., Suite 2101 – 1177 West Hastings Street, Vancouver, BC Canada V6E 2K3; or call +1 604 681 2153; or e-mail wclc2009@meet-ics.com; or see http://www.2009worldlungcancer.org/

Radiotherapy

August 30 – September 3, 2009
The 19th Biennial ESTRO Conference" will be held in Maastricht, the Netherlands.
Phone +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Oncology

September 4-8, 2009
The "34th ESMO Congress" will take place in Vienna, Austria.
Contact ESMO Head Office, Congress Department, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland; or +41 (0)91 973 19 19; or fax +41 (0)91 973 19 18; or e-mail congress@esmo.org; or see http://www.esmo.org

Medical physics

September 7-12, 2009
The "World Congress 2009 – Medical Physics and Biomedical Engineering" will take place in Munich, Germany.
See http://www. wc2009.org/world-congress-2009

Brachytherapy

September 10-12, 2009
The ESTRO teaching course ''3D Image-Based Brachytherapy for Gynaecological Malignancies'' will be offered in Amsterdam, The Netherlands.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Radiation oncology

September 13-16, 2009
The "8th International Conference on Dose, Time and Fractionation in Radiation Oncology" will be held in Madison, Wisconsin, USA.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; see http://www/astro.org

Oncology

September 20-24, 2009
The "15th ECCO and 34th ESMO Multidisciplinary Congress" will be offered in Berlin, Germany.
See http://www.ecco-org.eu

Nuclear medicine

October 10-14, 2009
The "EANM'09 Annual Congress of the European Association of Nuclear Medicine" will take place in Barcelona, Spain.
Contact EANM Executive Secretariat and call +43 1 212 80 30; or fax +43 1 212 80 309; or e-mail office@eanm.org; or see http://www. eanm.org

Radiation oncology

October 11-16, 2009
The ESTRO teaching course Evidence Based Radiation Oncology: Methodological Basis and Clinical Application '' will be offered in Vienna, Austria.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Lung Cancer

October 15-17, 2009
The ESTRO multidisciplinary teaching course on lung cancer will be held in Prague, Czech Republic.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org or http://www.estro-education.org/courses/Pages/Prague2009.aspx

Radiobiology

October 18-23, 2009
The ESTRO teaching course on basic clinical radiobiology will be offered in Toledo, Spain.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Therapeutic radiology and oncology

November 1-5, 2009
The "American Society for Therapeutic Radiology and Oncology Annual Meeting ASTRO" will take place in Chicago, USA.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; or see http://www.astro.org

Radiotherapy

November 15-19, 2009
The ESTRO teaching course on IMRT and other conformal techniques in practice will take place in Gliwice, Poland.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

PET in radiation oncology

November 21-22, 2009
The ESTRO / EANM educational seminar on PET in radiation oncology will take place in Vienna, Austria.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

PET in radiation oncology

December 13-17, 2009
The ESTRO teaching course on image-guided radiotherapy in clinical practice will take place in Brussels, Belgium.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2775 93 40; or fax 32 2779 5494; or e-mail events@estro.org; or see http://www/estro-events.org

Head and neck cancer

February 25-27, 2010
The multidisciplinary symposium on head and neck cancer will be offered in Chandler, Arizona, USA.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; see http://www/astro.org

Clinical oncology

June 4-8, 2010
The American Society of Clinical Oncology Conference (ASCO 2010) will be offered in Chicago, USA.
E mail enews@asco.org; or see http://www/asco.org

Oncology

October 8-12, 2010
The "35th ESMO Congress" will take place in Milan, Italy.
Contact ESMO Head Office, Congress Department, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland; or call +41 (0)91 973 19 19; or fax +41 (0)91 973 19 18; or e-mail congress@esmo.org; or see http://www.esmo.org

Nuclear medicine

October 9-13, 2010
The "EANM'10 Annual Congress of the European Association of Nuclear Medicine" will take place in Vienna, Austria.
Contact EANM Executive Secretariat and call +43 1 212 80 30; or fax +43 1 212 80 309; or e-mail office@eanm.org; or see http://www. eanm.org

Therapeutic radiology and oncology

October 31 – November 4, 2010
The "American Society for Therapeutic Radiology and Oncology Annual Meeting ASTRO" will take place in San Diego, California, USA.
Contact ASTRO, 8280 Willow Oaks Corporate Dr., Suite 500, Fairfax, VA 22031; or call +1 703 502-1550; or see http://www.astro.org

Clinical oncology

June 3-7, 2011
The American Society of Clinical Oncology Conference (ASCO 2010) will be offered in Chicago, USA.
E mail enews@asco.org; or see http://www/asco.org

Lung cancer

July 3-7, 2011
The "14th World Conference on Lung Cancer" will be offered in Amsterdam, The Netherlands.
See http://www.iaslc.org

Oncology

September 23-27, 2011
The "16th ECCO and 36th ESMO Multidisciplinary Congress" will be offered in Stockholm, Sweden.
See http://www.ecco-org.eu

Nuclear medicine

October 15-19, 2011
The "EANM'11 Annual Congress of the European Association of Nuclear Medicine" will take place in Birmingham, United Kingdom.
Contact EANM Executive Secretariat and call +43 1 212 80 30; or fax +43 1 212 80 309; or e-mail office@ eanm.org; or see http://www. eanm.org

Oncology

September 27 – October 1, 2013
The "17th ECCO and 38th ESMO Multidisciplinary Congress" will be offered in Amsterdam, The Netherlands.
See http://www.ecco-org.eu

Lung cancer

2013
The "15th World Conference on Lung Cancer" will be offered in Sydney, Australia.
See http://www.iaslc.org

As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.

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dejavnost v onkologiji.

Dunajska 106
1000 Ljubljana

ŽR: 02033-0017879431

Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the first quarter of 2009

Dr. J. Cholewa Foundation for Cancer Research and Education continues to support the activities and advancement of oncology related sciences and is of opinion that excellent and unorthodox ideas must not be prevented to succeed for the simple lack of funding. It primarily supports cancer research and education activities in Slovenia, it continues to assess carefully the requests for research grants and scholarships submitted by Slovenian experts in oncology and other associated scientific activities, and helps putting resulting advances in cancer therapy in practice. It can thus be concluded that the final goal of the Foundation is to transmit the latest diagnostic and therapy methods and knowledge to everyday research and clinical environment in Slovenia. This activity is regarded as the most directly beneficial for the ever increasing number of patients with various types of cancer in Slovenia, since the incidence rates of many cancers have kept raising in the recent years in this country.

The "Dr. L. Cholewa Foundation for Cancer Research and Education« continues to support the regular publication of "Radiology and Oncology" international medical scientific journal, that is edited, published and printed in Ljubljana, Slovenia. This support emphasizes the need for the spread of information advances in experimental and clinical cancer research to professionals and interested individuals in public in Slovenia and elsewhere. "Radiology and Oncology" is an open access journal, available free of charge on its own website, thus allowing its users and readers to access without hindrance. The Foundation is therefore active in promoting cancer education in general and especially to increase its impact in general population and among scientists with a particular interest in cancer research.

The Foundation considers the support to publish the results from cancer research in Slovenia and from Slovenian authors in international scientific journals and other means of communication worldwide as one of its main activities. It is also important to know that results of cancer research, supported by the Foundation, have in many cases found its way to the practical application in hospital wards across Slovenia in a significantly easier manner in recent years than before. Careful assessment of requests and proposals for research grants and scholarships submitted by experts in oncology and other associated scientific activities forms an essential part of the Foundation practices, serving the goal of spreading advanced knowledge of therapy and education in cancer.

Tomaž Benulič, MD
Borut Štabuc, MD, PhD
Andrej Plesničar, MD, MS

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Dako (Danska):
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Corning (Amerika):
specialna laboratorijska plastika za aplikacijo v imunologiji, mikrobiologiji, virologiji, ipd., mehanske eno- in večkanalne pipete in nastavki

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MICRONIC

Micronic (Nizozemska):
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Integra Biosciens (Švica):
laboratorijska oprema za mikrobiologijo, biologijo celic, molekularno biologijo in biotehnologijo

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Implantech (Amerika):
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SpectrumDesigns MEDICAL (Amerika):
moški pektoralni vsadki

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Erbitux 5 mg/ml raztopina za infundiranje (skrajšana navodila za uporabo)

Cetuksimab je monoklonsko IgG_1 protitelo, usmerjeno proti receptorju za epidermalni rastni faktor (EGFR). **Terapevtske indikacije:** Zdravilo Erbitux je indicirano za zdravljenje bolnikov z metastatskim kolorektalnim rakom in nemutiranim tipom KRAS; v kombinaciji s kemoterapijo in kot samostojno zdravilo pri bolnikih, pri katerih zdravljenje z oksaliplatinom in irinotekanom ni bilo uspešno. Zdravilo Erbitux je v kombinaciji z radioterapijo indicirano za zdravljenje bolnikov z lokalno napredovalim rakom skvamoznih celic glave in vratu. **Odmerjanje in način uporabe:** Zdravilo Erbitux pri vseh indikacijah infundirajte enkrat na teden. Začetni odmerek je 400 mg cetuksimaba na m^2 telesne površine. Vsi naslednji tedenski odmerki so vsak po 250 mg/m^2. **Kontraindikacije:** Zdravilo Erbitux je kontraindicirano pri bolnikih z znano hudo preobčutljivostno reakcijo (3. ali 4. stopnje) na cetuksimab. **Posebna opozorila in previdnostni ukrepi:** Če pri bolniku nastopi blaga ali zmerna reakcija, povezana z infundiranjem, lahko zmanjšate hitrost infundiranja. Priporočljivo je, da ostane hitrost infundiranja na nižji vrednosti tudi pri vseh naslednjih infuzijah. Če se pri bolniku pojavi huda kožna reakcija (≥ 3. stopnje po kriterijih *US National Cancer Institute, Common Toxicity Criteria;* NCI-CTC), morate prekiniti terapijo s cetuksimabom. Z zdravljenjem smete nadaljevati le, če se je reakcija pomirila do 2. stopnje. Priporoča se določanje koncentracije elektrolitov v serumu pred zdravljenjem in periodično med zdravljenjem s cetuksimabom. Po potrebi se priporoča nadomeščanje elektrolitov. Posebna previdnost je potrebna pri oslabljenih bolnikih in pri tistih z obstoječo srčno-pljučno boleznijo. Neželeni učinki: Zelo pogosti (≥ 1/10): dispneja, blago do zmerno povečanje jetrnih encimov, kožne reakcije, blage ali zmerne reakcije povezane z infundiranjem, blag do zmeren mukozitis. Pogosti (≥ 1/100, < 1/10): konjunktivitis, hude reakcije povezane z infundiranjem. Pogostost ni znana: Opazili so progresivno zniževanje nivoja magnezija v serumu, ki pri nekaterih bolnikih povzroča hudo hipomagneziemijo. Glede na resnost so opazili tudi druge elektrolitske motnje, večinoma hipokalciemijo ali hipokaliemijo. **Posebna navodila za shranjevanje:** Shranjujte v hladilniku (2 °C - 8 °C). Ne zamrzujte**. Vrsta ovojnine in vsebina:** 1 viala po 20 ml ali 100 ml. Imetnik dovoljenja za promet: Merck KGaA, 64271 Darmstadt, Nemčija. Podrobne informacije o zdravilu so objavljene na spletni strani Evropske agencije za zdravila (EMEA) http://www.emea.europa.eu.

Dodatne informacije so vam na voljo pri: Merck d.o.o., Dunajska cesta 119, 1000 Ljubljana, tel.: 01 560 3810, faks: 01 560 3831, el. pošta: info@merck.si

www.oncology.merck.de

MERCK SERONO

Arimidex®
anastrozol

Posodobili smo slovar

Skrajšan povzetek glavnih značilnosti zdravila Arimidex® 1 mg filmsko obložene tablete

Sestava zdravila: Ena tableta vsebuje 1 mg anastrozola.
Indikacije: Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji. Adjuvantno zdravljenje zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji pri ženskah po menopavzi, ki so se dve do tri leta adjuvantno zdravile s tamoksifenom. Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana razen pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.
Odmerjanje in način uporabe: Odrasle (tudi starejše) bolnice: 1 tableta po 1 mg peroralno, enkrat na dan. Odmerka zdravila ni treba prilagajati pri bolnicah z blago ali zmerno ledvično odpovedjo ali blagim jetrnim odpovedovanjem. Pri zgodnjem raku je priporočljivo trajanje zdravljenja 5 let.
Glavni neželeni učinki: Zelo pogosti (≥ 10 %): navali vročine, običajno blagi do zmerni. Pogosti (≥ 1 % in < 10 %): astenija, bolečine/okorelost v sklepih, suhost vagine, razredčenje las, izpuščaji, slabost, diareja, glavobol (vsi običajno blagi do zmerni)
Posebna opozorila in previdnostni ukrepi: Uporabe Arimidexa ne priporočamo pri otrocih, ker njegova varnost in učinkovitost pri njih še nista raziskani. Menopavzo je potrebno biokemično določiti pri vseh bolnicah, kjer obstaja dvom o hormonskem statusu. Ni podatkov o varni uporabi Arimidexa pri bolnicah z zmerno ali hudo jetrno okvaro ali hujšo ledvično odpovedjo (očistek kreatinina manj kakor 20 ml/min (oziroma 0,33 ml/s)). Pri ženskah z osteoporozo ali pri ženskah s povečanim tveganjem za razvoj osteoporoze je treba določiti njihovo mineralno gostoto kosti z denzitometrijo, na primer s slikanjem DEXA na začetku zdravljenja, pozneje pa v rednih intervalih. Po potrebi je treba začeti z zdravljenjem ali preprečevanjem osteoporoze in to skrbno nadzorovati. Ni podatkov o uporabi anastrozola z analogi LHRH. Arimidex znižuje nivo estrogena v obtoku, zato lahko povzroči zmanjšanje mineralne kostne gostote. Trenutno ni na voljo ustreznih podatkov o učinku bifosfonatov na izgubo mineralne kostne gostote, povzročene z anastrozolom, ali njihovi koristi, če se uporabijo preventivno. Zdravilo vsebuje laktozo.
Kontraindikacije: Arimidex je kontraindiciran pri: ženskah pred menopavzo, nosečnicah in doječih materah, bolnicah s hujšo ledvično odpovedjo (očistek kreatinina manj kot 20 ml/min (oziroma 0,33 ml/s)), bolnicah z zmernim do hudim jetrnim obolenjem, bolnicah, ki imajo znano preobčutljivost za anastrozol ali za katerokoli pomožno snov. Zdravila, ki vsebujejo estrogen, ne smete dajati sočasno z Arimidexom, ker bi se njegovo farmakološko delovanje izničilo. Sočasno zdravljenje s tamoksifenom.
Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Klinične raziskave o interakcijah z antipirinom in cimetidinom kažejo, da pri sočasni uporabi Arimidexa in drugih zdravil klinično pomembne interakcije, posredovane s citokromom P450, niso verjetne. Pregled baze podatkov o varnosti v kliničnih preskušanjih pri bolnicah, ki so se zdravile z Arimidexom in sočasno jemale druga pogosto predpisana zdravila, ni pokazal klinično pomembnih interakcij.
Imetnik dovoljenja za promet: AstraZeneca UK Limited, 15 Stanhope Gate, London, W1K 1LN, Velika Britanija
Režim predpisovanja zdravila: Rp/Spec
Datum priprave informacije: april 2007

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.

Dodatne informacije in literatura so na voljo pri:
AstraZeneca UK Limited
Podružnica v Sloveniji
Verovškova ulica 55
1000 Ljubljana

in na spletnih straneh:
www.arimidex.net
www.bco.org
www.breastcancersource.com

AstraZeneca
ONKOLOGIJA

ARI 03/07 P

*adjuvant [ae´džuv*nt]*

1. *adjective* pomagljiv, koristen; *~ treatment with Arimidex:* Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji.

*advanced [*dva:nst]*

1. *adjective* napreden; zvišan (cene); to be ~ napredovati; ~ in years visoke starosti; *treatment of ~ breast cancer with Arimidex:* Zdravljenje napredovalega raka dojke pri ženskah po menopavzi. Učinkovitost pri bolnicah z negativnimi estrogenskimi receptorji ni bila dokazana razen pri tistih, ki so imele predhodno pozitiven klinični odgovor na tamoksifen.

switch [swič]

1. *transitive verb* udariti, bičati s šibo (z repom); šibati z, hitro mahati z; naglo pograbiti; railway ranžirati, zapeljati (usmeriti) (vlak) na drug tir; electrical vključiti, vklopiti; spremeniti (pogovor), obrniti drugam (tok misli); to ~ back to figuratively (v mislih) vrniti se na;

~ to Arimidex: Adjuvantno zdravljenje zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji pri ženskah po menopavzi, ki so se dve do tri leta adjuvantno zdravile s tamoksifenom.

Ime vse pove
Gemcitabin Lek
gemcitabin

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Gemcitabin Lek 200 mg in 1 g prašek za raztopino za infundiranje
Sestava: Vsaka viala vsebuje 200 mg ali 1000 mg gemcitabina (v obliki gemcitabinijevega klorida). Vsak ml zdravila vsebuje 40 mg gemcitabina po redčenju na 5 ml (Gemcitabine Lek 200 mg) ali 40 mg gemcitabina po redčenju na 25 ml (Gemcitabiln Lek 1 g). **Indikacije:** Zdravilo prve izbire za zdravljenje bolnikov z lokalno napredovalim ali metastazirajočim nedrobnoceličnim pljučnim rakom. Za zdravljenje lokalno napredovalega ali metastazirajočega adenokarcinoma trebušne slinavke. Za zdravljenje lokalno napredovalega ali metastazirajočega raka na mehurju v kombinaciji z drugimi citostatičnimi zdravili. V kombinaciji s paklitakselom za zdravljenje bolnikov z neoperabilnim, lokalno ponavljajočim se ali metastazirajočim rakom na dojki, pri katerih se je bolezen ponovno pojavila po adjuvantni/neoadjuvantni kemoterapiji, ki je morala vključevati antraciklin, razen če ni bil klinično kontraindiciran.
Odmerjanje in način uporabe: Zdravljenje mora začeti zdravnik, ki ima precej izkušenj z zdravljenjem s citotoksičnimi zdravili. *Nedrobnocelični pljučni rak pri odraslih: Kombinirana uporaba*: Pri tritedenskem načrtu gemcitabin v odmerku 1250 mg/m² v 30-minutni intravenski infuziji prvi in osmi dan vsakega 21-dnevnega ciklusa. Pri štiritedenskem načrtu gemcitabin v odmerku 1000 mg/m² v 30-minutni intravenski infuziji prvi, osmi in petnajsti dan vsakega 28-dnevnega ciklusa. Cisplatin v odmerkih med 75 in 100 mg/m², enkrat na vsake tri ali štiri tedne. *Uporaba enega samega zdravila:* Priporočeni odmerek gemcitabina znaša 1000 mg/m² v 30-minutni intravenski infuziji, ponavljajoče enkrat tedensko v obdobju treh tednov, čemur sledi en teden premora. Štiritedenski ciklus se nato ponovi. *Rak trebušne slinavke:* Priporočeni odmerek znaša 1000 mg/m² v 30-minutni intravenski infuziji, ponavljajoče enkrat tedensko v obdobju do sedem tednov, čemur sledi en teden premora. Naslednji ciklusi morajo biti sestavljeni iz injiciranj enkrat tedensko v obdobju treh zaporednih tednov izmed vsakih štirih tednov. *Rak na mehurju:* Priporočeni odmerek znaša 1000 mg/m² v 30-minutni infuziji. Odmerek je treba dati prvi, osmi in petnajsti dan vsakega 28-dnevnega ciklusa v kombinaciji s cisplatinom. Cisplatin se daje v priporočenem odmerku 70 mg/m² prvi dan po dajanju gemcitabina oziroma drugi dan vsakega 28-dnevnega ciklusa. Ta štiritedenski ciklus se zatem ponovi. *Rak na dojki:* Priporočljiva je uporaba gemcitabina v kombinaciji s paklitakselom, pri čemer se paklitaksel (v odmerku 175 mg/m²) uporabi prvi dan v tri ure trajajoči intravenski infuziji, čemur sledi gemcitabin (v odmerku 1250 mg/m²) v 30 do 60 minut trajajoči intravenski infuziji prvi in osmi dan vsakega 21-dnevnega ciklusa. Pred začetkom dajanja kombinacije gemcitabin + paklitaksel mora pri bolnikih absolutno število granulocitov znašati najmanj 1,5 (× 10⁹/l). *Preverjanja:* Pri bolnikih, ki prejemajo gemcitabin, je treba pred dajanjem vsakega odmerka preverjati število trombocitov, levkocitov in granulocitov. Če je potrebno, se odmerek gemcitabina ob prisotnosti hematološke toksičnosti lahko zmanjša ali se ga preneha uporabljati. Treba je izvajati redne klinične preglede in preverjati delovanje jeter in ledvic, da bi lahko zaznali nehematološke škodljive vplive.
Kontraindikacije: Preobčutljivost za gemcitabin ali katerokoli pomožno snov. Uporaba med dojenjem pri ženskah, ki otroke dojijo. Sočasna uporaba s cepivom proti rumeni mrzlici. Kombinacija gemcitabina s cisplatinom pri bolnikih s hudo ledvično okvaro.

Posebna opozorila in previdnostni ukrepi: Gemcitabin lahko kratkotrajno zavre delovanje kostnega mozga, kar se kaže v levkopeniji, trombocitopeniji in anemiji.
Gemcitabin je treba uporabljati previdno pri bolnikih z okvarjeno ledvično funkcijo. Z uporabo gemcitabina je treba prenehati ob prvem pojavu kakršnihkoli znakov mikroangiopatske hemolitične anemije, kot je na primer hitro padajoča raven hemoglobina s spremljajočo trombocitopenijo, povečanje koncentracije bilirubina in kreatinina v serumu, povečanje ravni sečninskega dušika v krvi ali LDL, kar lahko nakazuje razvoj hemolitičnega uremičnega sindroma. Odpoved ledvic je lahko tudi po prenehanju zdravljenja ireverzibilna in lahko je potrebna dializa. Ne glede na to, ali zdravilo uporablja moški ali ženska, je treba med zdravljenjem upoštevati ukrepe za preprečevanje nosečnosti.
Medsebojno delovanje z zdravili in druge oblike interakcij: Sočasno zdravljenje z obsevanjem (ki se izvaja obenem ali s časovnim presledkom ≤ 7 dni). Zaporedno zdravljenje z obsevanjem (ki se izvaja s časovnim presledkom > 7 dni). Gemcitabin deluje radiosenzitizirajoče. Zaradi povečanega tveganja za trombozo pri bolnikih z rakom je uporaba antikoagulacijskega zdravljenja pogosta. Velika razlika v koagulacijskem statusu med posamezniki v času bolezni in možnost medsebojnega delovanja oralnih antikoagulantov in kemoterapije zahteva bolj pogosto spremljanje INR-ja v primeru uporabe antikoagulantov. *Kontraindicirana sočasna uporaba*: cepivo proti rumeni mrzlici. *Nepriporočljiva sočasna uporaba:* živa, oslabljena cepiva (razen rumene mrzlice). *Sočasna uporaba, ki zahteva premislek:* ciklosporin, takrolimus.
Vpliv na sposobnost vožnje in upravljanja s stroji: Gemcitabin lahko povzroči blago do zmerno zaspanost. Bolnike je zato treba posvariti pred vožnjo ali upravljanjem s stroji, dokler se ne izkaže, da zdravilo nanje nima omenjenega vpliva.
Neželeni učinki: Na pogostnost in hudost neželenih učinkov vplivajo odmerek, hitrost infundiranja in časovni presledki med odmerki. *Zelo pogosti* (> 1/10): anemija, levkopenija, trombocitopenija, nevtropenija, dispneja, navzea, bruhanje, povečane vrednosti jetrnih transaminaz (AST in ALT) in alkalne fosfataze, alergijski kožni izpuščaj, ki ga pogosto spremlja srbenje; plešavost – običajno blaga, hematurija, proteinurija, edemi/periferni edemi, gripi podobni simptomi (povečana telesna temperatura, glavobol, bolečine v hrbtu, drgetanje, bolečine v mišicah, astenija, pomanjkanje teka, kašelj, rinitis, občutek slabosti, znojenje, motnje spanja). *Pogosti* (> 1/100 do < 1/10): febrilna nevtropenija, zaspanost, stomatitis in razjede v ustih, driska, zaprtje, povečana koncentracija bilirubina, povečana telesna temperatura, astenija. Neželeni učinki, zaradi katerih je treba odmerek omejiti, so zmanjšanja števila trombocitov, levkocitov in granulocitov.
Oprema: Škatla z eno vialo s praškom.
Način izdaje zdravila: H
Imetnik dovoljenja za promet: Lek farmacevtska družba d.d., Verovškova 57, 1526 Ljubljana, Slovenija.
Informacija pripravljena: julij 2008

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Temodal 20 mg, 100 mg, 140mg, 180 mg, 250 mg.

Sestava zdravila: Vsaka kapsula zdravila Temodal vsebuje 20 mg, 100 mg, 140 mg, 180 mg ali 250 mg temozolomida.

Terapevtske indikacije Temodal kapsule so indicirane za zdravljenje bolnikov z:

- za zdravljenje novo diagnosticiranega glioblastoma multiforme, sočasno z radioterapijo in kasneje kot monoterapija
- malignim gliomom, na primer multiformnim glioblastomom ali anaplastičnim astrocitomom, ki se po standardnem zdravljenju ponovi ali napreduje.

Odmerjanje in način uporabe Temodal smejo predpisati le zdravniki, ki imajo izkušnje z zdravljenjem možganskih tumorjev. **Odrasli bolniki z novo diagnosticiranim glioblastomom multiforme** Temodal se uporablja v kombinaciji z žariščno radioterapijo (faza sočasne terapije), temu pa sledi do 6 ciklov monoterapije z temozolomidom. **Faza sočasne terapije** Zdravilo Temodal naj bolnik jemlje peroralno v odmerku 75 mg/m^2 na dan 42 dni, sočasno z žariščno radioterapijo (60 Gy, danih v 30 delnih odmerkih). Odmerka ne boste zmanjševali, vendar se boste vsak teden odločili o morebitni odložitvi jemanja temozolomida ali njegovi ukinitvi na podlagi kriterijev hematološke in nehematološke toksičnosti. Zdravilo Temodal lahko bolnik jemlje ves čas 42-dnevnega obdobja sočasne terapije do 49 dni, če so izpolnjeni vsi od naslednjih pogojev: absolutno število nevtrofilcev ≥ 1,5 x 109/l, število trombocitov ≥ 100 x 109/l, skupni kriteriji toksičnosti (SKT) za nehematološko toksičnost ≤ 1. stopnje (z izjemo alopecije, slabosti in bruhanja). Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko. **Faza monoterapije** Štiri tedne po zaključku faze sočasnega zdravljenja z zdravilom Temodal in radioterapijo naj bolnik jemlje zdravilo Temodal do 6 ciklov monoterapije. V 1. ciklu (monoterapija) je odmerek zdravila 150 mg/m^2 enkrat na dan 5 dni, temu pa naj sledi 23 dni brez terapije. Na začetku 2. cikla odmerek povečajte na 200 mg/m^2, če je SKT za nehematološko toksičnost za 1. cikel stopnje ≤ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (AŠN) ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Če odmerka niste povečali v 2. ciklusu, ga v naslednjih ciklusih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m^2 na dan v prvih 5 dneh vsakega naslednjega ciklusa, razen če nastopi toksičnost. Med zdravljenjem morate pregledati celotno krvno sliko na 22. dan (21 dni po prvem odmerku zdravila Temodal). **Ponavljajoči se ali napredujoči maligni gliom Odrasli bolniki** Posamezen ciklus zdravljenja traja 28 dni. Bolniki, ki še niso bili zdravljeni s kemoterapijo, naj jemljejo Temodal peroralno v odmerku 200 mg/m^2 enkrat na dan prvih 5 dni, temu pa naj sledi 23-dnevni premor (skupaj 28 dni). Pri bolnikih, ki so že bili zdravljeni s kemoterapijo, je začetni odmerek 150 mg/m^2 enkrat na dan, v drugem ciklusu pa se poveča na 200 mg/m^2 enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov (glejte poglavje 4.4). **Pediatrični bolniki** Pri bolnikih starih 3 leta ali starejših, posamezen ciklus zdravljenja traja 28 dni. Temodal naj jemljejo peroralno v odmerku 200 mg/m^2 enkrat na dan prvih 5 dni, potem pa naj sledi 23-dnevni premor (skupaj 28 dni). Otroci, ki so že bili zdravljeni s kemoterapijo, naj prejmejo začetni odmerek 150 mg/m^2 enkrat na dan 5 dni, s povečanjem na 200 mg/m^2 enkrat na dan 5 dni v naslednjem ciklusu, če ni bilo hematoloških toksičnih učinkov (glejte poglavje 4.4). **Bolniki z motnjami v delovanju jeter ali ledvic** Pri bolnikih z blagimi ali zmernimi motnjami v delovanju jeter je farmakokinetika temozolomida podobna kot pri tistih z normalnim delovanjem jeter. Podatki o uporabi zdravila Temodal pri bolnikih s hudimi motnjami v delovanju jeter (razred III po Child-u) ali motnjami v delovanju ledvic niso na voljo. Na podlagi farmakokinetičnih lastnosti temozolomida obstaja majhna verjetnost, da bo pri bolnikih s hudimi motnjami v delovanju jeter ali ledvic potrebno zmanjšanje odmerka zdravila. Kljub temu je potrebna previdnost pri uporabi zdravila Temodal pri teh bolnikih. **Starejši bolniki:** Analiza farmakokinetike je pokazala, da starost ne vpliva na očistek temozolomida. Kljub temu je potrebna posebna previdnost pri uporabi zdravila Temodal pri starejših bolnikih. **Način uporabe** Temodal mora bolnik jemati na tešče. Temodal kapsule mora bolnik pogoltniti cele s kozarcem vode in jih ne sme odpirati ali žvečiti. Predpisani odmerek mora vzeti v obliki najmanjšega možnega števila kapsul. Pred jemanjem zdravila Temodal ali po njem lahko bolnik vzame antiemetik Če po zaužitju odmerka bruha, ne sme še isti dan vzeti drugega odmerka. **Kontraindikacije** Temodal je kontraindiciran pri bolnikih, ki imajo v anamnezi preobčutljivostne reakcije na sestavine zdravila ali na dakarbazin (DTIC). Temodal je kontraindiciran tudi pri bolnikih s hudo mielosupresijo. Temodal je kontraindiciran pri ženskah, ki so noseče ali dojijo. **Posebna opozorila in previdnostni ukrepi** Pilotno preskušanje podaljšane 42-dnevne sheme zdravljenja je pokazalo, da imajo bolniki, ki so sočasno prejemali zdravilo Temodal in radioterapijo, še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s Pneumocystis carinii (PCP). Profilaksa proti tovrstni pljučnici je torej potrebna pri vseh bolnikih, ki sočasno prejemajo zdravilo Temodal in radioterapijo v okviru 42-dnevne sheme zdravljenja (do največ 49 dni), ne glede na število limfocitov. Če nastopi limfopenija, mora bolnik nadaljevati s profilakso, dokler se limfopenija ne povrne na stopnjo ≤ 1. Antiemetična terapija: Z jemanjem zdravila Temodal sta zelo pogosto povezana slabost in bruhanje. **Laboratorijske vrednosti**: Pred jemanjem zdravila morata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC mora biti ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Na 22. dan (21 dni po prvem odmerku) ali v roku 48 ur od navedenega dne, morate pregledati celotno krvno sliko in jo nato spremljati vsak teden, dokler ni ANC nad 1,5 x 109/l in število trombocitov nad 100 x 109/l. Če med katerimkoli ciklusom ANC pade na < 1,0 x 109/l ali število trombocitov na < 50 x 109/l, morate odmerek zdravila v naslednjem ciklusu zmanjšati za eno odmerno stopnjo. Odmerne stopnje so 100 mg/m^2, 150 mg/m^2 in 200 mg/m^2. Najmanjši priporočeni odmerek je 100 mg/m^2. **Moški bolniki** Temozolomid lahko deluje genotoksično, zato morate moškim, ki se zdravijo z temozolomidom svetovati, da naj ne zaplodijo otroka še šest mesecev po zdravljenju. **Interakcije** Sočasna uporaba zdravila Temodal in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali monometiltriazenoimidazol karboksamida (MTIC). Jemanje zdravila Temodal s hrano je povzročilo 33 % zmanjšanje Cmax in 9 % zmanjšanje površino pod krivuljo (AUC). Ker ne moremo izključiti možnosti, da bi bila sprememba Cmax lahko klinično pomembna, naj bolniki jemljejo zdravilo Temodal brez hrane. Analiza populacijske farmakokinetike v preskušanjih druge faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka temozolomida. Sočasno jemanje z valprojsko kislino je bilo povezano z majhnim, a statistično značilnim zmanjšanjem očistka temozolomida. Uporaba zdravila Temodal v kombinaciji z drugimi mielosupresivnimi učinkovinami la hko poveča verjetnost mielosupresije. **Nosečnost** Študij na nosečih ženskah ni bilo. Predklinične študije na podganah in kuncih z odmerkom 150 mg/m^2 so pokazale teratogenost in/ali toksičnost za plod. Zato naj noseče ženske načeloma ne bi jemale zdravila Temodal. Če pa je uporaba v času nosečnosti nujna, morate bolnico opozoriti na možne nevarnosti zdravila za plod. Ženskam v rodni dobi svetujte, naj med zdravljenjem z zdravilom Temodal preprečijo zanositev. **Dojenje** Ni znano, ali se temozolomid izloča v materino mleko, zato ženske, ki dojijo ne smejo jemati zdravila Temodal. **Neželeni učinki** V kliničnih preskušanjih so bili najpogostnejši neželeni učinki, povezani z zdravljenjem, prebavne motnje, natančneje slabost (43 %) in bruhanje (36 %). Oba učinka sta bila ponavadi 1. ali 2. stopnje (od 0 do 5 epizod bruhanja v 24 urah) in sta prenehala sama, ali pa ju je bilo mogoče hitro obvladati s standardnim antiemetičnim zdravljenjem. Incidenca hude slabosti in bruhanja je bila 4 %. Laboratorijski izvidi: Trombocitopenija in. nevtropenija 3. in. 4. stopnje sta se pojavili pri 19 % in. 17 % bolnikov, zdravljenih zaradi malignega glioma. Zaradi njiju je bila potrebna hospitalizacija in/ali prekinitev zdravljenja z zdravilom Temodal pri 8 % in. 4 % bolnikov. Mielosupresija je bila predvidljiva (ponavadi se je pojavila v prvih nekaj ciklusih in je bila najizrazitejša med 21. in 28. dnem), okrevanje pa je bilo hitro, ponavadi v 1 do 2 tednih. Opazili niso nobenih dokazov kumulativne mielosupresije. Trombocitopenija lahko poveča tveganje za pojav krvavitev, nevtropenija ali levkopenija pa tveganje za okužbe. **Imetnik dovoljenja za promet** SP Europe 73, rue de Stalle B-1180 Bruxelles Belgija. **Način in režim izdaje** Zdravilo se izdaja samo na recept, uporablja pa se pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Datum priprave informacije** marec 2009.

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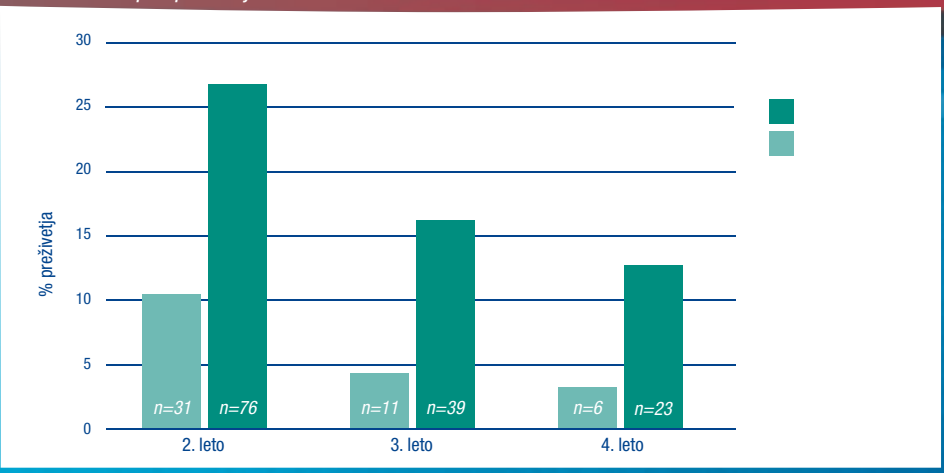

Literatura: 1 Stupp R, Mason WP, van den Bent MJ, s sod. RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GLIOBLASTOMA N Engl J Med.2005;352:987-996. 2 Mirmanoff RO et al; IS LONG-TERM SURVIVAL IN GLIOBLASTOMA POSSIBLE?; 49th annual meeting of the ASRO, Los Angeles, okt. 2007.

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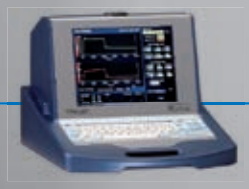
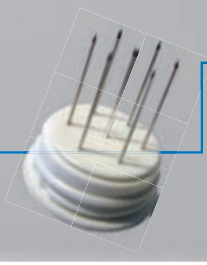
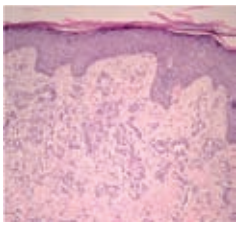
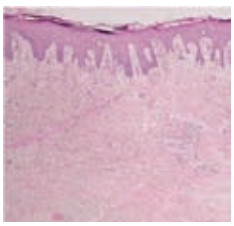




Before electrochemotherapy



60 days after electrochemotherapy



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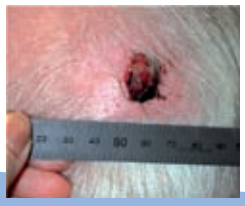
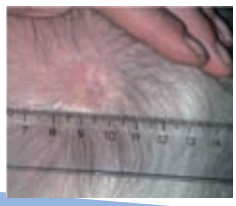
Before electrochemotherapy



10 weeks after electrochemotherapy



Gehl J, EJC Supplements, Volume 4, N° 11: 35-37, 2006

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Ime zdravila: Tarceva 25 mg/100 mg/150 mg filmsko obložene tablete

Kakovostna in količinska sestava: Ena filmsko obložena tableta vsebuje 25 mg, 100 mg ali
150 mg erlotiniba (v obliki erlotinibijevega klorida).

Terapevtske indikacije: Nedrobnocelični rak pljuč: Zdravilo Tarceva je indicirano za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč po neuspehu vsaj ene predhodne kemoterapije. Pri predpisovanju zdravila Tarceva je treba upoštevati dejavnike, povezane s podaljšanim preživetjem. Koristnega vpliva na podaljšanje preživetja ali drugih klinično pomembnih učinkov zdravljenja niso dokazali pri bolnikih z EGFR-negativnimi tumorji. Rak trebušne slinavke: Zdravilo Tarceva je v kombinaciji z gemcitabinom indicirano za zdravljenje bolnikov z metastatskim rakom trebušne slinavke. Pri predpisovanju zdravila Tarceva je treba upoštevati dejavnike, povezane s podaljšanim preživetjem. Koristnega vpliva na podaljšanje preživetja niso dokazali za bolnike z lokalno napredovalo boleznijo.

Odmerjanje in način uporabe: Zdravljenje z zdravilom Tarceva mora nadzorovati zdravnik z izkušnjami pri zdravljenju raka. Zdravilo Tarceva vzamemo najmanj eno uro pred zaužitjem hrane ali dve uri po tem. Kadar je potrebno odmerek prilagoditi, ga zmanjšujemo v korakih po 50 mg. Pri sočasnem jemanju substratov in modulatorjev CYP3A4 bo morda potrebna prilagoditev odmerka. Pri dajanju zdravila Tarceva bolnikom z jetrno okvaro je potrebna previdnost. Če se pojavijo hudi neželeni učinki pride v poštev zmanjšanje odmerka ali prekinitev zdravljenja z zdravilom Tarceva. Uporaba zdravila Tarceva pri bolnikih s hudo jetrno ali ledvično okvaro ter pri otrocih ni priporočljiva. Bolnikom kadilcem je treba svetovati, naj prenehajo kaditi, saj so plazemske koncentracije erlotiniba pri kadilcih manjše kot pri nekadilcih. Nedrobnocelični rak pljuč: Priporočeni dnevni odmerek zdravila Tarceva je 150 mg. Rak trebušne slinavke: Priporočeni dnevni odmerek zdravila Tarceva je 100 mg, v kombinaciji z gemcitabinom. Pri bolnikih, pri katerih se kožni izpuščaj v prvih 4 do 8 tednih zdravljenja ne pojavi, je treba ponovno pretehtati nadaljnje zdravljenje z zdravilom Tarceva.

Kontraindikacije: Huda preobčutljivost za erlotinib ali katero koli pomožno snov.

Posebna opozorila in previdnostni ukrepi: Močni induktorji CYP3A4 lahko zmanjšajo učinkovitost erlotiniba, močni zaviralci CYP3A4 pa lahko povečajo toksičnost. Sočasnemu zdravljenju s temi zdravili se je treba izogibati. Bolnikom, ki kadijo, je treba svetovati, naj prenehajo kaditi, saj so plazemske koncentracije erlotiniba pri kadilcih zmanjšane v primerjavi s plazemskimi koncentracijami pri nekadilcih. Verjetno je, da je velikost zmanjšanja klinično pomembna. Pri bolnikih, pri katerih se akutno pojavijo novi in/ali poslabšajo nepojasnjeni pljučni simptomi, kot so dispneja, kašelj in vročina, je zdravljenje z zdravilom Tarceva treba prekiniti, dokler ni znana diagnoza. Bolnike, ki se sočasno zdravijo z erlotinibom in gemcitabinom, je treba skrbno spremljati zaradi možnosti pojava toksičnosti, podobni intersticijski pljučni bolezni. Če je ugotovljena intersticijska pljučna bolezen, zdravilo Tarceva ukinemo in uvedemo ustrezno zdravljenje. Pri približno polovici bolnikov, ki so se zdravili z zdravilom Tarceva, se je pojavila driska. Zmerno do hudo drisko zdravimo z loperamidom. V nekaterih primerih bo morda potrebno zmanjšanje odmerka. V primeru hude ali dolgotrajne driske, navzeje, anoreksije ali bruhanja, povezanih z dehidracijo, je zdravljenje z zdravilom Tarceva treba prekiniti in dehidracijo ustrezno zdraviti. O hipokaliemiji in ledvični odpovedi so poročali redko. Posebno pri bolnikih z dejavniki tveganja (sočasno jemanje drugih zdravil, simptomi, bolezni ali drugi dejavniki, vključno z visoko starostjo) moramo, če je driska huda ali dolgotrajna oziroma vodi v dehidracijo, zdravljenje z zdravilom Tarceva prekiniti in bolnikom zagotoviti intenzivno intravensko rehidracijo. Dodatno je treba pri bolnikih s prisotnim tveganjem za razvoj dehidracije spremljati ledvično delovanje in serumske elektrolite, vključno s kalijem. Pri uporabi zdravila Tarceva so poročali o redkih primerih jetrne odpovedi. K njenemu nastanku je lahko pripomogla predhodno obstoječa jetrna bolezen ali sočasno jemanje hepatotoksičnih zdravil. Pri teh bolnikih je treba zato premisliti o rednem spremljanju jetrnega delovanja. Dajanje zdravila Tarceva je treba prekiniti, če so spremembe jetrnega delovanja hude. Tablete vsebujejo laktozo in jih ne smemo dajati bolnikom z redkimi dednimi stanji: intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Erlotinib se pri ljudeh presnavlja v jetrih z jetrnimi citokromi, primarno s CYP3A4 in v manjši meri s CYP1A2. Presnova erlotiniba zunaj jeter poteka s CYP3A4 v črevesju, CYP1A1 v pljučih in CYP1B1 v tumorskih tkivih. Z zdravilnimi učinkovinami, ki se presnavljajo s temi encimi, jih zavirajo ali pa so njihovi induktorji, lahko pride do interakcij. Erlotinib je srednje močan zaviralec CYP3A4 in CYP2C8, kot tudi močan zaviralec glukuronidacije z UGT1A1 *in vitro*. Pri kombinaciji ciprofloksacina ali močnega *zaviralca CYP1A2* (npr. fluvoksamina) z erlotinibom je potrebna previdnost. V primeru pojava neželenih dogodkov, povezanih z erlotinibom, lahko odmerek erlotiniba zmanjšamo. Predhodno ali sočasno zdravljenje z zdravilom Tarceva ni spremenilo očistka prototipov *substratov CYP3A4*, midazolama in eritromicina. Inhibicija glukoronidacije lahko povzroči interakcije z zdravili, ki so *substrati UGT1A1* in se izločajo samo po tej poti. Močni *zaviralci aktivnosti CYP3A4* zmanjšajo presnovo erlotiniba in zvečajo koncentracije erlotiniba v plazmi. Pri sočasnem jemanju erlotiniba in močnih zaviralcev CYP3A4 je zato potrebna previdnost. Če je treba, odmerek erlotiniba zmanjšamo, še posebno pri pojavu toksičnosti. Močni *spodbujevalci aktivnosti CYP3A4* zvečajo presnovo erlotiniba in pomembno zmanjšajo plazemske koncentracije erlotiniba. Sočasnemu dajanju zdravila Tarceva in induktorjev CYP3A4 se je treba izogibati. Pri bolnikih, ki potrebujejo sočasno zdravljenje z zdravilom Tarceva in močnim induktorjem CYP3A4 je treba premisliti o povečanju odmerka do 300 mg ob skrbnem spremljanju njihove varnosti. Zmanjšana izpostavljenost se lahko pojavi tudi z drugimi induktorji, kot so fenitoin, karbamazepin, barbiturati ali šentjanževka. Če te zdravilne učinkovine kombiniramo z erlotinibom, je potrebna previdnost. Kadar je mogoče, je treba razmisliti o drugih načinih zdravljenja, ki ne vključujejo močnega spodbujanja aktivnosti CYP3A4. Bolnikom, ki jemljejo varfarin ali druge *kumarinske antikoagulante*, je treba redno kontrolirati protrombinski čas ali INR. Sočasna uporaba *zaviralcev P-glikoproteina*, kot sta ciklosporin in verapamil, lahko vodi v spremenjeno porazdelitev in/ali spremenjeno izločanje erlotiniba. Za erlotinib je značilno zmanjšanje topnosti pri pH nad 5. *Zdravila, ki spremenijo pH v zgornjem delu prebavil*, lahko spremenijo topnost erlotiniba in posledično njegovo biološko uporabnost. Učinka antacidov na absorpcijo erlotiniba niso proučevali, vendar je ta lahko zmanjšana, kar vodi v nižje plazemske koncentracije. Kombinaciji erlotiniba in zaviralca protonske črpalke se je treba izogibati. Če menimo, da je uporaba antacidov med zdravljenjem z zdravilom Tarceva potrebna, jih je treba jemati najmanj 4 ure pred ali 2 uri po dnevnem odmerku zdravila Tarceva. če razmišljamo o uporabi ranitidina, moramo zdravili jemati ločeno: zdravilo Tarceva je treba vzeti najmanj 2 uri pred ali 10 ur po odmerku ranitidina. V študiji faze Ib ni bilo pomembnih učinkov *gemcitabina* na farmakokinetiko erlotiniba, prav tako ni bilo pomembnih učinkov erlotiniba na farmakokinetiko gemcitabina. Erlotinib poveča koncentracijo platine. Pomembnih učinkov *karboplatina* ali paklitaksela na farmakokinetiko erlotiniba ni bilo. *Kapecitabin* lahko poveča koncentracijo erlotiniba. Pomembnih učinkov erlotiniba na farmakokinetiko kapecitabina ni bilo.

Neželeni učinki: *Zelo pogosti neželeni učinki* so kožni izpuščaj in driska, kot tudi utrujenost, anoreksija, dispneja, kašelj, okužba, navzeja, bruhanje, stomatitis, bolečina v trebuhu, pruritus, suha koža, suhi keratokonjunktivitis, konjunktivitis, zmanjšanje telesne mase, depresija, glavobol, nevropatija, dispepsija, flatulenca, alopecija, okorelost, pireksija. *Pogosti neželeni učinki* so gastrointestinalne krvavitve, krvavitev iz nosu, nenormalnosti testov jetrne funkcije, keratitis, zanohtnica. *Redko* so poročali o jetrni odpovedi. *Občasno* pa o poraščenosti moškega tipa pri ženskah, spremembah trepalnic/obrvi, krhkih nohtih, odstopanju nohtov od kože, resni intersticijski pljučni bolezni, vključno s smrtnimi primeri.

Režim izdaje zdravila: H/Rp.

Imetnik dovoljenja za promet: Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, Velika Britanija.

Verzija: 1.0/09.

Informacija pripravljena: marec 2009.

DODATNE INFORMACIJE SO NA VOLJO PRI:
Roche farmacevtska družba d.o.o.
Vodovodna cesta 109, 1000 Ljubljana.
Povzetek glavnih značilnosti zdravila
je dosegljiv na www.roche.si.

Roche

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[1] Povzetek glavnih značilnosti zdravila TARCEVA, www.emea.europa.eu

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Viri: 1. Spremembe in dopolnitve Pravil obveznega zdravstvenega zavarovanja (Ur. l. RS 33/2008); 2. Okrožnica ZZZS - MTP št. 14 (0072-11/2008-DI/1 z dne 17.4.2008); www.zzzs.si

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Illustrations and tables must be numbered and referred to in the text, with appropriate location indicated in the text margin. Illustrations must be labelled on the back with the author's name, figure number and orientation, and should be accompanied by a descriptive legend on a separate page. Line drawings should be supplied in a form suitable for high-quality reproduction. Photographs should be glossy prints of high quality with as much contrast as the subject allows. They should be cropped as close as possible to the area of interest. In photographs mask the identities of the patients. Tables should be typed double spaced, with descriptive title and, if appropriate, units of numerical measurements included in column heading.

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Dent RAG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.

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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BISTVENE INFORMACIJE IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

AROMASIN® 25 mg obložene tablete

Sestava in oblika zdravila: obložena tableta vsebuje 25 mg eksemestana. **Indikacije:** Adjuvantno zdravljenje žensk po menopavzi, ki imajo invazivnega zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji in so se uvodoma vsaj 2 do 3 leta zdravile s tamoksifenom. Zdravljenje napredovalega raka dojke pri ženskah z naravno ali umetno povzročeno menopavzo, pri katerih je bolezen napredovala po antiestrogenskem zdravljenju. Učinkovitost še ni bila dokazana pri bolnicah, pri katerih tumorske celice nimajo estrogenskih receptorjev. **Odmerjanje in način uporabe:** 25 mg enkrat na dan, najbolje po jedi. Pri bolnicah z zgodnjim rakom dojke je treba zdravljenje nadaljevati do dopolnjenega petega leta adjuvantnega hormonskega zdravljenja oz. do recidiva tumorja. Pri bolnicah z napredovalim rakom dojke je treba zdravljenje nadaljevati, dokler ni razvidno napredovanje tumorja. **Kontraindikacije:** znana preobčutljivost na učinkovino zdravila ali na katero od pomožnih snovi, ženske pred menopavzo, nosečnice in doječe matere. **Posebna opozorila in previdnostni ukrepi:** predmenopavzni endokrini status, jetrna ali ledvična okvara, bolniki z redko dedno intoleranco za fruktozo, malabsorpcijo glukoze/galaktoze ali pomanjkanjem saharoza-izomaltaze. Lahko povzroči alergijske reakcije ali zmanjšanje mineralne gostote kosti ter večjo pogostnost zlomov. Ženskam z osteoporozo ali tveganjem zanjo je treba na začetku zdravljenja izmeriti mineralno kostno gostoto s kostno denzitometrijo. Čeprav še ni dovolj podatkov, kako učinkujejo zdravila za zdravljenje zmanjšane mineralne kostne gostote, ki jo povzroča Aromasin, je treba pri bolnicah s tveganjem uvesti zdravljenje ali profilakso osteoporoze ter bolnice natančno spremljati. **Medsebojno delovanje z drugimi zdravili:** Sočasna uporaba zdravil – npr. rifampicina, antiepileptikov (npr. fenitoina ali karbamazepina) ali zdravil rastlinskega izvora s šentjaževko – ki inducirajo CYP 3A4, lahko zmanjša učinkovitost Aromasina. Uporabljati ga je treba previdno z zdravili, ki se presnavljajo s pomočjo CYP 3A4 in ki imajo ozek terapevtski interval. Kliničnih izkušenj s sočasno uporabo zdravila Aromasin in drugih zdravil proti raku ni. Ne sme se jemati sočasno z zdravili, ki vsebujejo estrogen, saj bi ta izničila njegovo farmakološko delovanje. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Po uporabi zdravila je lahko psihofizična sposobnost za upravljanje s stroji ali vožnjo avtomobila zmanjšana. **Neželeni učinki:** neželeni učinki so bili v študijah, v katerih so uporabljali standardni odmerek 25 mg, ponavadi blagi do zmerni. *Zelo pogosti (> 10 %):* vročinski oblivi, bolečine v sklepih, mišicah in kosteh, utrujenost, navzea, nespečnost, glavobol, močnejše znojenje, ginekološke motnje. **Način in režim izdajanja:** 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:** Pfizer Luksembourg SARL, 283, route d'Arlon, L-8011 Strassen, Luksemburg. **Datum zadnje revizije besedila:** 11.4.2008
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Pfizer

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PFIZER, Podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Letališka 3c, 1000 Ljubljana, SLOVENIJA

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