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ALIMTA®
pemetreksed

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

Edina histološko usmerjena citostatična terapija

ALIMTA/cisplatin:
Zdravljenje prvega reda pri bolnikih z nedrobnoceličnim pljučnim karcinomom, ki nimajo pretežno luskaste histologije

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

*vs. Gemcitabine/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). Po pripravi vsebuje vsaka viala 25 mg/ml pemetrekseda. Pomožne snovi: Vsaka viala vsebuje približno 11 mg natrija. Manitol, klorovodikova kislina, natrijev hidroksid. ALIMTA 500 mg: vsaka viala vsebuje 500 mg pemetrekseda (v obliki dinatrijevega pemetrekseda). Po pripravi vsebuje vsaka viala 25 mg/ml pemetrekseda. Pomožne snovi: Vsaka viala vsebuje približno 54 mg natrija. 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 celične histologije. ALIMTA je indicirana kot monoterapija za zdravljenje lokalno napredovalega ali metastatskega nedrobnoceličnega pljučnega karcinoma, ki nima pretežno luskaste celične histologije pri bolnikih, pri katerih bolezen ni napredovala neposredno po kemoterapiji na osnovi platine. Zdravljenje prvega izbora naj bo platinasta dubleta z gemcitabinom, paklitakselom ali docetakselom. ALIMTA je indicirana kot monoterapija za zdravljenje drugega izbora bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom, ki nima pretežno luskaste celične 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 antiemetično zdravljenje, pred in/ali po prejemanju cisplatina jih moramo tudi ustrezno hidrirati. ALIMTA kot samostojno zdravilo 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. Dojenje. 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 zaploditev otroka v času zdravljenja in še 6 mesecev zatem. Priporočamo ukrepe prosti 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. Zdravilo Alimta 500 mg vsebuje približno 54 mg natrija na vialo. Pomembno za bolnike, ki so na dieti z nadzorovanim vnosom natrija. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno dajanje nefrotoksičnih 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 perioralnimi antikoagulacijskimi učinkovinami ter kemoterapijo proti raku zahtevata povečano pogostnost spremljanja INR. **Kontraindicirana sočasna uporaba:** Cepivo proti rumeni mrzlici: tveganje za smrtno generalizirano 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 pogosti:* znižani nevtrofili/granulociti, znižani levkociti, znižan hemoglobin, znižani trombociti, nevropatija-senzorična, diareja, bruhanje, stomatitis/faringitis, slabost, anoreksija, zaprtje, izpuščaj, alopecija, povišan kreatinin, znižan očistek kreatinina, utrujenost. *Pogosti:* dehidracija, motnje okusa, konjuktivitis, dispepsija. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA monoterapija, zdravljenje 2. izbora. *Zelo pogosti:* znižan nevtrofili/granulociti, znižani levkociti, znižan hemoglobin, diareja, bruhanje, stomatitis/faringitis, slabost, anoreksija, izpuščaj/luščenje, utrujenost. *Pogosti:* znižani trombociti, zaprtje, povišanje SGPT (ALT), povišanje SGOT (AST), srbenje, alopecija, povišana telesna temperatura. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA v kombinaciji s cisplatinom, zdravljenje 1. izbora. *Zelo pogosti:* znižan hemoglobin, znižani nevtrofili/granulociti, znižani levkociti, znižani trombociti, slabost, bruhanje, anoreksija, zaprtje, stomatitis/faringitis, diareja brez kolostomije, alopecija, izpuščaj/luščenje, povišan kreatinin. *Pogosti:* nevropatija-senzorična, motnje okusa, dispepsija/zgaga. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA monoterapija, vzdrževalno zdravljenje: *Zelo pogosti:* znižan hemoglobin, slabost, anoreksija, utrujenost, izpuščaj/luščenje, utrujenost. *Pogosti:* infekcija, znižani levkociti, znižani nevtrofili, nevropatija-senzorična, bruhanje, mukozitis/stomatitis, diareja, povišanje ALT (SGPT), povišanje AST (SGOT). 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 intersticijske pljučnice z respiratorno insuficience, primerih edema in o ezofagitisu/radiacijskem ezofagitisu. 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 21.09.2009. **Način izdaje zdravila:** H
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review

Post-treatment surveillance in colorectal cancer

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Background. Though the post treatment surveillance of patients with colorectal cancer (CRC) treated with curative intent is common practice, its value is controversial. In the absence of conclusive clinical data, various modalities for the routine follow-up of patients with CRC have been proposed. In practice, the guidelines across countries and regions differ and are influenced by different health care policies, resource availability and doubts about effectiveness of follow-up.

Conclusions. The results of metaanalyses of available clinical trials demonstrated a survival benefit of intensified monitoring, but the questions regarding the optimal frequency of visits and the examinations to be performed remain unanswered. Furthermore, intensive monitoring of CRC survivors may be difficult to be administrated, causes discomfort and morbidity to the patient and can have serious cost-implications to the healthcare system. However, as it seems from available data, a comprehensive surveillance program does not affect the quality of patients' life. Ongoing large prospective multi-institutional randomised trials might elucidate some of the crucial questions and existing dilemmas to establish adequate surveillance strategy for CRC patients.

Key words: surveillance; colorectal cancer

Introduction

Colorectal cancer (CRC) is a significant public health problem. In Slovenia, CRC is the second most frequently diagnosed cancer in both men and women and the second leading cause of cancer death, with estimated 1,284 new cases and 682 related deaths in 2006.[1] Five year relative survival in 2005 was 57.7% for colon cancer and 45.4% for rectal cancer, increasing by 16.2% and 11.4%, respectively, from 1991.[2] Over the last two decades, CRC research has lead to better understanding of disease behaviour, resulting in more efficient treatments and higher prevalence of cancer survivors. In spite of radical treatment, approximately 30-50% of patients will develop recurrent disease of whom only 5–30% would be considered eligible for further surgery; of those only 3-5% will be actually cured.[3,4] In addition, the reported rates of second primary tumours in CRC patients are ranging from 5% to 10%.[5-10] Furthermore, long-term analyses of Scandinavian trials have shown an increased risk of second cancers in the patients treated with preoperative radiotherapy for rectal cancer in organs within or adjacent to the irradiated volume.[11]

The main aim of post-treatment surveillance after potentially curative treatment of CRC is to improve survival through early detection of polyps and new primaries or recurrent tumours when efficient treatment is possible.[12-15] Secondary goals are to assess the efficacy of initial treatment, management of long-term post-treatment complications, to offer comprehensive psychologic support and support in disease prevention.[16]

Studies of CRC follow-up strategies

To define the value of varying levels of follow-up intensity in surveillance programs among CRC survivors, six randomized controlled trials were conducted (Table 1).[17-22] Two of them have showed a survival benefit from more intensive follow-up.[21,22] There was a great variability between the

TABLE 1. Studies comparing intensive with less intensive follow-up

Studies	Year	No	CEA testing	Liver imaging	5-y OS IFU (less IFU)	P value
Makela17	1995	106	Yes	Yes	59 (54)	0.26
Ohlsson18	1995	107	Yes	No	75 (67)	0.50
Kjeldsen19	1997	597	No	No	68 (70)	0.48
Schoemaler20	1998	325	No	Yes	76 (70)	0.20
Pietra21	1998	207	Yes	Yes	73 (58)	0.02
Secco22	2002	358	Yes	Yes	62 (43)	<0.05

Abbreviations: No = number of patients; OS = overall survival; IFU = intensive follow-up

studies in defining the follow-up. For example, the kind of follow-up that was considered as "intensive" in the study by Makela *et al.*[17], was assessed by Shoemaker *et al.*[20] as "less intensive". In some of the studies, the sample size was not sufficient to detect survival differences with different surveillance strategies, and some of the studies included patients with stage I disease.

Therefore, some meta-analysis were performed as a systematic approach to identification and abstraction of critical information from different randomised, controlled trials.[23] Two meta-analyses of five randomised trials identified a survival advantage for the patients followed more intensely as significantly higher incidence of asymptomatic local or systemic recurrence was recognized among the patients monitored closely and, consequentially, reoperation for cure was more frequent in this group.[24,25] These results were confirmed by another, recently published meta-analysis including six randomised trials on this topic with a significant improvement in survival favouring more intense follow-up (Relative Risk Ratio 0.80; 95%CI, 0.70 to 0.91; p = 0.0008). A significant improvement in survival was observed only those trials which included CEA testing and/or liver imaging.[26] Another two meta-analyses (on randomised and nonrandomised trials) concluded that intensive follow-up programmes can improve survival[27,28], and should be »individualised« according to a person's characteristics.[27]

In an attempt to rationalize CRC follow-up, three prospective multi-institutional randomised trials comparing more intensive with less intensive monitoring are being carried out at the moment: the FACS trial in United Kingdom, the FFCD trial in France and the GILDA trial in Italy.[29] The GILDA follow-up schemes are presented in Table 2. The results of these trials are pending.

Potential limitations of follow-up

Few considerations have to be taken into account when promoting surveillance and there are some limitations to this approach.

First, there is a small risk of adverse events associated with colonoscopy itself or with polipectomy during the follow-up. Only one of the prospective randomised follow-up studies reported these data: two perforations and two gastrointestinal haemorrhages from a total of 731 colonoscopies.[20]

Secondly, frequent visits to physician might be inconvenient to the patients and even harmful due to unnecessary exposition to radiation.[30] Fear of recurrence or unnecessary stress resulting from false positives results may also have a negative impact on the quality of their lives. False positive results are on average 16 times (0.2-200) more common than true positive results.[31] On the other hand, reassuring effect of normal test results and psychological support from physician might be beneficial. The data about the effect of follow-up on patients' health-related quality of life (HRQL) are limited and conflicting. While Stiggelbout *et al*. and Wattchow *et al*. indicated that HRQL was not improved through follow-up visits, Kjeldsen *et al*. demonstrated a small but significant increase in HRQL with a more intensive follow up.[32-34] However, Stiggelbout *et al*. emphasized that most patients would prefer regular contacts even if they showed no benefit in terms of earlier detection of recurrence.[32]

The third factor to be taken into consideration when promoting surveillance is high cost of such program. A wide variety of follow-up schemes are associated with large differences in costs. Few studies focused on this issue. Virgo *et al*. reported a 28-fold difference in costs between minimal and

TABLE 2. GILDA trial for rectal cancer follow-up

	Months from randomisation										
	4	8	12	16	20	24	30	36	42	48	60
Less intensive											
Office visit	+	+	+	+	+	+	+	+	+	+	+
CEA	+	+	+	+	+	+	+	+	+	+	+
Proctoscopy	+										
Colonoscopy			+							+	
Chest X-ray			+								
Liver ultrasound		+		+							
More intensive											
Office visit	+	+	+	+	+	+	+	+	+	+	+
Blood tests	+	+	+	+	+	+	+	+	+	+	+
Proctoscopy	+	+									
Colonoscopy			+			+		+		+	+
Chest X-ray			+			+		+		+	+
Liver ultrasound	+	+	+	+		+		+		+	+
Abdominal-pelvic CT	+		+			+				+	

Abbreviations: blood tests include complete blood count, liver tests, tumour markers CEA and Ca 19-9.

most extensive 5-year follow-up in USA, ranging from US$ 910 to US$ 26.717.[35] Audisio *et al*. calculated the 5-year follow-up costs in Italy as follows: US$ 3.800 per patient; US$ 13.580 for each recurrence; US$ 59.841 for every recurrence treated for cure and US$ 13.6779 for each cured patient; the difference in costs between minimal and aggressive 5-year follow-up protocol was US$ 4.800 per patient. Authors recommended that the programmes should be tailored to the stage and site of primary cancer in order to reduce costs[36] and that controlled economic studies are required.[37] The cost-effectiveness analysis of five randomized trials showed that the cost for the intensive follow-up resulted in a net extra cost of US$ 4.214–4.299 per patient compared with the less intensive follow-up arm. Each life year saved through the intensive follow-up was calculated to cost between US$ 5.230–5.783.[24]

When resectability of recurrences was considered, a cost minimization analysis performed by Rodrigues *et al*. demonstrated that the cost per resectable tumour recurrence was lower in the intensively followed group.[38] This is a logical conclusion despite the fact that the overall cost of intensive follow up was higher in the intensive strategy group than in less intensive one.

Other authors pointed to the high cost of follow-up suggesting that it should be transferred to the primary care setting. The arguments were that the specialist care is more intense and that specialists tend to propose more expensive follow-up strategies.[39]

The question remains, who should carry out the follow-up visits. With increasing numbers of CRC survivors, primary care physicians (PCPs) are more and more engaged in CRC follow-up programs.[40-42] The data from the literature regarding the utility of general versus specialist care in CRC survivors are sparse. In a study by Nissen *et al*., PCPs reported dissatisfaction with this transfer of care for survivors; they also felt uncertain about the appropriate frequency and duration of surveillance testing for cancer recurrence.[43] Moreover, in a recently published study by Snyder *et al*., the authors reported a decreased intensity of cancer-related screening program as oncologists were becoming less involved in survivor care. The survivors followed up by both a PCP and an oncologist were most likely to receive both noncancer-related recommended care and cancer surveillance.[42] The authors concluded that a shared model of survivorship care should be developed with a clear and detailed description of roles of both sides, PCP's and oncologist's, to gain maximal coordination and efficacy.[44] On the other hand, some data suggest that the survivors followed up by PCP only did not perceive lower qua-

TABLE 3. Follow-up guidelines of main professional societies

Modality	ASCO47	NCCN48,49	ESMO50,51
History, physical exam	Every 3-6 m for 3 y, then every 6 m up to 5 y	Every 3-6 m for 2 y, then every 6 m up to 5 y	every 3-6 m for 3 y, then every 6-12 m for 2 y (colon) every 6 m for 2 y (rectal cancer)
Colonoscopy	at 3y, every 5y thereafter	At 1y, then at 3y, every 5y thereafter	After 1y, then every 3y (colon) every 5y (rectal cancer)
Flexible proctoscopy (rectal cancer)	every 6m for 5y (for not irradiated patients)	every 6m for 5y (for patients with LAR)	every 6 m for 2 years
Blood tests	not recommended	not recommended	not recommended
CEA	every 3-6m for 3y (stage II and III)	every 3-6m for 2y, then every 6m up to 5y (staged as T2 or greater)	if initially elevated: every 3-6m for 3y, then every 6-12m for 2y (colon) not recommended (rectal cancer)
Chest x-rays	not recommended	not covered	not recommended
US abdomen	not covered	not covered	not recommended
CT thorax and CT abdomen	annually for 3y for pts with high risk of recurrence	annually for 3-5y for stage II and III	Every 6m for 3y for pts with high risk of recurrence (colon) Not recommended (rectal cancer)
Pelvic CT (rectal cancer)	negative prognostic features, especially for not irradiated pts (no frequency)	Not covered	not recommended

Abbreviations: m=months; y=years; ASCO=American Society Clinical Oncology; NCCN=National Comprehensive Cancer Network; ESMO=European Society Medical Oncology

lity of care[40], which was also confirmed by others mentioning that no difference was recorded in the rate of recurrence and death as well as time to detection of recurrence in comparison to the patients followed by a surgeon or PCP.[45]

Finally, with respect to cost and time consumption of follow-up, it seems reasonable that the surveillance of patients for whom additional therapeutic options when recurrence occurs are available[4,46], should be more intense. Furthermore, particular attention was paid to determine the subgroups of CRC patients which might benefit the most from follow-up with regard to tumour site or stage. The results of a prospective randomized trial on 259 CRC survivors conducted by Rodrigues-Moranta *et al*. indicated that the patients with stage II tumours or lesions in the rectum had higher overall survival when followed more intensively than those on less intensive follow-up program. No difference was found between the patients with stage III lesions or lesions located in colon.[38]

Current recommendations and adherence to them by physicians

Several guidelines have been published on the surveillance of CRC survivors. Follow-up program is recommended by all leading professional societies, *e.g*. the American Society of Clinical Oncology (ASCO)[47], National Comprehensive Cancer Network (NCCN)[48,49] and European Society Medical Oncology (ESMO).[50,51] Surveillance protocols include regular outpatient's visits followed by physical examination, CEA monitoring, radiological and endoscopic examinations. It must be stressed that none of diagnostic procedures by itself is sensitive or specific enough to detect the recurrence at early, treatable stage; so, the guidelines recommend different packages of tests.

Although there are differences in frequency, intensity and combinations of investigations as proposed by various programs, some parts of recommendations are similar (Table 3). Monitoring is more intense during the first two to three years after radical treatment, as most of the recurrences

occur within this period of time. There is a debate when to stop performing individual tests or monitoring the patients as they are an increased lifetime risk of developing recurrent disease or new primary CRC. The guidelines recommend continued, albeit less frequent visits during 3-5 years after therapy. Although local recurrences after adjuvant therapy are less common, irradiated rectal cancer patients may experience late relaps.[52,53] Many experts believe that follow-up beyond five years is necessary for such patients.[54]

While recommendations concerning colonoscopy in high risk patients are consistent, there is a great variability in the standards of other tests. In ESMO guidelines the routine clinical, laboratory and radiological examinations are not indicated in rectal cancer patients at all. Furthermore, pelvic CT scanning for rectal cancer is recommended only in ASCO guidelines (Table 3).

Due to aggressive therapy, CRC survivors can exhibit late *sequel* of treatment[54-59], most common being impaired bowel, voiding, sexual malfunctioning and quality of life impairment, bone fractures after pelvic radiation, oxaliplatin-induced neuropathy and *psychosocial distress*. Among the three guidelines mentioned only the NCCN ones describe potential late effects of treatment; unfortunately, they include only little information on how to manage the symptoms.

The consequence of lacking uniform guidelines is that the heterogeneity among physicians regarding the use of follow-up tests is serious. For example, a postal survey of all the active members of the American Society of Colon and Rectal Surgeons (ASCRS) undertaken in 1994 found that only 50% of surgeons who returned the questionnaire adhere to official recommendations.[60] Twelve years later, Giordano *et al*. reported that only 30% of surgeons followed any guidelines. Of these, only 20% stuck to the national guidelines and 80% followed local recommendations.[61]

Disparities in follow-up care are also observed when patient's race and age are taken into account. The report from Rolnick *et al*. highlighted that one of the reasons for poorer survival of black CRC patients in comparison with white patients might be that they have less follow-up surveillances.[62] A study conducted by Cooper *et al*. in 9.426 patients aged over 65 revealed that less than half of older CRC patients in the US during post-therapy period receive recommended screening for recurrence, indicating that the physician's preferences may influence the choice of testing.[63]

Conclusions

Follow-up of CRC survivors is a common practice. Intensive surveillance enhances the probability of diagnosing precancerous lesions, recurrences or new primaries at early stage when the existing treatment options could be used with curative intent. Consequentially, comprehensive surveillance program improves the survival and at the same time – as it seems from available data, does not affect the quality of patients' life. On the other hand, the increased costs and time consumption of intensive surveillance limit its utility. Due to limited, and to some extent conflicting data, there are no uniform guidelines for the CRC survivors regarding the frequency of visits and tests to be performed at each visit. Ongoing large prospective multi-institutional randomised trials might elucidate some of the crucial questions and existing dilemmas to establish an adequate surveillance strategy for CRC patients.

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review

Fluorescence imaging agents in cancerology

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Background. One of the major challenges in cancer therapy is to improve early detection and prevention using novel targeted cancer diagnostics. Detection requests specific recognition. Tumor markers have to be ideally present on the surface of cancer cells. Their targeting with ligands coupled to imaging agents make them visible/detectable.
Conclusions. Fluorescence imaging is a newly emerging technology which is becoming a complementary medical method for cancer diagnosis. It allows detection with a high spatio-temporal resolution of tumor markers in small animals and in clinical studies. In this review, we focus on the recent outcome of basic studies in the design of new approaches (probes and devices) used to detect tumor cells by fluorescence imaging.

Keywords: Photonic imaging; fluorescence; cancerology; apramers; smart probes

State of the art

Specific visualization of carcinogenesis or established tumor cells offers opportunities to guide surgery and monitor the response to therapy. In the clinic, radio-imaging uses contrast agents Indium-111 and Technetium-99 coupled to antibodies to target prostate[1,2], colorectal[3], ovarian[4] or small-cell lung cancers.[5] These radioelement-based technologies are powerful tools for the detection and therapy of cancers but they cannot be used during surgery. Fluorescence imaging is more user-friendly and provides on-line information. Therefore, fluorescence imaging agents which allow fast detection with a high spatio-temporal resolution can increase detection of the edge of the primary tumor, the presence of metastasis and therefore help tissue resection by the surgeon.

Fluorescence imaging

Why the NIR (near infra red) light?

In tissue fluorescence imaging, it is necessary to take into account five important parameters: reflection, absorption, refraction, background autofluorescence and distribution of photons emitted by the fluorochrome targeted to tissues. Skin is an obstacle because the emitted light is reflected by this barrier and this reflection brings a loss in the penetration of the excitation light.

In tissue, different chromophores in biomolecules strongly absorb the incident (or emitted) light. This is a major limit for the near UV and visible part of the spectrum. Light absorption by hemoglobin is a problem in the visible range (from 400 to 670 nm). Indeed, the absorption coefficient (cm^{-1}) decreases when the wavelength increases. Absorption due to the chromophores in biomolecules is very strong below 460 nm and remains important up to 580 nm. Thus, only a weak penetration in the tissue can be obtained. The same problem is of course present if emission is in the same wavelength range as absorption. A deeper penetration is obtained when working in the near infrared (NIR) part of the spectrum between 600 and 1000 nm (Figure 1).[6] The upper limit in the wavelength (around 1200 nm) is due to water which is a strong light filter in IR spectroscopy.

Light scattering due to turbid media is also reduced in this high wavelength window as predict-

ed by the Rayleigh law. Nevertheless, scattering in tissues remains high, due to refractive index mismatches between the different cellular components and fluids. This is a limit in the spatial definition.

Finally, light absorption by endogenous tissue fluorochromes can result in light emission, the so called autofluorescence of the tissue. This phenomenon is due to the oxidized forms of riboflavin, the co-enzymes flavin and NADH reduced inside cells.[7,8] Other molecules like lipofuscin and ceroides or other components of the skin, such as collagen and melanin, also contribute to this effect. Autofluorescence is also a consequence of food that contains chlorophyll.[9,10] Tissue autofluorescence is mainly present in the UV and visible range of the spectrum.

Compared to fluorescence imaging in the visible light range, fluorescence imaging in the NIR bandwidth offers less photon absorption by blood hemoglobin, lipid and water, and a limited light scattering, enabling photon transmission deeper into the body. Thus, substantially reduced tissue autofluorescence, enabling higher sensitivity detection of target NIR molecular imaging agents due to a low background, can be achieved.

For a greater discussion of the physics underlying efficient NIR photon delivery through tissues, fluorescence chemistry synthesis approaches and fluorescence hardware systems, the interested reader can consult several reviews.[11,12]

As a conclusion, an accurate quantitative and spatially resolved detection *in vivo* by an optical method faces intrinsic limitations due to the optical properties of intact biological tissues. Taking into account these optical properties of living tissues, optimized conditions by choosing the relevant biological reporter fluorophores could be obtained.

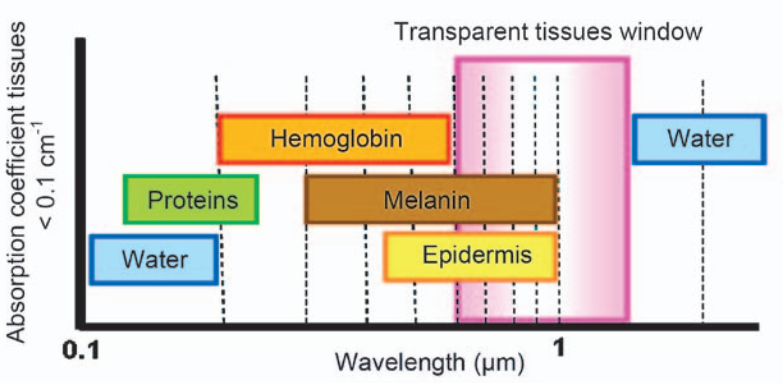

FIGURE 1. Absorption spectra of different molecules present in biological tissues. The tissue optical window (600-1200 nm) is ideally sought in fluorescence imaging of small animals. Hemoglobin and water absorb light below and above the optical window.

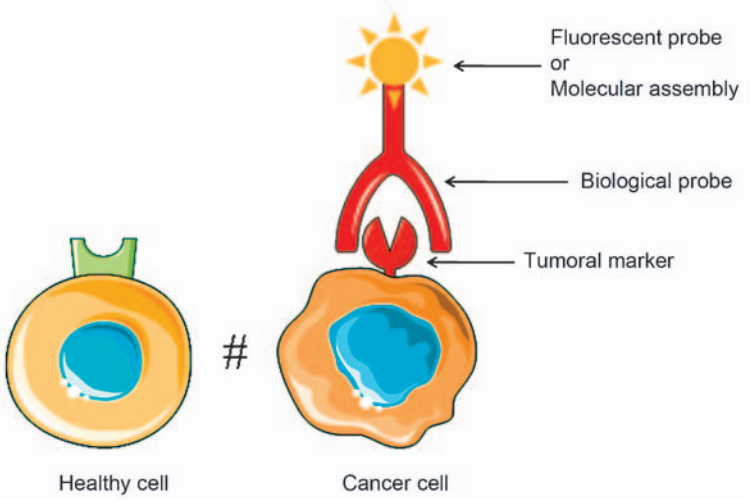

FIGURE 2. Principle of targeting tumor cells by fluorescence imaging.

Which fluorophore?

Two kinds of commercial organic fluorochromes emitting in the NIR wavelength domain are available: cyanine[13] and Alexa Fluor.[14] They can be grafted on any kind of molecules of interest such as nucleic acids, proteins or antibodies. They have several advantages such as weak toxicity, a small molecular weight, a functional group allowing their grafting and weak photo-degradation. Their limit is a weak fluorescent quantum yield.[13] Therefore, multigrafting of these molecules on "rafts"[15] or on dendrimers[16] is performed to overcome this problem by increasing the local number of emitters on the target. Company brand fluorophores are now on the market (DyLight Fluor family by Dyomics in collaboration with Thermo Fisher Scientific, KODAK X-SIGHT Large Stokes Shift Dyes and nanospheres, XenoLight CF by Caliper).

Commercially available quantum dots are promising competitors of organic probes for fluorescent imaging (Qdot® nanocrystals by Molecular probes, Quantum Dot Corporation Qtracker). Indeed, they have a strong fluorescent quantum yield[13], a weak sensibility to photobleaching and a strong stability. However, they have significant toxicity *in vivo* due to their chemical core (nanotoxicology).[17] *In vivo*, they are used with success in biphoton microscopy and some reports are cited in small animal imaging studies.[18]

Probe design

Targeting tumor cells by fluorescence imaging can be achieved by coupling a fluororescent agent with biological probes (antibodies, aptamers, peptides or enzymatic ligands or metabolites) that recognize specific tumor markers only expressed or over-expressed by tumor cells. The labeling of the biological probes can be done by fluorescent markers or complex molecular assemblies (Figure 2).

Tumor markers

Tumor cells differ from healthy cells by tumor markers which are expressed and located on their plasma membrane. These tumor markers are proteins or glycoconjugates over-expressed on the membrane surface of tumor cells such as protein receptors that interact with a panel of probes (or ligands) described in the following paragraph.

Several membrane antigens are recognized by monoclonal antibodies and used for imaging of tumors: prostate specific membrane antigen (PSMA) [16,19,20], the carcino embryo antigen (CEA) [21], the VEGF receptor (*Vascular Endothelial Growth Factor*) or the Human Epidermal Growth Factor Receptor-2 (HER-2).[22,23] These antigens are membrane proteins over-expressed by tumor cells and involved in life processes such as exogenous or endogenous transduction of signals or the cell cycle. In addition, they can be used in imaging to detect various tumors.

PSMA is a membrane and cytoplasmic glutamate carboxypeptidase which is involved in the cell cycle and in carcinogenesis associated with prostate cancer. CEA is involved in cell adhesion and is found in various cancers such as colorectal, gastric, pancreatic, lung and breast cancers. The VEGF receptor is over-expressed in most tumor and endothelial cells involved in angiogenesis. HER-2 is a tyrosine kinase membrane receptor involved in signal transduction pathways inducing growth and cellular differentiation. It is over-expressed in breast and ovarian cancers and other carcinomas.

There are other proteins over-expressed on the surface of several types of tumor cells such as metalloproteinase-2 (MMP-2) [24], integrins αVβ3 [25,26] and lectins.[27] These molecules are less specific for tumor cells than the antigens described above because they are also expressed by healthy cells but in much smaller quantities. Their natural ligands are used as probes.

Biological probes

Antibodies. Antigenic tumor markers used in molecular imaging are generally derived from anatomopathological tissues studies. A large library of antibodies specific for tumor cells has been gathered. They have been adapted for human administration (humanized and recombinant antibodies). Monoclonal antibodies are widely used in fluorescence imaging due to their strong affinity for their target. On the other hand, one should keep in mind their disadvantage of triggering immune reactions. It is difficult to find a good compromise between modifications (humanization, chimerization) of antibodies to make them more biocompatible and their loss of affinity for their target. Several monoclonal antibodies are available for *in vivo* fluorescence imaging applications: the anti-PSMA antibody that targets prostate tumor cells[20,28], the anti-CEA antibody that targets tumor cells of prostate, pancreas and colorectal cancer[29,21], the anti-VEGF receptor antibody that targets tumor cells and those associated with the angiogenic process[30] or the anti-HER-2 targeting tumor cells in breast, ovary, and other carcinomas (Table 1).[23,31]

Peptides and proteins. Peptides or proteins can also be used to target tumor cells but they are still at an experimental stage. This approach consists of using the binding properties of the peptide (or protein) with glycoconjugates or membrane proteins over-expressed in tumor cells (Table 1). For example, Chlorotoxin is used to detect various tumor cells (glioma, medulloblastoma, prostate cancer, bowel cancer and sarcomas).[24] This peptide, derived from scorpion venom, is composed of 36 amino acids with 4 disulfide bonds and interacts with MMP-2. Due to its anti-cancer properties, it can be used to target tumor cells. *In vivo* detection of cells over-expressing MMP-2 was obtained by non-invasive fluorescence imaging.[24] Cyanine 5.5 was coupled to primary amines of Chlorotoxin (3 amino functions). Another example is the RGD peptide, which is a cyclo-peptide that mimics angiotensin. It is used to detect tumor cells because it specifically interacts with $\alpha_V\beta_3$ integrins over-expressed on the surface of many different tumor cells.[25,26]

Metabolites. Another approach is to use metabolic properties of tumor cells that differ from normal cells. Indeed, they absorb more nutrients because they over-express proteins involved in cell growth. Thus, administration of metabolites is used to target receptors over-expressed in tumor cells (Table 1). For example, albumin that interacts with

TABLE 1. Examples of tumors markers and probes used in fluorescence imaging

Tumor markers	Probes	Fluorescence and platforms	Cancers	References
PSMA	Antibody	PAMAM + (x6) rhodamine or (x6) FITC	Prostate	20, 28
PSMA	Aptamer	Rhodamine, QDots	LNCap	19, 39
CEA	Antibody	AlexaFluor 488; Cyanine (DY-676)	Colorectal, gastric, pancreatic, lung, breast	21, 29
HER-2	Antibody	PAMAM + (x5) AlexaFluor 488	Breast, ovarian carcinoma	23, 31
VEGF Receptor	Antibody	NIR-800 Licor	Brain	30
Integrin $\alpha_v\beta_3$	RGD Peptide (c(RGDyK); RGD-4C (doubly cyclised RGD); c(RGDfK))	Q-Dot 705; PAMAM +(x3) Alexa Fluor 488; PAMAM +(x4) FITC; RAFT +(x2) Cy5	U87MG, brain, HUVEC, HEK293	26, 49, 52
β-D-galactose receptor (lectin)	BSA / GSA	Rhodamine G	Ovarian and adenocarcinoma	27
MMP-2	Chlorotoxin	Cyanine 5.5	Glioma, neuroectoderma	24
Folate receptor	Folate	Q-Dots	Brain	32, 33
Mucine MUC1	Aptamer	Rhodamine	MCF7	34

the β-D-galactose receptor [27] or folic acid (vitamin B9) that interacts with the folate receptor (or folate-binding protein (FBP) [32,33],are both effective for locating various tumor cells (ovary, kidney, uterus, brain, colon, lung adenocarcinoma). This approach is less specific for tumor cells than approaches targeting tumor antigenic markers but it is widely used in imaging modalities such as MRI and PET for the specific detection of tumor cells and also for drug-targeted delivery to tumors.

Aptamers. Aptamers can be used for targeting live cells. Aptamers are highly structured oligonucleotides selected by Systematic Evolution of Ligands by Exponential Enrichment (SELEX) to bind tightly (nanomalor range) and specifically to a target molecule. Recently, specific aptamers have been selected against tumor markers like PSMA or MUC1 (Table 1).[19,34]

Nucleotidic aptamers present all characteristics, which make them suitable as imaging probes: they are smaller (10-15 kDa) than antibodies (150 kDa), hence they exhibit higher tissue penetration and faster blood clearance. In addition, compared with antibodies, aptamers present a low immunogenicity, are not toxic and they can be chemically modified.[35]

The first aptamer used in imaging was designed against human neutrophil elastase.[36] This work demonstrated for the first time the potential feasibility of using an aptamer labeled with technetium-99m (^{99m}Tc) as reagents for diagnostic imaging. The aptamer had a signal-to-noise ratio higher and more rapid than the antibody.

More recently, an aptamer labeled with ^{99m}Tc directed against human tenascin-C was also used for *in vivo* imaging.[37] These authors showed a rapid uptake of aptamers by tumor and a rapid clearance from blood and other non-target tissues, which enabled clear tumor imaging.

Another report used ^{99m}Tc -labeled-aptamer directed against MUC1 and was tested in MCF-7 tumor-bearing mice.[38] Their first results showed the necessity to optimize the radiolabeled aptamer in terms of pharmacokinetics prior to use in imaging.

Actually, fluorescently-labeled aptamers that bound the tumor cell surface were either used for *in vitro* imaging on culture cells that expressed, for example, PSMA[39] and MUC1[34], or by injections of a fluorescent aptamer against tenascin-C into tumor-bearing mice followed by fluorescence microscopy on tissues sections.[37] However, they are still not often used in fluorescence imaging of small animals.

Smart probes. "Smart probes" or "smart sensors" are probes activated by an intracellular proteolytic reaction of targeted tumor cells that become fluorescent. These probes give an excellent signal-to-noise ratio because they are activated only when internalized in target cells. Basically, they are activated by proteases or intracellular reductases (metalloproteinases MMP-2, cathepsins B and D, cysteine proteases, thioreductases) over-expressed in tumor cells which cut Lys-Lys or disulfide bonds of the complex and release the fluorophore.[35,40]

ProSense probes developed by Weissleder (VisEn Medical, Inc., Woburn, MA) are polylysines labeled by non-fluorescent cyanines. When the probe is internalized into cells by endocytosis, the peptide link (between lysines) separating the cyanines is broken by the action of intracellular proteases such as cathepsins (B or D) or metalloproteinases (MMP-2) and fluorophores are released into the cells which become fluorescent.[24,41]

Razkin *et al.* have shown that the molecule RAFT-RGD-Cy5-SS-Q penetrates effectively and specifically in tumor cells and is activated once inside. The complex consists of 4 RGD peptides specifically targeting the $\alpha V\beta 3$ receptors over-expressed on the surface of cancer cells, and of a quencher (Q) connected to a cyanine 5 via a disulfide bond. This bond is reduced by thioredoxin in the cytoplasm and endosomes after internalization into cells. Once internalized, the quencher is spatially separated from the cyanine and the complex becomes fluorescent. The phenomenon of quenching can be achieved by combining two identical fluorophores but the rate of cleavage of the disulfide bond is weaker and the contrast obtained *in vivo* is much smaller.[40]

Engelman *et al.* demonstrated that the pH low insertion peptide (pHLIP) is able to insert into the lipid bilayer of the plasma membrane by forming an α helix when the acidity increases in the extracellular matrix.[42] Indeed, the extracellular matrix surrounding tumors and areas of inflammation or infection are relatively acidic environments compared to healthy tissues. The insertion of the peptide in the cell membrane occurs at a pH below 6.5. The C terminal end of the complex is translocated into the cytoplasm. Two applications are then possible — the targeted delivery of drugs in tumor cells and the fluorescence imaging of these cells. Engelman *et al.* first grafted a disulfide bond to the C terminal end of the peptide, linking it to a fluorescent molecule or a drug that can be released into the cells by cleavage of the disulfide bond by thioredoxin. They also showed that this peptide is effective *in vivo* for detection of tumor cells by non-invasive fluorescence imaging. It is shown that this peptide localizes specifically in tumor cells within 20 hours.[43]

Molecular assemblies. Functionalization of fluorescent agents by coupling with enzymatic ligands[44], antibodies[45] or peptides[46], enable their targeting to tumor cells. Classically, tumor probes are bound to an organic fluorophore[45,21] or quantum dot[28,31] to visualize tumor cells by fluorescence imaging. The commercial fluorophores have reactive groups such as amine, carboxylic acid or thiol of the amino acid of the protein probe. However, the number of reactive groups per probe is low. According to protein size and the number of reactive groups, 4 to 10 fluorophores can be grafted per protein. In order to increase the fluorescence signal of tumor probes and/or increase their specificity for target cells, molecules called "platforms" were used as a covalent support to several fluorophores and/or several probes (Table 1).

The quantum dots can be used as "platforms" because they allow several connections with biological probes. Cai *et al.* have shown this with the RGD peptide by grafting multiple RGD peptides onto a quantum dot.[26] This greatly increases the specificity of quantum dots for tumor cells.

The work of Coll *et al.* on the regioselectively addressable functionalized template RGD peptide (RAFT RGD) showed the specific labeling of tumor cells over-expressing integrin $\alpha V\beta 3$ receptor. This molecule is a deca-peptide accepting 4 cyclo-RGD peptides and one fluorochrome of the cyanine 5 type. They showed that it was necessary to have at least 4 RGD peptides per platform to specifically detect tumor cells *in vivo.*[44]

Dendrimers are now experiencing their first major applications as diagnostic agents when grafted with contrast agents[47,48] or fluorochromes[23,20,49] and targeting agents. PAMAM dendrimers are used in imaging because they are water-soluble, biocompatible and biodegradable.[50,51] They allow an increase in the sensitivity of detection because several imaging agents are bound per dendrimer. Furthermore, by increasing the number of biological probes by complex, it is possible in some cases to increase the specificity of the detection signal. The work of Hill and that of Thomas show the detection efficiency in fluorescence imaging of tumor cells *in vivo* by a complex composed of a PAMAM dendrimer with multiple RGD peptides[52,53] and several fluorochromes.[52,49] This approach can increase both the fluorescence signal of tumor probes and their specificity for tumor cells. Several studies

using dendrimers as imaging agents are reported in Table 1.

Dendrimers are real molecular platforms that may also be grafted to drugs. These systems allow us to specifically target cells and provide local delivery of drugs in patients.[54]

Conclusion

In small animals, optical imaging is a low-cost technology by which tumor cells are detected over several weeks depending on the mouse strain. Whole-body imaging gives access to relative quantitative detection with a "crude" topological definition over a long period. The technology is rather simple and is now available on the market (Berthold, www.bertholdtech.com; Hamamatsu, www.hama-comp.com; Caliper Xenogen, www.caliperls.com; Fuji, www.fuji-sciences.com; Carestream, www.carestreamhealth.com; Cambridge Research Instrumentation, www.cri-inc.com; Biospace, www.biospacelab.com). This was recently reviewed as a technological feature in "Nature". Detection is associated with a light signal. The major limit is sensitivity and topological definition which remains associated with the turbidity of tissues. It could be improved by selecting the probes, light source and detector suitable for red fluorescence detection to avoid tissue absorption. More accurate data is obtained by other methods (intravital microscopy) but over a more limited period of time due to the associated surgery (Cellvizio, www.visualsonics.com; macrofluo, www.leica-microsystems.com; macroscope, www.nikoninstruments.eu). Real-time imaging of tumors by an IV injected probe sensitive to angiogenesis (AngioStamp®, Angiosense), can be obtained by a user-friendly intra-operative imager (Fluobeam®) that will drastically improve cancer surgery. Preclinical devices are available. The new ("smart") fluorescent probes associated with fluorescence endoscopy should help surgeons with tumor resection in the near future (Fluoptics, www.fluoptics.com; Visen, www.visenmedical.com). A preclinical study just showed a better survival over a 6-month period when tumors in the animal were resected by using a Cy5-labeled cell-penetrating peptide conjugated to a dendrimer to guide surgery.[56]

Therefore, following and quantifying tumor progression *in vivo* by optical imaging is a fantastic tool to monitor the expression of therapeutic genes in target tissues, in disease models and/or to assess the effectiveness of cancer therapies (surgery, radiotherapy, gene therapy). Added to the routinely used imaging techniques[57,58], it can be used for diagnostic evaluation and surgical management.

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case report

Infrahepatic caudal/inferior vena cava interruption with azygos/hemiazygos continuation. Vascular anomaly in swine

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Background. Swine are commonly used as a model to study congenital cardiovascular defects that occur in humans and these models have been both spontaneous and experimentally induced. Ventricular septal defect, patent ductus arteriosus, and atrial septal defect (ASD) are examples of experimentally induced models. Absence of caudal/inferior vena cava (CVC/IVC) with azygos/hemiazygos continuation is an uncommon vascular anomaly.

Case report. The vascular anomaly presented in this case report was an incidental finding on a pig that was evaluated for experimental percutaneous atrial septal defect creation and its closure using a percutaneous femoral vein approach. Absence of CVC/IVC was confirmed by venography and necropsy.

Conclusions. To the best of the investigators knowledge, this is the first report of absence of CVC/IVC with azygos/hemiazygos continuation in the swine.

Key words: experimental animal model; congenital vascular anomaly; azygos vein; hemiazygos vein; inferior vena cava

Introduction

Swine and ovine are frequent used for the experimental studies of interventional radiology procedures.[1,2] However, swine are commonly used as a model to study congenital cardiovascular defects that occur in humans and these models have been both spontaneous and experimentally induced. Ventricular septal defect, patent ductus arteriosus, and atrial septal defect (ASD) are examples of experimentally induced models. In necropsy surveys of commercial breeds of farm pigs, ASD was detected in 31/1906 pigs for an incidence of 1.6%.[1] Swine have been used as a model to produce a functional ASD by using a transeptal stationary angioplasty balloon technique.[1]

Caudal vena cava (CVC) in animals is the equivalent of inferior vena cava (IVC) in humans and normally, CVC/IVC provides the main channel of drainage for the hind limbs, abdominal muscles, and abdominal organs through the portal and hepatic veins. The main tributaries of the CVC/IVC are common iliac, lumbar, deep circumflex iliac, right testicular or right ovarian, renal phrenicoabdominal, hepatic, and phrenic veins.[3,4,5]

The vascular anomaly presented in this case report was an incidental finding on a pig that was evaluated for experimental percutaneous atrial septal defect creation and its closure using a percutaneous femoral vein approach. To the best of the investigators knowledge, this is the first report of absence of CVC/IVC with azygos/hemiazygos continuation in the swine.

Case report

The study protocol was approved by the Oregon Health & Science University's (OHSU) Animal Care and Use Committee (IACUC). The animal facilities are accredited by the American Association for the Accreditation of Laboratory Animal Care

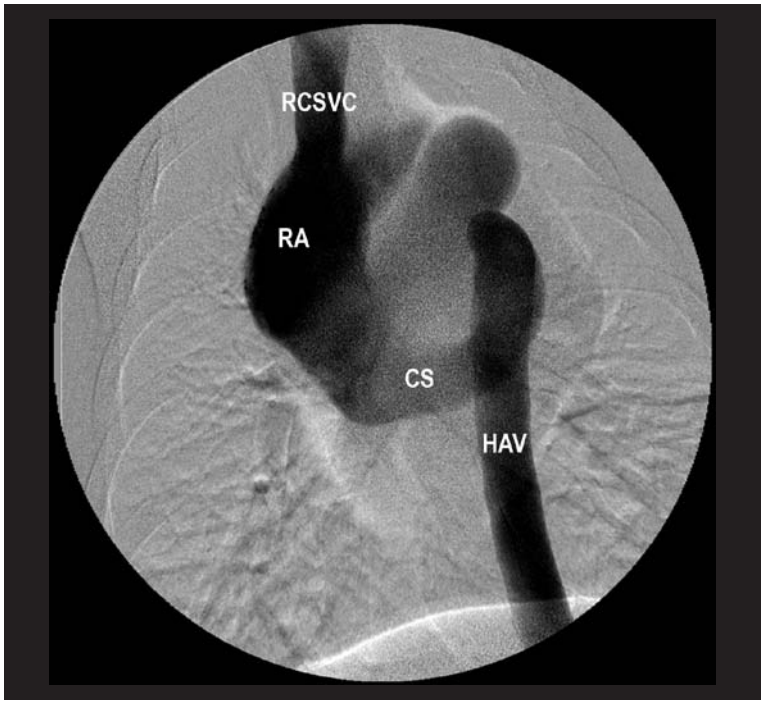

FIGURE 1. Ventrodorsal subtraction venogram of the chest in a swine after simultaneous contrast injection into the right jugular vein and right femoral veins. Injection into the right femoral vein demonstrates the large hemiazygos trunks (HAV) draining into the coronary sinus (CS), which then communicates directly with the right atrium (RA). Injection into the right jugular vein shows normal right cranial/superior vena cava (RCSVC) draining into right atrium.

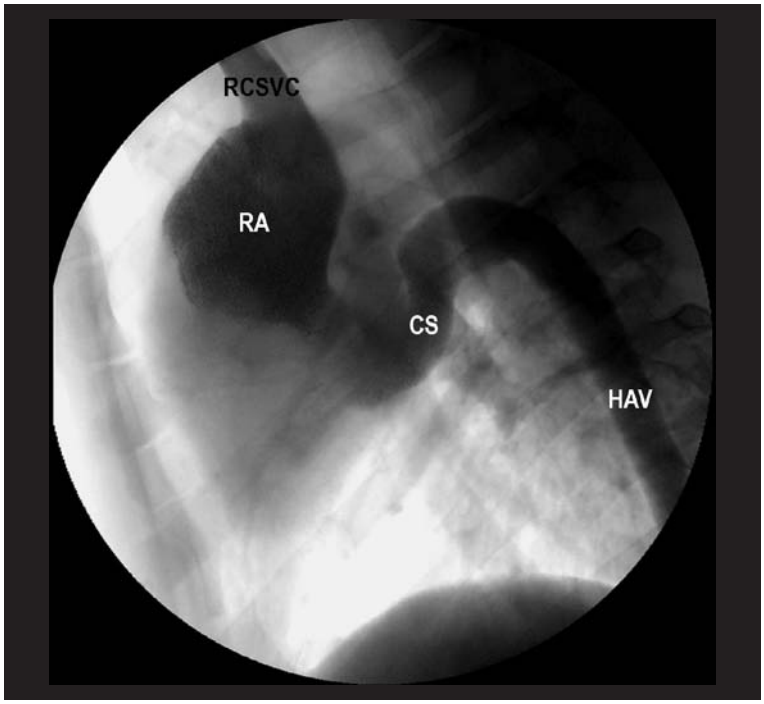

FIGURE 2. The lateral venogram of the chest in a swine after simultaneous injection of the right femoral vein and right jugular veins. The large hemiazygos vein (HAV) ascends along the vertebral column and joins the coronary sinus (CS), which then communicates the directly with the right atrium.

international (AAALAC international) and meet all federal (AWA and PHS) guidelines for animal care. The animal room was maintained at an average temperature of 68º F and a relative humidity of 30-70%. A female domestic swine (*Sus scrofa domestica*), 38 kg of body weight and approximately 4 months of age, was evaluated for experimental transcatheter implantation of a closure device for foramen ovale, using the percutaneous femoral vein approach. The swine was acclimated for at least 48 h before the terminal procedure.

Preanesthesia treatment included 0.01 mg/kg of atropine sulfate (American Regent Laboratories, Shirley, NY, USA) and 1 g dose of Cephasolin (Ancef; Abbot Laboratories, Chicago, IL, USA) intramuscularly. Anesthesia was induced with Telazol (tiletamine HCI and zolazepam HCI; Fort Dodge Animal Health, Fort Dodge, IA) 3-6 mg/kg, IM, and an endotracheal tube was placed. Maintenance of anesthesia was done with 2-3% isoflurane (Isothesia, Burns Veterinary Supply, Rockville Center, NY, USA). During anesthesia, oxygen, carbon dioxide, EKG, respiration and heart rate were monitored, and a GE/OEC 9800 cardiac mobile system with digital imaging (GE Medical Systems, OEC, Salt Lake City, UT) was used for imaging.

A size 7 French vascular sheath (Cook Inc., Bloomington, IN, USA) was percutaneously introduced into right femoral vein, and then a guide wire and a size 5 French catheter (Cook Inc., Bloomington, IN, USA) were inserted into right femoral vein and advanced cranially. After fluoroscopy showed the catheter located on the left side of the spine, contrast medium (Hypaque-76, Amersham, Piscataway, NJ, USA) was injected to perform a venogram for evaluation of venous anatomy. In addition, two size 7 French vascular sheaths were percutaneously introduced, one into the right femoral artery and the other into the right jugular vein for performance of bilateral renal artery angiograms and a jugular venogram, respectively. The right hepatic vein was then catheterized and visualized from the right jugular approach using a size 5 French H1 catheter (Cook Inc., Bloomington, IN, USA) passed through the right atrium. At the end of the procedure the animal was euthanized while under anesthesia with an overdose of sodium pentobarbital (Euthasol: Delmarva Lab, Midlothian, VA, USA).

Diagnostic findings

The ventrodorsal subtraction venogram after simultaneous injection via the right femoral vein and the

right jugular vein is shown in Figure 1. Normal superior or cranial vena cava was seen on the right side, but CVC/IVC was not observed. A dilated hemiazygos vein was seen on the left side of the lumbar vertebra, emptying into the coronary sinus, which communicated directly with the right atrium. The lateral venogram after simultaneous injection of the right femoral and right jugular vein shown in Figure 2 demonstrated anomalous drainage of blood from the hemiazygos vein that abnormally emptied into the coronary sinus and then into the right atrium.

The lateral subtraction venogram after simultaneous injection of contrast via right femoral vein and right hepatic vein identified the hepatic vein as the only drainage into the suprahepatic CVC/IVC. The infrahepatic CVC/IVC was not seen or identified during the venogram. The hemiazygos vein drainage into the coronary sinus was the major channel from the abdomen. Both renal veins seen on late images of renal arterigrams drained into the azygos and hemiazygos chains. The abnormality was diagnosed as infrahepatic CVC/IVC interruption with azygos/hemiazygos continuation. This finding of infrahepatic CVC/IVC interruption with azygos/hemiazygos continuation was confirmed at necropsy (Figure 3). Because of the found anomaly, the planed percutaneous creation of ASD using a femoral approach could not be performed.

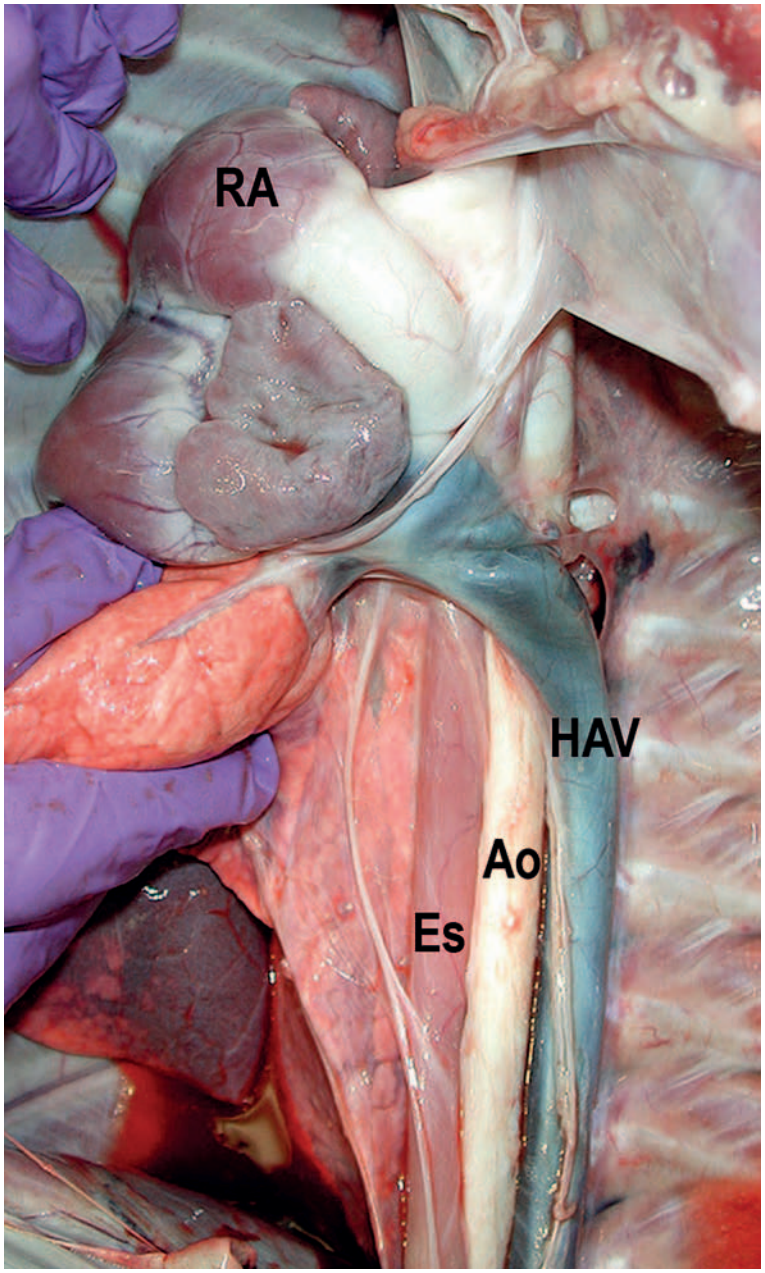

FIGURE 3. Gross specimen of the mediastinum demonstrates entrance of the hemiazygos vein (HAV) into right atrium (RA). The large hemiazygos vein drains into the right atrium across the aorta (Ao) and esophagus (Es).

Discussion

Anomalies of the CVC/IVC are often associated with congenital heart disease. Its prevalence is 0.6-2.0% in patients with congenital heart disease and less than 0.3% among otherwise normal patients.[6] During embryogenesis, the IVC/CVC is made up of the hepatic, prerenal, renal, post renal segments, which by segmental fusion, regression, and midline anastomosis form the CVC/IVC.[7] Failure of fusion between the hepatic and prerenal segments results in infrahepatic CVC/IVC interruption that is the most common developmental anomaly of CVC/IVC.[8] The infrahepatic CVC/IVC may continue as the azygos vein[7,9,10], or it may continue as the hemiazygos vein to the persistent left superior vena cava[10], intrathoracic veins[11], or anomalous intrahepatic veins.[12] Infrahepatic CVC/IVC interruption with azygos and hemiazygos continuation is associated with congenital cardiac or visceral malformation in the human.[5,8]

Segmental lumbar veins are joined by a longitudinal vessel called the ascending lumbar vein. On either side of the lumbar vertebrae there may be one or two ascending lumbar veins. The right ascending lumbar vein becomes the azygos vein as it enters the thorax, and the left ascending lumbar vein is continuous with hemiazygos chain.[13] If the inferior caudal vein (CVC/IVC) is occluded, blood from the lower extremities may reach the heart through the paravertebral and azygos systems. If the inferior vena cava is congenitally absent, the same avenues is utilized.[13] Normally in species

such as the dog the azygos vein empties into the cranial vena cava and then into the right atrium.[4] The presence of the hemiazygos vein is variable, and when present it is located left to the aorta, communicating the azygos vein with the CVC.[4] In the present case, the enlarge hemiazygos vein was the major drainage channel from the abdomen, and it emptied into the coronary sinus that opens into the right atrium, and similar findings have been reported in the human literature.[13]

Larger azygos/hemiazygos vein can be misinterpreted as an aortic dissection or mediastinal mass.[5] Moreover, the enlarged azygos/hemiazygos arch may be mistaken for a right paratracheal adenopathy on the chest radiography.[14] The authors were able to make the correct diagnosis by means of CT scan, which has been accepted as a valuable modality for demonstrating IVC anomalies.[15] Although most of IVC interruption with azygos/hemiazygos continuation is usually an asymptomatic malformation, a dozen cases of deep vein thrombosis have been causally linked to IVC anomaly in the English literature.[5,9,15,16] Theoretically, this anomaly may predispose to venous thrombosis because an inadequate blood return through the collaterals may increase the venous pressure in the veins of the leg, thereby favoring venous stasis.[15,16,17]

The absence of CVC/IVC may lead to procedural difficulties during femoral vein catheter advancement[9], IVC filter placement[18], temporary pacing through the transfemoral route[1], electrophysiology studies[19,20], and cardiopulmonary bypass surgery.[21] Awareness of the existence of these anomalies before femoral vein catheter advancement or other procedure through femoral vein would avoid unnecessary injury or undue delay. The recognition of this congenital venous anomaly (CVC/IVC interruption with azygos/hemiazygos continuation) is important for interventional radiologist and cardiologist, especially for conditions such as venous thromboembolism, IVC filter placement, transcatheter closure of the ASD, ventricular septal defect (VSD) patent foramen ovale (PFO) shunt[22], or pacing and electrophysiology, cardiopulmonary bypass surgery, and palliative systemic venous-pulmonary artery shunt surgery.

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research article

Direct coronary stenting in reducing radiation and radiocontrast consumption

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Introduction. Coronary stenting is the primary means of coronary revascularization. There are two basic techniques of stent implantation: stenting with balloon predilatation of stenosis and stenting without predilatation (direct stenting). Limiting the time that a fluoroscope is activated and by appropriately managing the intensity of the applied radiation, the operator limits radiation in the environment, and this saves the exposure to the patient and all personnel in the room. Nephrotoxicity is one of the most important properties of radiocontrast. The smaller amount of radiocontrast used also provides multiple positive effects, primarily regarding the periprocedural risk for the patients with the reduced renal function. The goal of the study was to compare fluoroscopy time, the amount of radiocontrast, and expenses of material used in direct stenting and in stenting with predilatation.

Patients and methods. In a prospective study, 70 patients with coronary disease were randomized to direct stenting, or stenting with predilatation.

Results. Fluoroscopy time and radiocontrast use were significantly reduced in the directly stented patients in comparison to the patients stented with balloon-predilatation. The study showed a significant reduction of expenses when using a direct stenting method in comparison to stenting with predilatation.

Conslusions. If the operator predicts that the procedure can be performed using direct stenting, he is encouraged to do so. Direct stenting is recommended for all percutaneous coronary interventions when appropriate conditions have been met. If direct stenting has been unsuccessful, the procedure can be converted to predilatation.

Key words: coronary stenting; balloon predilatation; percutaneous transluminal coronary angioplasty; expenses

Introduction

Heart is supplied with blood through coronary arteries. Disbalance in myocardial oxygen supply and demand may cause myocardial ischemia with contractile dysfunction, arrhythmias, infarction, and possibly death.[1] Interventional cardiology deals with catheter-based interventions in the treatment of the structural heart disease. Coronary stent implantation is the primary means of coronary revascularization.[2] Stenting of arterial stenosis in other organs is also the method of choice as the minimally invasive interventional procedure.[3] There are two basic techniques of the coronary stent implantation. The first one consists of PTCA (percutaneous transluminal coronary angioplasty)-balloon predilatation of stenosis before stenting, a sort of 'preparing the ground' for stenting itself. This technique is the usual, or the conventional one, evolved from bail-out stenting used to treat complications, such as coronary dissection, in the era of PTCA. The second technique is somewhat newer. It implies stent implantation without predilatation, and is called 'direct stenting'.

Fluoroscopic radiation is a carcinogen that can also cause a severe injury (radiation burns) to patients and practitioners.[4] When fluoroscopy is well managed, the likelihood that these severe effects

could occur is extremely low. Medical practitioners who have accumulated considerable radiation doses have been shown to have developed radiation-induced cancers, cataracts, or skin injury.[5-7] Attention to rigorous radiation abatement measures is therefore warranted and required.[8] Time, intensity, distance, and shielding (TIDS) describes the management of the radiation exposure by minimizing the time to which one is exposed to radiation, by minimizing the intensity of the radiation that is deployed, by maximizing the distance from the source, and by shielding the personnel from the radiation. The operator can limit the radiation in the cathlab by limiting the time that the fluoroscope is activated and by appropriately managing the intensity of the applied radiation, thus reducing the exposure to the patient and all personnel in the room. Cardioangiographic equipment is one of the most sophisticated and complex equipment used in medicine.[4] The goal in cardioangiographic imaging is to produce an X-ray beam that results in an excellent compromise between the appropriate image quality and the radiation dose. Limiting the beam-on time limits the exposure time for the patient, but also for the personnel.

Blood vessel walls and myocardium have similar X-ray absorbance to that of blood, making their imaging by conventional radiographic techniques virtually impossible without the use of the intravascular contrast agent. Therefore, the use of radiocontrast is absolutely necessary in order to obtain images of coronary arteries. Those images are obtained by directly injecting the radiocontrast into the coronaries and recording an X-ray image, or sequence. Adverse reactions to radiocontrast are most importantly anaphylactoid, but also toxic effects, such as nausea or vomiting, but the incidence of adverse reactions has been significantly reduced with the use of nonionic contrast media.[9] Nephrotoxicity is one of the most important properties of radiocontrast. The smaller amount of radiocontrast used also provides multiple positive effects, primarily regarding the periprocedural risk for the patients with the reduced renal function. Contrast induced nephropathy (CIN) causes renal failure, increased morbidity, prolonged hospital stay, higher hospitalization costs, and increased mortality.[10] Although its pathogenesis remains unclear, CIN is probably due to a combination of decreased renal medullary perfusion (possibly because of alterations in renin-angiotensin system, nitric oxide synthesis, adenosine metabolism, prostacyclin production, and endothelin synthesis)[11-13], resulting in critical medullary ischemia and direct tubular toxicity.[14] Patients with diabetic nephropathy are at especially great risk from CIN. Although it is logical to assume that the risk is reduced when using smaller amounts of contrast per procedure, there is no consensus regarding a 'safety dose'. Additional benefits from the reduced radiocontrast use are primarily economical, for these agents are relatively expensive.

The goals of the study were:

To compare fluoroscopy time as a measure of radiation exposure during direct coronary stenting and stenting with predilatation.

To compare the amount of radiocontrast used during direct coronary stenting and stenting with predilatation.

To compare expenses of material used in direct stenting and in stenting with predilatation.

Patients and methods

In a prospective study, 70 patients that have undergone coronary stent implantation as the treatment of coronary disease were analyzed. The patients were randomized into two groups of 35 patients each. The patients in one group were treated by stenting with PTCA-balloon predilatation, and the patients in the other group – by direct stenting. Groups were similar by the criteria of age, gender, affected coronary arteries, types of stents used for the treatment, and severity of coronary stenoses. Exclusion criteria were: acute myocardial infarction, two or more stenoses treated per patient per procedure, and chronic total coronary occlusions on coronary angiography finding.

All patients have undergone prior selective coronary angiography. Thereafter, the patients randomized to conventional stenting had their coronary stents implanted after PTCA-balloon predilatation, and those randomized to direct stenting had their stents implanted directly into coronary lesions, without the prior PTCA-balloon predilatation.

Fluoroscopy time measured in seconds and radiocontrast dye use measured in milliliters were recorded for all patients. Selective coronary angiography and percutaneous coronary interventions (PCIs) were performed on cardioangiograph Siemens Axiom.

Results

There were no significant differences in age (p=0.17) or gender (p=0.51) between the groups.

TABLE 1. Intensity of coronary stenoses, observed by coronary arteries in investigated groups

Characteristics		Stenting method				
		DS n = 35		SWP n = 35		p
		n	% stenosis	n	% stenosis	
Artery	-RCA	9	86.11 ± 6.50	7	86.42 ± 5.56	0.91
	-LAD	21	84.28 ± 6.18	17	87.64 ± 5.62	0.09
	-CX	5	83.00 ± 6.70	11	87.72 ± 5.64	0.16

Legend: RCA – right coronary artery, LAD – left anterior descending coronary artery, CX – circumflex coronary artery, DS – direct stenting; SWP – stenting with predilatation. Values are displayed as mean, standard deviation, and in absolute numbers.

TABLE 2. Amount of radiocontrast used and fluoroscopy time in investigated groups

Paremeters:		Stenting method		
		DS n = 35	SWP n = 35	p
Fluoroscopy time	s	204.1 ± 98.46	392.8 ± 207.7	‡*0.0001
Radiocontrast	ml	280 (100 – 350)	350 (200 – 400)	◊0.0001

Legend: s-second, ml-millilitre; DS – direct stenting; SWP – stenting with predilatation ‡*Student T-test (df 68, test statistic 4.85, p < 0.0001); ◊Mann-Whitney test (Large sample test statistic Z -4.58; p < 0.0001).

The average age in directly stented group was 57.40±10.03, and that in the conventionally stented group 54.31±8.70. The most often affected coronary artery was left anterior descending coronary artery in both groups (p=0.23). There was no significant difference in stenosis intensity between the groups (Table 1).

During the study, no ECG showed signs of newly onset myocardial necrosis (new Q-wave), nor new bundle-branch blocks, which would speak in favor of significant myocardial necrosis.

Fluoroscopy time and radiocontrast use were significantly reduced in patients that were stented directly, in comparison to patients stented with prior balloon-predilatation (Table 2).

In both groups, using quantitative coronary angiography (QCA), we found a complete elimination of previous stenosis to 0% in all patients, without residual stenoses. We found no major adverse cardiac events (MACE), defined as urgent coronary revascularization, myocardial infarction, lethal outcome in either of the groups.

A financial analysis of the expenses of materials used during direct stenting, and stenting with predilatation showed an average reduction of costs of 27.86±2.81 % (p<0.05) when using the direct stenting method in comparison to stenting with predilatation. The basic role in this cost reduction plays the elimination of the use of PTCA balloon for predilatation and lower amount of radiocontrast used in direct stenting.

Discussion

During 1993 two important trials compared the implantation of Palmaz-Schatz coronary stents to conventional PTCA, and established coronary stenting as the standard treatment. The BENESTENT trial involved 520, and the STRESS trial 410 patients, independently demonstrating that coronary stents reduce restenoses (>50% of new stenosis of the earlier treated artery at the site of treatment – PTCA or stenting).[15,16] As early as 1999, stenting took 84.2% of all PCIs.[17] Direct stenting is defined as positioning and implantation of stent without balloon-predilatation of coronary stenosis.[18] It is a new strategy of the coronary disease treatment enabled by the development of the advanced stent and the implantation system design with the low cross-section area, high safety standards, and high rated burst pressures.[19] Initial registers show a high success rate in combination with low complication rates.[20] The procedure is safe in selected cases, and can help reducing the expense of coronary interventions through the reduction in total procedural and fluoroscopy time, the amount of radiocontrast and the number of angiographic catheters used.[21,22]

Wilson *et al.* showed that direct stenting has positive effects on total procedural time, radiation exposure, and the use of radiocontrast.[23] In our research, direct stenting has significant positive effects regarding these criteria too, in comparison to stenting with predilatation. The procedural outcome seems to be superior without predilatation, because of the reduced incidence of coronary dissections at stent edges.[24] In our study, the procedural outcome was the same in both groups: the reduction of coronary stenoses, measured by quantitative coronary angiography, was complete to 0% in all patients, without residual stenoses. We have found no edge-dissections as a periprocedural complication. In the group of patients treated by stenting with predilatation, 2 out of 35 patients had localized small, non-obstructive coronary dissections after balloon-predilatation, which were routinely covered by stent implantation immediately afterwards. In the directly stented group, out of 35 patients, there were no coronary dissections after stenting. In the DISCO trial, conducted in 10 centers in Spain, 416 patients with 446 coronary lesions were randomized to conventional or direct stenting.[25] The main goal of this trial was to evaluate safety, feasibility, and the effect on angiographical restenosis of direct stenting in comparison to the conventional method of stenting with predilatation. The direct stenting strategy was effectively accomplished in 97% of lesions, and the patients converted to the predilatation strategy were all treated successfully. In our research (on a much smaller sample), the direct stenting strategy was successfully accomplished in all patients of that group, and there was no conversion to the predilatation strategy. Of course, it is only realistic to assume that a randomized sample that would include a larger number of patients would result in a certain small number of patients to be converted to predilatation, which we observe sometimes in our daily practice, especially in patients with critical sub-occlusions or highly calcified lesions. In our study, we found no MACE in either group. We have also found no major peri- or postprocedural complications. There were no electrocardiographical signs of myocardial necrosis, periprocedurally, or during the one-month follow-up.

The reduction of fluoroscopy time is very important both for the patient and for the staff. Ionizing radiation is one of the leading causes of malignancies[26], and the staff, especially the operator who is close to the radiation source and the source of scattered radiation during the entire intervention, is under a significant health risk.[27] According to our study, the fluoroscopy time was significantly reduced during direct stenting ($p=0.0001$) in comparison to conventional stenting, regardless of the artery treated. While we found fluoroscopy time to be 392.8±207.7 s during stenting with predilatation, we observed that this value in direct stenting was 204.1±98.46s. In the study of Martinez-Elbal *et al.*, the most important differences between the patients treated by direct or conventional stenting were significant fluoroscopy time reduction in direct stenting when compared to stenting with predilatation (6.4 min: 9.2min, respectively, $p<0.0005$) and significant reduction of total procedural time (21.2 min: 27.8 min, respectively, $p<0.0005$).[25] The interventional radiation environment creates the conditions for accumulation of high doses in the staff. That is why it is essential to pay attention to rigorous measures of decreasing radiation exposure.[8]

The smaller amount of radiocontrast used also provides multiple positive effects, primarily regarding the peri-procedural risk for the patients with reduced renal function. The main adverse effects from radiocontrast use are anaphylactic reactions and contrast-induced nephropathy (CIN). The use of radiocontrast, measured in milliliters, in our research was significantly lower in direct stenting, than in stenting with predilatation (280 (100-350) : 350 (200-400), respectively, $p=0.0001$). We found no CIN in either of the groups. Additional benefits from the reduced radiocontrast use are primarily economical, for these agents are relatively expensive.

With the elimination of expenses by saving PTCA-balloons and their dilatation catheters, the reduction in radiocontrast use also significantly reduces the overall cost of the intervention. In our study, a 27.86±4.81 % ($p<0.05$) cost reduction was recorded when using direct stenting in comparison to stenting with predilatation. The expenses related to the material used were taken into account. This sort of cost saving is similar to the reports of other authors, who describe cost savings in the range 20%-40% with the use of direct stenting.[18]

Conclusions

Direct stenting is defined as positioning and implantation of coronary stents without prior balloon dilatation of coronary stenosis. It can be used to accelerate the procedure and reduce intimal trauma. Complex lesions in small arteries and severe calcifications limit the use of this technique. Direct

stenting reduces health risks connected to radiation by significantly reducing fluoroscopy time. It also decreases the risk of contrast induced nephropathy by using significantly less radiocontrast when compared to stenting with predilatation. Direct stenting is not connected to an increased risk of major adverse cardiac events (acute myocardial infarction, urgent coronary revascularization, lethal outcome) in comparison to stenting with predilatation. New low-profile stents with high rated burst pressure values have enabled the routine use of this PCI technique. If direct stenting has been unsuccessful, the procedure can be converted to predilatation. If the operator predicts that the procedure can be performed using direct stenting, he is encouraged to do so. Direct stenting is recommended for all percutaneous coronary interventions when appropriate conditions have been met.

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research article

Diagnostic imaging of traumatic pseudoaneurysm of the thoracic aorta

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Background. The purpose of the study was the presentation of findings and diagnostic imaging in patients with traumatic pseudoaneurysms of the thoracic aorta, as a rare consequence of road traffic accidents.

Patients and methods. In 22 years we have found 8 traumatic pseudoaneurysms of the thoracic aorta, out of which 7 (87.5%) in male and 1 (12.5%) in female patients. At the time of accidents the youngest patient was 21 and the oldest was 55 (mean age 33.8 years), and at the moment of diagnosing a pseudoaneurysm they were 26 and 55 years old, respectively (mean age 38.7 years). In all patients chest radiography was performed as well as CT scan, in 6 (75%) patients intra-venous digital subtraction angiography was performed (*i.v.* DSA) and in 1 (12.5%) MRI. CT was performed with the application of 120 ml, and *i.v.* DSA with 60 ml of contrast medium, respectively.

Results. In 8 (100%) patients, who suffered a road traffic accident, and whose chest radiograph showed the enlargement of the aortic knob and widening of the mediastinum, CT, *i.v.* DSA and MRI revealed a traumatic pseudoaneurysm of the thoracic aorta. Periods of time between the accidents and the initial diagnosis of the pseudoaneurysm varied from 7 days to 18 years (median 2.0 years). The diameter of the pseudoaneurysm was from 4.5 to 9.2 cm (median 5.5 cm). In 7 (87.5%) isthmus was involved, and in 1 (12.5%) descending thoracic aorta, respectively. The chest radiograph revealed marginal calcifications in 4 (50%), and on the CT in 5 (62.5%) patients. Intraluminal thrombosis was found by CT in 2(25%) traumatized patients.

Conclusions. Traumatic pseudoaneurysm should be taken into consideration in blunt chest trauma, where a chest radiograph shows suspicious regions. A multislice CT is a diagnostic method of choice.

Key words: traumatic pseudoaneurysm; chest radiography; CT; *i.v.* DSA; MRI

Introduction

Back in 1557, Vesalius described a post mortem finding of an aortic rupture, which he suspected had been caused by a trauma. During the First World War, the aortic rupture was frequently noticed in victims of plane crashes. Immediately after the Second World War, in 1947, Strassman published 72 cases of aortic traumas with frequency of 1%.[1] The development of traffic and motor vehicles generated more interest in traumatic changes, which became more and more frequent. In Ireland, the annual mortality caused by damage to thoracic blood vessels during motor vehicle accidents was approximately 3% for the period 1995 – 1998. In 1966, Greendyke reported about a number of victims of accidental deaths whose bodies had been examined in an autopsy, where 10% of whom had suffered from aortic rupture, mostly in motor traffic accidents. He stated that in one out of six fatal accidents, the victim suffered from the aortic rupture.[2,3]

Injuries to the aorta may be caused by a direct penetration of the aorta by a knife, bullet or a foreign body, or they can be a result of a blunt trauma.[4] They can appear as incomplete aortic rupture, and as traumatic aortic dissection.[5] Survivors may develop chronic traumatic aneurysm or pseudoaneurysm.[6]

Chronic post-traumatic thoracic aneurysm of aorta is a secondary dilatation in the rupture of the isthmus of aorta, which may be unnoticed in the moment of trauma.[7] Most cases of aneurysm are located in the inner side of the aortic arch with a ven-

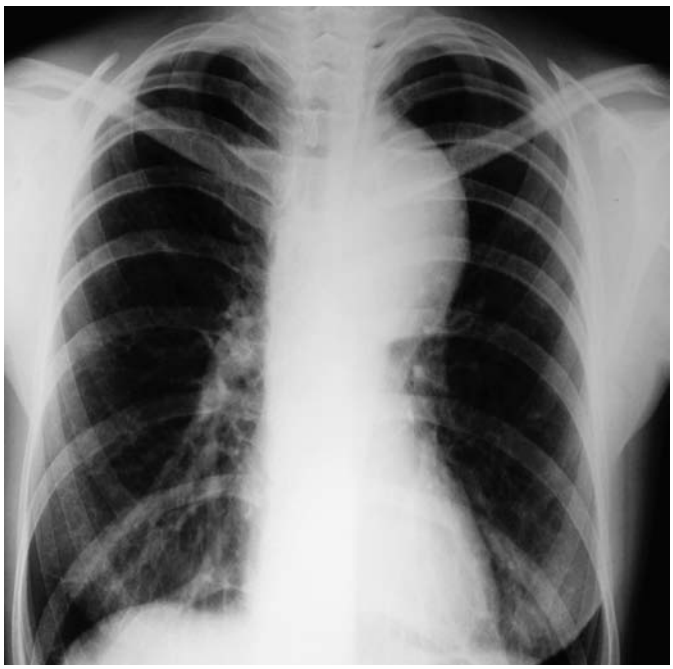
tral extension.[8] In contrast to atherosclerotic aneurysm, post-traumatic aneurysm occurs in younger people, where 90% patients are younger than 45. In almost 50% of cases, they were detected accidentally during a systematic radiographic examination. A detailed medical history can assist in associating this aneurysmatic formation with a trauma which had previously occurred many years ago.[7] The traumatic aortic rupture may be difficult to be diagnosed, and if missed, it almost always leads to a fatal result. Thoracic radiography is considered to be a very useful screening method.

Patients and methods

During the period of 22 years we have found 8 posttraumatic pseudoaneurysms of thoracic aorta, in 7 (87.5%) male and 1 (12.5%) female patient. At the moment of their accident the youngest patient was 21 and the oldest was 55 (mean age 33.8), and at the moment of diagnosing a pseudoaneurysm they were 27 and 55 years old (mean age 38.7). Over the period of 22 years different diagnostic methods were used, depending on technological achievements and diagnostic tools that we have had on disposal at different times. All 8 (100%) patients had a chest radiograph and CT scan performed (7 examinations were performed on sequential Somatom DR, and 1 on the four-row Volume Zoom Siemens), 6 (75%) patients had *i.v.* DSA and 1 (12.5%) patient had a MRI scan. CT examinations were performed with the *i.v.* application of 120 ml, and *i.v.* DSA with 60 ml of contrast medium. MRI scan examination was performed on Magnet 1T Siemens unit, with the "time of flight" (TOF) sequence. Considering that 7 examinations were performed on sequential CT unit, and only one on the multislice machine, the "road maps" review was acquired with *i.v.* DSA in 6 cases and once with MRI, before making a decision concerning the surgical treatment.

Results

In 8 (100%) patients who suffered road traffic accidents, who had signs of mediastinal widening and enlargement of the aortic knob (Figure 1A, B), some had lamellar calcifications as well, the traumatic pseudoaneurysm was proved by CT (Figure 2A, B), *i.v.* DSA and MRI (Figure 3). In 7 (87.5%) patients it was a chronic posttraumatic pseudoaneurysm, and in only one case it was an acute posttraumatic pseudoaneurysm. The period from the accident to the diagnosis of the pseudoaneurysm was 7 days in the last patient, and in the others it was between 2 months and 18 years (median 2.0 years). The diameter of the pseudoaneurysm was 4.5 to 9.2 cm (median 5.5 cm). In 7 (87.5%) injured patients the isthmus was involved, and in 1 (12.5%) case it was the descending thoracic aorta. In all 8



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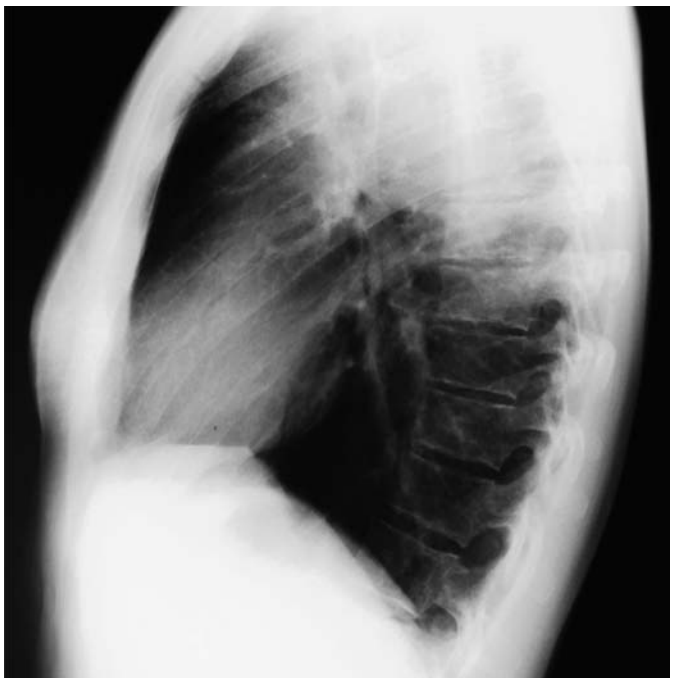
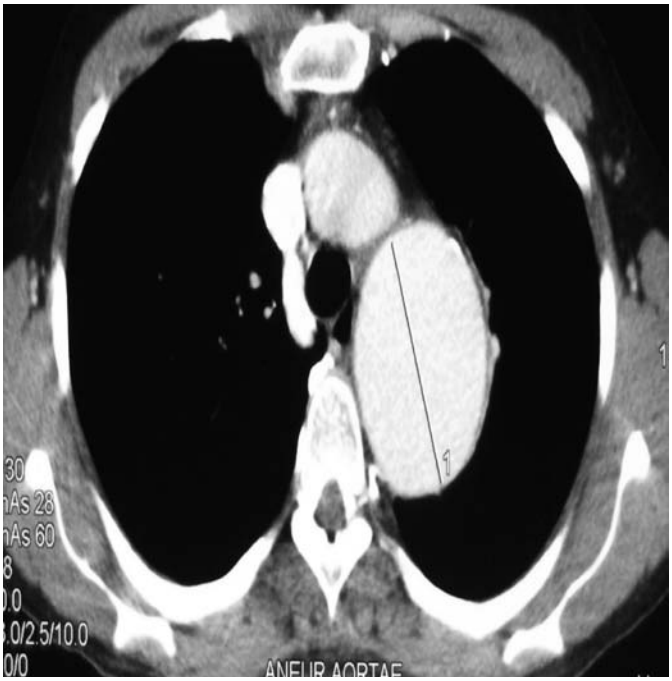


B

FIGURE 1A, B. Chest x – ray of aortic knob enlargement.



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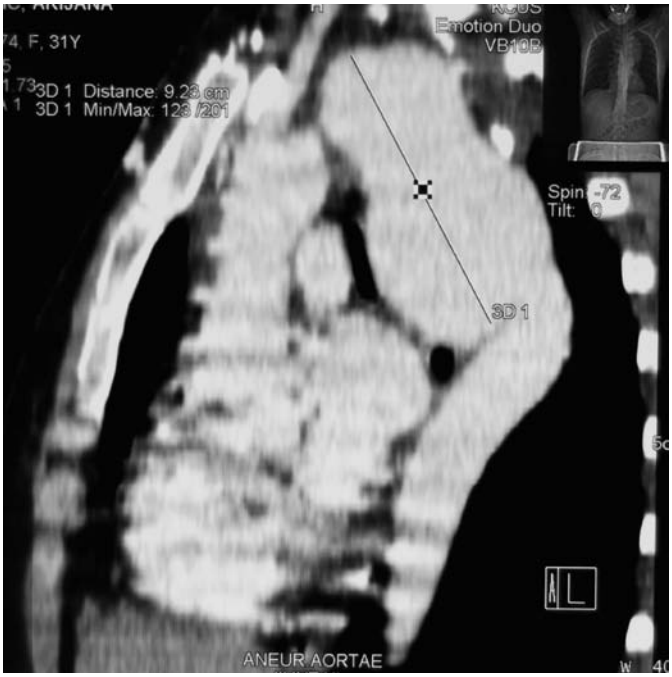

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FIGURE 2A, B. CT of posttraumatic pseudoaneurysm of the aortic isthmus.

(100%) patients the chest radiograph has shown the enlargement of the aortic knob and widening of the mediastinum. The chest radiographs have shown marginal calcifications in 4 (50%), and CT in 5 (62.5%) patients. Intraluminal thrombosis was discovered by CT examinations in 2 (25%) traumatized patients. All three methods have shown the presence of the posttraumatic pseudoaneurysm of the thoracic aorta. The chest radiograph was the initial method indicating pathology (Figure 1A, B). The largest diameter of the posttraumatic pseudoaneurysm was 9.2 cm, and it was detected in the pregnant patient 8 years after the accident, while the aneurysm detected 18 years after the accident in a male patient had a diameter of 7 cm. The characteristics and localization of the posttraumatic pseudoaneurysms are presented in Table 1.

CT scanning had a 100% specificity and sensitivity, and also provided the additional information on the wall calcification and thrombotic masses, as well as some other findings in the thorax.

Six (75%) patients were treated with the surgical placement of a Dacron graft, and the last case diagnosed with multislice CT 7 days after the injury, was treated with the placement of a stent graft. One patient did not agree to undergo a surgical operation, and has been occasionally checked up for a longer period.

Discussion

The traumatic rupture of the thoracic aorta is a rare condition in critically injured victims of a blunt trauma. The cause for the trauma are falls from heights >3 m, and motor vehicle crashes, so that some authors believe that all victims of significant decelerating traumas should be referred to an angiographic examination of the aorta.

A blunt trauma can damage the thoracic aorta with several mechanisms, by the fracture dislocating thoracic vertebrae, or by the penetration of the first rib and clavicula. A very high pressure may occur in the aorta due to various forces occurring in the thorax caused by acceleration, either in horizontal or vertical plane in the moment of impact (the effect of a water hammer) and the rupture is caused by an explosive burst.

During a motor traffic accident, the descending aorta remains fixed to the back thoracic wall by means of interosseous arteries, whilst the heart and ascending aorta contort toward the front and the split occurs within the isthmus, which is the most common rupture site.[1]

According to the referential data, about 90% of injuries include the region of the aortic isthmus, immediately distal from ligamentum arteriosum, and the left subclavical artery with ripping of vessels of the arch. Splits of ascending aorta, of distal descending aorta, or of abdominal aorta are much less common.[7,9] In this analysis we had 7 (87.5%)

TABLE 1. Characteristics and localization of the posttraumatic pseudoaneurysms

No.	Sex	Period from trauma to diagnosis	Diameter of the aneurysm	Calcifications	Thrombotic masses	Involved segment of the aorta	Treatment
1	M	7 days	4.8 cm	-	-	Isthmus	Stent
2	M	2 years	5.2 cm	+	-	Isthmus	Dacron graft
3	M	60 days	4.5 cm	-	-	Isthmus	Dacron graft
4	M	18 years	7.0 cm	+	+	Isthmus	Dacron graft
5	M	2 years	5.5 cm	+	+	Descending aorta	Dacron graft
6	M	9 years	6.0 cm	+	-	Isthmus	Refused treatment
7	M	180 days	5.5 cm	-	-	Isthmus	Dacron graft
8	F	8 years	9.2 cm	+	-	Isthmus	Dacron graft

isthmic lesions and one lesion of the descending thoracic aorta.

According to the literature, most victims die immediately (85%), whilst those who manage to get to hospital, if they are properly diagnosed, may have a surgical or another reparation procedure done. The aortic injury may be limited to a partial circumferential split in the intima and/or media of the aortic wall.[5] About 15-20% of them survive an acute episode long enough to manage to get to hospital, with a periaortic haematoma and false aneurysm since adventitia has not been ruptured yet.[3,4,10]

The traumatic rupture of the thoracic aorta may occur at any time, sometimes during the examination procedure, whilst some patients appear to be in a more stable condition. Many patients can be referred to treatments of other life threatening conditions before the reparation of the traumatic rupture of the thoracic aorta, although a postponed therapy is not routinely recommended.[11]

According to some data, about 2% to 5% of patients are discharged from hospital without being diagnosed with the traumatic pseudoaneurysm of the thoracic aorta, so that a chronic post-traumatic aneurysm develops later on.[4,7,8] In most cases, they suffer a secondary rupture, which results in death later on. However, there are rare reports in medical literature about a prolonged period of surviving.[3]

It has been suggested in medical literature that the enlargement and the risk of the rupture progressively increase the longer the aneurysm is present.[8] In this analysis, posttraumatic pseudoaneurysm of the aorta was found in 8 patients, out of which in 7 (87.5%) cases at the isthmus, which is in accordance with the literature.

The median time period from the accident until the detection of pseudoaneurysm was 2,0 years, while in one patient it was as long as 18 years. This demonstrates the potentially long survival period in some patients.

The primary damage of the aortic wall probably influences the development and the size of the aneurysm. With time, lamellar calcifications will develop around the pseudoaneurysm, which were found in 62.5% of cases, mainly in patients with the pseudoaneurysms over 2 years old. Calcifications can be seen in a chest radiograph, and especially on multislice CT. It is possible that they have a certain role in the length of the survival in such patients.

Intramural thrombosis in these patients was rare, in only 2 (25%) patients. All described posttraumatic pseudoaneurysms were chronic, except in one patient where it was detected 7 days after the accident.

The traumatic rupture of the thoracic aorta is a highly lethal condition and is often combined with multiple injuries, all of which may require an immediate evaluation and treatment.[11]

Clinicians keep perplexed how such a catastrophic lesion presents with so few real symptoms and signs. It is crucial that the emergency health practitioner recognizes it in making an initial diagnosis. Quite often those subtle changes remain unnoticed in the initial stage and remain undetected until the complete rupture and death occur.[3]

Symptoms of the traumatic rupture of the thoracic aorta include: chest pain, dyspnoea, backache, harsh voice, dysphasia and cough, as well as contusion of the front wall of the chest, with the impression of the wheel on the front part of the chest, and the acute coarctation syndrome.[3,9] The unstable condition of a bleeding patient should also raise suspicion.

Thoracic radiography is an initial analysis most frequently used for verifying the traumatic rupture of the thoracic aorta. It is indicative in almost half

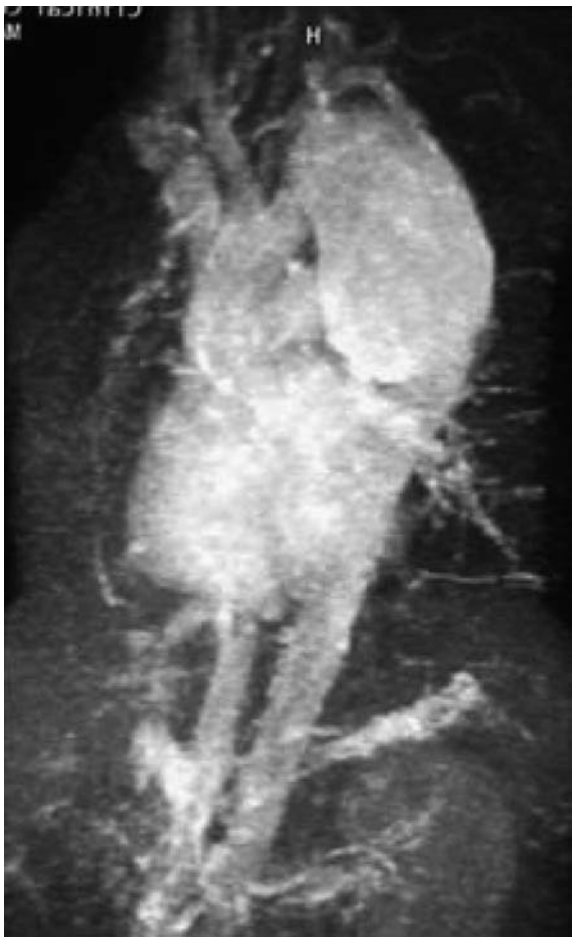

FIGURE 3. TOF MRI of posttraumatic pseudoaneurysm of the aortic isthmus.

of all cases. The interpretation of thoracic radiography in the patient in lying position is difficult. The extension and changes in the shape of the mediastinum on radiography are the most important signs of the aortic rupture and traumatic pseudoaneurysm of the aorta (Figure 1A, B). The most frequently radiographic signs reported are: abnormal shape of the aorta, shading of aortic-pulmonary window, left major bronchus shift downwards, deviation of trachea to the right from the medial line, shift of the nasogastric tubus, apical cap and border calcifications on the outer part of the mass, etc. Haematomas most commonly come from small arteries and veins in the mediastinum. Some 7.3% of patients have a normal mediastinum presented on the initial radiography, unless the traumatic pseudoaneurysm has been followed by a mediastinal haemorrhage, or haematoma, or the pseudoaneurysm has been very small, or it has been located in such manner as to keep the mediastinal shape unchanged.[3,8]

In this study, the chest radiography in 8 patients (100%) with post-traumatic pseudoaneurysm of the thoracic aorta, showed an enlargement in the mediastinum, as well as an enlargement of the aortal knob. In 4 patients (50%), lamellar border calcifications were also noticed. History of the road traffic accident directed the diagnostic method.

Until recently, aortography was the most accepted standard amongst methods of screenings for the signs of the traumatic rupture of the thoracic aorta. The problem with aortography is that it is an invasive method which uses iodine as a contrast medium, and it also gives an inadequate picture of intraluminal thrombosis. Although aortography was the most accepted standard, it was not free from false-positive and false-negative results. The problem is also the transportation of a potentially unstable patient to the area for the vascular examination.

In this analysis, the posttraumatic pseudoaneurysm was in 7 (87.5%) cases confirmed with sequential CT scan and in 6 (75%) cases it was supplemented with *i.v*. DSA. In 1 (12.5%) case the posttraumatic pseudoaneurysm was confirmed with MRI, and the last one with the multislice CT (Figure 2A, B).

In 1976, transoesophageal echocardiography appeared, as a method to complement and possibly substitute aortography of the arch in the evaluation of unstable multiple traumatized patients with a potential rupture of the aorta. The examination is less invasive, it does not require a contrast medium, it can be performed with the patient lying in bed, and lasts for 15 minutes. However, it depends highly on the professional who performs it, it is not always available, and there is also a problem due to securing airways and cervical spine.

With the emergence of a spiral CT (SCT), it has confirmed to be efficient for screening of critically injured patients with the traumatic rupture of the thoracic aorta. In 1998, Wicky *et al.* reported that with the blunt trauma to the chest and injury to the aorta, CT has 100% of sensitivity, and 99.8% of specificity, with 89% positive and 100% negative predictive values, and the total diagnostic accuracy of 99.7%.[12] CT examination results typically consist of a sack-shape bulge which has been demarked from the aortal lumen with a collar. According to this author, an operation based on CT is safe and expeditious. A positive SCT leads to thoracotomy, whereas a negative one excludes it. According to this author, an angiogram is unnecessary and it only delays a definite therapy, whilst a positive CT is the only diagnostic method which needs to be done prior to referring a patient to the theatre.[10]

Contrary to the conventional angiography, a multilayered CT angiography not only shows blood vessels, but it also allows an evaluation of nearby structures, or determining of optimal stent-graft values.[13] The endovascular stent graft, is a very useful method in managing the aneurism as a minimally invasive procedure.[14]

A more liberal use of CT in evaluation of patients with a blunt trauma has resulted in making more diagnoses of aortal splits, which could certainly be treated without surgery.[13] The diagnosis of post-traumatic pseudoaneurysm in this study has been confirmed by using CT in 8 (100% cases), *i.v.* DSA in 6 cases (75%), and MRI in 1 case (12.5%). CT has confirmed to be an excellent method in depicting the aneurismal sack, calcifications and thrombus within the pseudoaneurysm (Figure 2A, B).

A cardiovascular MRI is a non-invasive examination, without irradiation, for the evaluation of the real and false aneurysm of aorta. 3D gadolinium-enriched magnet resonance angiography collects information and thus enables a detailed examination of aneurysm and its relationship with other structures.[6] The weakness of this procedure is in its slowness, also its frequent inability to connect to monitoring devices needed in urgent situations, and a poor visibility of calcified deposits and changes in pulmonary parenchyma (Figure 3).

Until recently the treatment of patients with the traumatic injury of the thoracic aorta has been surgical with an operative death rate between 3.5-4.6%, or the risk of a post-operative paraplegia.[8,9,15] However, the latest studies emphasise that patients treated with the endovascular stent graft stay shorter in hospital compared to those who have been referred to the open surgery.[15]

In this study, 6 patients were treated with the open surgery and the placement of a Dacron graft, 1 patient was treated with the placement of an endovascular stent graft, while one patient has rejected an open surgery and has been periodically checked up.

Conclusions

It is significant to point out the hidden nature of the traumatic rupture of the thoracic aorta, which may be undiagnosed and many years later accidentally revealed as a chronic posttraumatic pseudo aneurysm of the thoracic aorta, unless it ruptures in the meantime and threatens the patient's life.

Pseudoaneurysm should be considered in patients with a blunt chest trauma, and with suspicious chest radiographic findings. Multislice SCT angiography is a fast, safe and non-invasive imaging technique which can prevent the occurrence of late pseudoaneurysm formation of the thoracic aorta, with an excellent depiction of the aneurysmatic sack, marginal calcifications and thrombotic masses within the pseudoaneurysm, as well as of associated thoracic lesions. All departments that receive trauma patients should have a multislice CT. In most trauma centres CT screening is an integral part of the diagnosis and care of patients with serious blunt injuries.

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case report

Radiological considerations in von Hippel-Lindeau disease: imaging findings and the review of the literature

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Background. Von Hippel Lindau disease is an autosomal dominant multisystem/multitumoral cancer disease diagnosed by clinical, radiologic and genetic findings. Its prevalence has been estimated to be of 1/36000 inhabitants. The tumours can be benign or malignant.

Case report. We represent MR findings of a family with ten children. Mother and five siblings had von Hippel-Lindau disease.

Conclusions. Radiologic imaging is very important for the early diagnosis and treatment of asymptomatic patients. Diagnosing it early is important because the tumours in von Hippel Lindau disease are treatable. Also, an early detection allows the patient's survival and quality of life. A multidisciplinary team approach is important in screening.

Key words: von Hippel-Lindau; magnetic resonance imaging; brain; spine; tumours

Introduction

von Hippel Lindau (VHL) disease was described in von Hippel's literature in 1911 and Lindau's literature in 1926.[1] Symptoms caused by VHL disease depend on the organ which was involved. Patients with the involvement of the central nervous system (CNS) at presentation are usually aged 25-35 years. CNS haemangioblastoma is the most commonly recognized manifestation of VHL disease and occurs in 40% of patients.[2,3] CNS lesions include haemangioblastomas and endolymphatic sac tumours. Visceral manifestations include renal/pancreatic carcinomas and cysts, neuroendocrine tumours and epididymal cysts. The most important causes of mortality are renal cell carcinoma and cerebellar haemangioblastomas. We represent a family with von Hippel-Lindau disease and discuss imaging findings with regard to the literature.

Case report

Patients' medical history and family history

The MR findings of an intermarriaged family with VHL disease were presented. The family had ten children. Two female siblings died from central nervous system haemangioblastomas as like their mother (Figure 1). A 22 year-old male sibling had intraventricular choroid plexus papillomas (Figure 2) with cerebellar and spinal haemangioblastomas (Figure 3). A 33 year-old female patient had headache, tinnitus and abdominal pain. She had a history of endolymphatic sac tumour (Figure 4) treated by surgery. She was found to have cerebellar/spinal haemangioblastomas, pancreas and kidney cystic masses (Figure 5). The younger (21 year-old) asymptomatic female sibling was referred to the radiology department for magnetic resonance (MR) imaging. She was investigated for possible tumours. She was found to have ELST and cerebellar/spinal haemangioblastomas (Figure 6) and

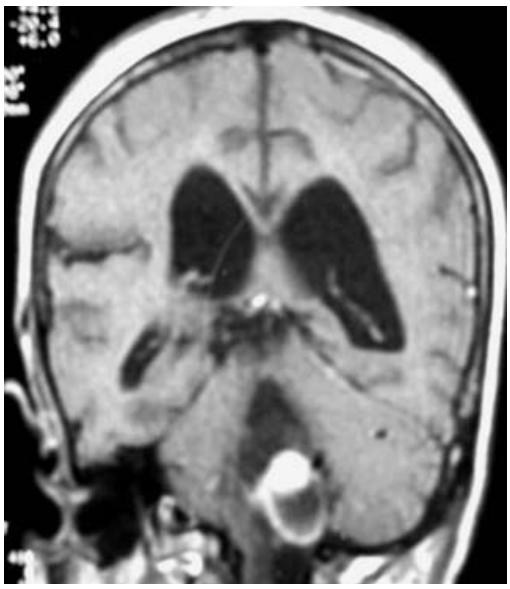

FIGURE 1. Coronal T1 post-contrast MR image shows a large cystic tumour with enhancing mural nodule in medulla oblongata. There are surgical changes in the *posterior fossa* with dilated fourth and lateral ventricles.

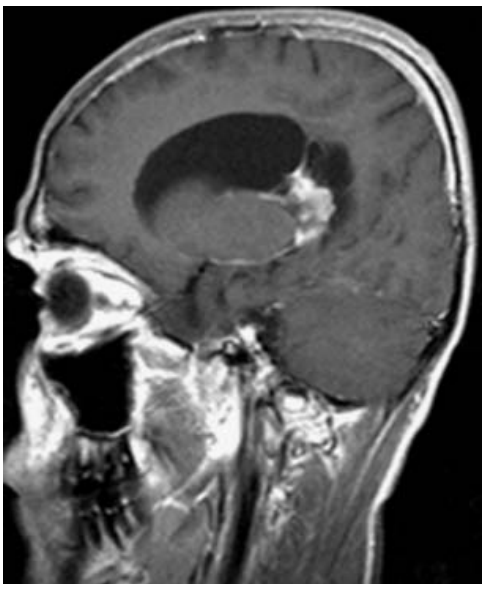

FIGURE 2. Axial T1 post-contrast MR image shows choroid plexus papilloma in the lateral ventricle.

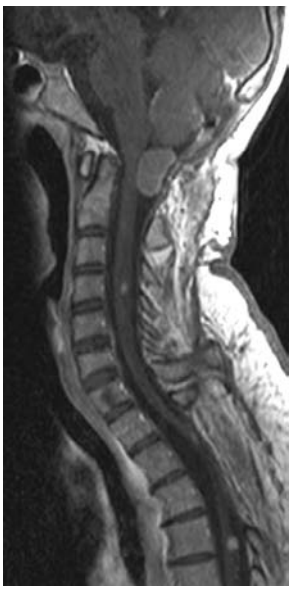

FIGURE 3. Sagittal T1 post-contrast MR image shows cerebellar haemangioblastoma in the foremen magnum with spinal haemangioblastomas.

underwent radiosurgical ablation (gamma-knife) therapy twice. She has been stabile for three years. The father and the other five siblings were found to be free of the disease.

Discussion

VHL disease is an autosomal dominant progressive disorder that is associated with various tumours and cysts in the CNS and other visceral organs.[1-5] The VHL gene was identified in 1993 by Latif *et al.* by positional cloning.[2] The responsible gene is located on the chromosome 3p25-26. The gene has high penentrance but delayed or variable expression and may cause widely different clinical manifestations. VHL disease causes tumours in multiple organs.[4] Some studies showed that the VHL gene is also inactivated in sporadic renal cell carcinoma, haemangioblastoma and pheochromocytoma.[1]

The clinical manifestation of the disease is reported in 14 different organs with 40 different lesions. These include retinal and CNS haemangioblastomas, endolymphatic sac tumours, renal cell carcinomas and cysts, pancreatic tumours and cysts, pheochromocytomas, and epididymal cystadenomas.[4,5] The most common CNS tumour is haemangioblastoma and occurs in 40% of patients.[3] Symptoms often begin in the second to third decades of life. Patients may present with neurologic symptoms such as headache, ataxia, and blindness. The exact neurologic deficit depends on the site of the primary lesion.[6,7] The median life expectancy is 49 years.[4] Usually morbidity and mortality are associated with frequent surgeries to the tumour recurrence. Renal cell carcinomas are the cause of death in 30-50% of the patients.[1]

Molecular genetic testing allows the identification of a deletion or significant mutation that confirms the diagnosis of VHL disease.[4] But there is also a clinical diagnosis in VHL disease.

The diagnostic criteria for VHL disease are:

- More than 1 haemangioblastoma in the CNS,
- 1 CNS haemangioblastoma and visceral manifestations of VHL, or
- 1 manifestation and a known family history of VHL.[6]

VHL disease was clinically classified into two types. Pheocromocytoma predicts the type. Those which accompanied with this tumour are VHL type 2.[1]

Imaging plays a key role in the identification of abnormalities and in the subsequent follow-up of lesions. It is also important in screening of individuals who are not yet symptomatic.[2]

Recent VHL disease-associated CNS molecular base studies enable new knowledge into their origin and development.[6] Also the timely diagnosis of this syndrome is important for manifestations.[7] The high-risk gene carriers must be screened regularly

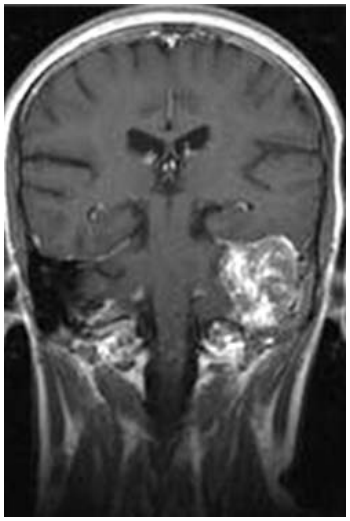

FIGURE 4. Coronal T1 post-contrast MR image shows endolymphatic sac tumour on the left vestibular aqueduct.

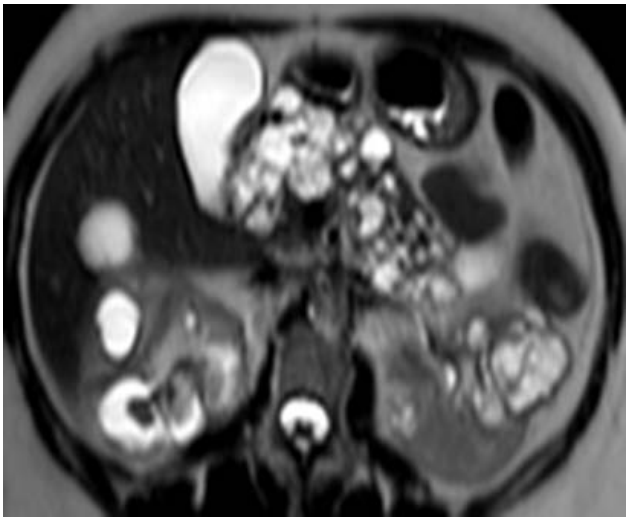

FIGURE 5. Axial T2 weighted MR image shows multiple cysts in kidney and pancreas.

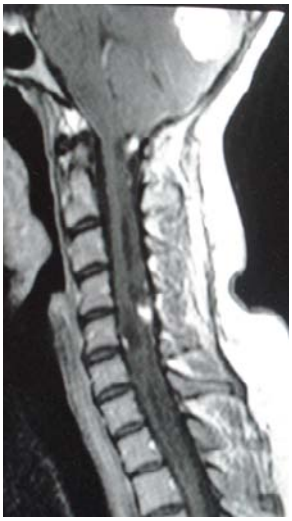

FIGURE 6. Sagittal Axial T2 weighted MR image shows multiple cysts in kidney and pancreas.

by clinically and radiologically examinations.[4] One asymptomatic female sibling was found to have endolymphatic sac tumour. She received the therapy before she became symptomatic.

VHL disease can be detected easily by a simple blood test. Accuracy is approaching 100% but the test is not widely available.[5] A multidisciplinary approach is necessary. Geneticists, neurologists, urologists, gastroenterologists, ophthalmologists, and radiologists are needed to constitute this team.[6] Screening protocols will vary between centres, but the protocol of National Institute of Health, USA is being widely accepted.[8] Computed tomography (CT) has the risk of ionizing radiation, which is a problem when screening asymptomatic patients or at-risk relatives.[6] MRI should be considered instead of CT[5], because of avoiding ionizing radiation.[9] CNS manifestations can be detected with great accuracy by MRI.[4,6,7] MRI is also effective in the differential diagnosis of the abdominal involvement.[10-13] It is very important not to use gadolinium base MR contrast agents in patients with the renal involvement whose estimated glomerular filtration rate of less than 30 mL/min. There is a risk of *nephrogenic systemic fibrosis*.[14,15] However, *nephrogenic systemic fibrosis* incidence in at-risk patients receiving contrast-enhanced MRI can be reduced after changing contrast administration protocols that include changing the type and dose of the contrast agent.[16] VHL patients usually have multiple operations for haemangioblastoma. Recently, it is believed that postoperative morbidities are major causes of the physical disability in VHL disease.[6] The important point is to decide the perfect time for the operation. Mother of the family had died due to haemangioblastoma and hydrocephalus after having multiple operations. Her tumour was located in medulla oblongata. Three siblings had multiple CNS haemangioblastomas. One underwent operation, the other two received stereotactic radiosurgical ablation (gamma knife therapy). This therapy was found to be useful in patients with multiple small haemangioblastomas in VHL disease. Renal cell carcinomas of less than 3 cm in diameter have to be followed by 6 to 12 months period.[4] One of our patients has multiple cysts in kidney. She has been under MRI follow up in every year with laboratory testing.

There have been important improvements in the management of VHL in the last two decade. The morbidity and mortality of patients with VHL disease has been reduced.[5] The resection of the tumour, cyst aspiration, stereotactic radiosurgical ablation, photocoagulation, and cryotherapy of any retinal lesions are the choices of the treatment.[4] VHL is a lifetime disease. Patients need to be constantly checked for the tumours and cysts that develop at various sites in the CNS and visceral organs throughout his/her lifetime. Some patients even receive up to 20 surgical operations in their lifetime to remove tumours.[1,17]

The conservative approach to the treatment of VHL lesions is now more widely accepted, a radiologic follow-up with non-invasive imaging especially with MRI is important.

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research article

Loss of heterozygosity of *CDKN2A (p16INK4a)* and *RB1* tumor suppressor genes in testicular germ cell tumors

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Background. Testicular germ cell tumors (TGCTs) are the most frequent malignances in young adult men. The two main histological forms, seminomas and nonseminomas, differ biologically and clinically. pRB protein and its immediate upstream regulator p16INK4a are involved in the RB pathway which is deregulated in most TGCTs. The objective of this study was to evaluate the occurrence of loss of heterozygosity (LOH) of the *CDKN2A (p16INK4a)* and *RB1* tumor suppressor genes in TGCTs.

Materials and methods. Forty TGCTs (18 seminomas and 22 nonseminomas) were analyzed by polymerase chain reaction using the restriction fragment length polymorphism or the nucleotide repeat polymorphism method.

Results. LOH of the *CDKN2A* was found in two (6%) out of 34 (85%) informative cases of our total TGCT sample. The observed changes were assigned to two (11%) nonseminomas out of 18 (82%) informative samples. Furthermore, LOH of the *RB1* was detected in two (6%) out of 34 (85%) informative cases of our total TGCT sample. Once again, the observed changes were assigned to two (10.5%) nonseminomas out of 19 (86%) informative samples. Both LOHs of the *CDKN2A* were found in nonseminomas with a yolk sac tumor component, and both LOHs of the *RB1* were found in nonseminomas with an embryonal carcinoma component.

Conclusions. The higher incidence of observed LOH in nonseminomas may provide a clue to their invasive behavior.

Key words: loss of heterozygosity; *CDKN2A*; *RB1*; seminomas; nonseminomas

Introduction

Testicular germ cell tumor (TGCT) is diagnosed mainly after puberty and is the most frequent malignancy in young adult men[1], however, it is also not rare in childhood.[2] The two main histological forms, seminomas and nonseminomas, differ biologically and clinically. About 50% of TGCTs are pure seminomas and 40% pure or mixed nonseminomas. The remaining 10% containing both seminoma and nonseminoma components are classified as being nonseminoma according to the World Health Organization (WHO) classification system.[3] The genetic alterations underlying the development of these neoplasms have not been understood fully, although much has been done to elucidate them.[4,5]

The cell cycle regulatory pathway deregulated in almost all human tumors appears to be the G_1 phase-controlling mechanism centered around the pRB protein. Different cancers seem to have altered different key components of that mecha-

nism, which may be connected with gene activity patterns in different target cells.[6] The mechanism involves pRB and its immediate upstream regulators, the cyclin dependent kinases (CDK4 and CDK6), their catalytic partners (cyclin D1, cyclin D2 and cyclin D3), and the members of the INK4 family of CDK inhibitors (p16INK4a, p15INK4b, p18INK4c and p19INK4d). This mechanism seems to be a common point for various signaling pathways, serving as a growth factor dependent cell cycle switch. Deregulation of the RB pathway may be an obligatory step in oncogenesis, making tumor cells less dependent on growth stimuli.[6,7]

The pRB is essential in cell cycle regulation and its function is regulated by phosphorylation. In G_0 and the early G_1 phase, hypophosphorylated pRB is complexed with the transcription factor E2F.[8] In late G_1, a significant hyperphosphorylation of the pRB by CDK4 and CDK6 in complex with D cyclins (D1, D2, D3) occurs.[9]

The *CDKN2* locus at chromosomal region 9p21 encodes p16INK4a tumor suppressor protein involved in the RB cell cycle control pathway.[10] p16INK4a functions as a regulator of G_1/S phase transition by inhibiting the activity of CDK4 and CDK6. Thus, by inhibiting pRB phosphorylation, p16INK4a can promote the formation of a pRB-E2F repressive transcriptional complex, which blocks cell cycle progression past G_1/S restriction point.[11]

In diverse types of cancer the RB pathway becomes deregulated through alterations in one or more of its components. The most common defects of the RB pathway are mutations or deletions of *RB1* and inactivating mutations or promoter methylation of the *CDKN2A* (*p16INK4a*) tumor suppressor gene, as well as the overexpression of the cyclin D2/CDK4 complex.[6,12,13]

The objective of this study was to evaluate the occurrence of the loss of heterozygosity (LOH) of the *CDKN2A* and *RB1* tumor suppressor genes in TGCTs.

Materials and methods

Patients and tumor material

Fourty TGCT samples (18 seminomas and 22 non-seminomas) were collected from Sisters of Mercy University Hospital and University Hospital Center, Zagreb, Croatia. The samples were formalin-fixed and paraffin-embedded. Clinical and pathological data for 40 TGCTs according to the WHO 2004 classification are shown in Table 1.

DNA extraction

For each specimen, 20 μm paraffin-embedded section was prepared for DNA extraction. In addition, 4 μm section was stained with hematoxylin-eosin to identify the tumor and normal tissue areas which were removed separately from the microscopic slide, transferred to microtubes and extracted using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany).

LOH analysis of CDKN2A gene

A previously described polymorphic microsatellite marker hMp16α-I1 consisting of a mononucleotide tract of $(A)_{23}$ located close to intron 1 of the *CDKN2A* gene was analyzed in this study.[14] Primers used for polymerase chain reaction (PCR) amplifications were 5′-CAATTACCACATTCTGCGCTT-3′ and 5′-CAGGCAGAGAGCACTGTGAG-3′, which produced 190-210 bp fragments. PCR amplifications were performed in 25 μl reaction volume with a final concentration 0.2 mM of each dNTP, 3 mM $MgCl_2$, 0.2 μM of each primer (Sigma-Aldrich, St. Louis, MI, USA), 1x Flexi buffer (Promega, Madison, WI, USA) and 0.5 U of GoTaq® Hot Start Polymerase (Promega, Madison, WI, USA). One hundred nanograms of DNA were used in each PCR reaction. PCR amplifications were carried out in a Eppendorf Mastercycler Personal (Hamburg, Germany), with cycling times of 96ºC for 5 min (one cycle), then 45 cycles of 96ºC for 30 s, 57ºC for 45 s, and 72ºC for 30 + 1 s. The final step was incubation at 72º C for 10 min. Amplified DNA fragments were analyzed on silver-stained 15% polyacrylamide gels. LOH of *CDKN2A* was considered to had occured if one out of two alleles (heterozygous samples) of a gene marker was missing or significantly reduced in comparison to alleles from adjacent normal tissue.

LOH analysis of RB1 gene

LOH of *RB1* was detected using polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP). Amplification with *RB1* primers 5′- TCCCACCTCAGCCTCCTTAG-3′ and 5′-GTAGGCCAAGAGTGGCAGCT-3′ used in our study produced a 190 bp segment of intron 17.[15] PCR amplifications were performed under conditions mentioned above. To generate the RFLP pattern for LOH analysis, 10 μl of PCR product were digested with 5 U of XbaI restriction enzyme (Fermentas, Vilnius, Lithuania) in a total volume of

TABLE 1. Clinical and pathological data for 40 testicular germ cell tumor cases

Patient no.*	Age	pTNM	Histology
1	26	pT1NXMX	ITGCN, S
2	26	pT1NXMX	ITGCN, S
3	37	pT1NXMX	S
4	33	pT1NXMX	ITGCN, S
5	31	pT1NXMX	ITGCN, S
6	29	pT1NXMX	ITGCN, S
7	39	pT1NXMX	ITGCN, S
8	27	pT3NXMX	S
9	41	pT1NXMX	ITGCN, S
10	48	pT1NXMX	S
11	48	pT2NXMX	S
12	34	pT1NXMX	ITGCN, S
13	60	pT1NXMX	ITGCN, S
14	29	pT1NXMX	ITGCN, S
15	60	pT1NXMX	S
16	29	pT1NXMX	ITGCN, S
17	28	pT1NXMX	ITGCN, S
18	32	pT1NXMX	ITGCN, S
19	37	pT1NXMX	EC
20	18	pT2NXMX	EC, IT, MT, S
21	24	pT1NXMX	EC, ITGCN, S
22	22	pT2NXMX	EC, YST
23	37	pT1NXMX	EC, ITGCN, S
24	28	pT2NXMX	C, EC, IT, MT
25	17	pT2NXMX	EC, MT
26	34	pT2NXMX	EC
27	19	pT1NXMX	EC, ITGCN, MT, YST
28	39	pT1NXMX	MT, YST
29	21	pT2NXMX	EC, MT, YST
30	23	pT2NXMX	EC, IT, MT
31	22	pT1NXMX	MT, YST
32	25	pT3NXMX	EC
33	45	pT2NXMX	EC, ITGCN, S, YST
34	NK	pT2NXMX	C, EC, ITGCN, S, YST
35	23	pT2NXMX	EC, IT, ITGCN, MT, YST
36	39	pT1NXMX	EC, ITGCN, S, YST
37	24	pT2NXMX	EC, ITGCN, YST
38	30	pT1NXMX	EC, ITGCN, YST
39	36	pT1NXMX	EC, ITGCN, MT, YST
40	58	pT2NXMX	EC, ITGCN, YST

*seminomas, patients no. 1-18; nonseminomas, pateints no. 19-40

C = choriocarcinoma; EC = embryonal carcinoma; IT = immature teratoma; ITGCN = intratubular germ cell neoplasia; MT = mature teratoma; S = seminoma; YST = yolk sac tumor; NK = not known

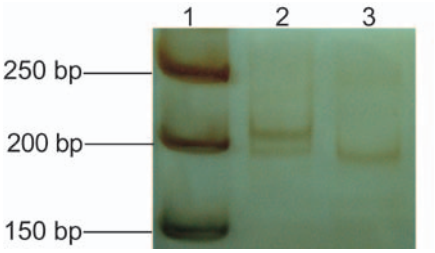

Figure 1. Loss of heterozygosity (LOH) of the *CDKN2A* gene at polymorphic microsatellite marker hMp16a-I1. Silver-stained 15% polyacrylamide gel. Lane 1: 50-bp DNA ladder (Fermentas, Vilnius, Lithuania); lane 2: heterozygous normal testis tissue; lane 3: LOH in the corresponding testicular germ cell tumor (nonseminoma, patient no. 31).

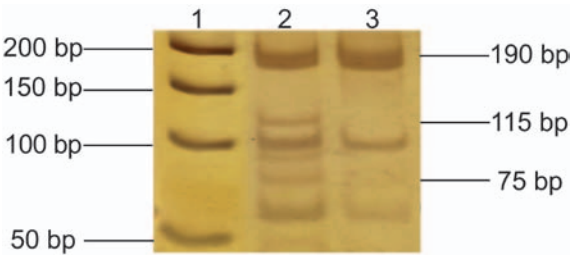

Figure 2. Loss of heterozygosity (LOH) of the *RB1* gene at intron 17 (XbaI restriction polymorphism). Silver-stained 15% polyacrylamide gel. Lane 1: 50-bp DNA ladder (Fermentas, Vilnius, Lithuania); lane 2: heterozygous normal testis tissue; lane 3: LOH in the corresponding testicular germ cell tumor (nonseminoma, patient no. 25).

25 μl for 12 h. The restriction digestion resulted in fragments of 75 and 115 bp. DNA fragments were analyzed on silver-stained 15% polyacrylamide gels. LOH was recognized as a partial or complete loss of either the uncleaved (190 bp) or the cleaved (75 + 115 bp) allele.

Results

In this study 40 TGCTs, 18 seminomas and 22 nonseminomas, were analyzed. First, we searched for LOH of the intragenic polymorphic microsatellite marker hMp16α-I1 in the *CDKN2A* gene. From 40 TGCTs, 34 (85%) tumors were informative for this polymorphism, 16 (89%) seminomas and 18 (82%) nonseminomas. Our analysis revealed that two (6%) samples showed LOH of hMp16α-I1 marker. The observed changes were assigned to two nonseminomas (11%, patients no. 31 and 34, Table 2). In both tumor cases, one out of two allels of gene marker was missing in comparison to alleles from the adjacent normal tissue (Figure 1). In addition, both LOHs of the *CDKN2A* were found in nonseminomas with a yolk sac tumor component. LOH of the *CDKN2A* gene was not observed among seminomas.

The analysis of intragenic polymorphic restriction marker of the *RB1* gene showed that 34 (85%) of total TGCTs were heterozygous for this polymorphism; 15 (83%) seminomas and 19 (86%) nonseminomas. LOH was observed in two (6%) samples when looking at the total TGCTs analyzed. Once again the observed allelic losses were assigned to nonseminomas: two samples (10.5%, patients no. 20 and 25, Table 2) had one of the alleles missing in comparison to bands from the adjacent normal testis tissue. These nonseminoma samples showed loss of the cleaved allele (75- and 115-bp fragments), as the single uncleaved allele (190-bp fragment) appeared on the silver stained 15% polyacrylamide gel (Figure 2). Furthermore, both LOHs of the *RB1* were found in nonseminomas with an embryonal carcinoma component. None of the seminomas demonstrated LOH of the *RB1* gene.

No statistically relevant correlation between the occurrence of LOH, form of TGCT, histological type of contained components and tumor stage according to TNM classification could be determined by Fisher's exact test.

Discussion

TGCT is associated with characteristic abnormalities in the RB pathway including upregulation of cyclin D2, and downregulation of pRB and the CDK inhibitors such as p16INK4a.[7]

The inactivation of the *CDKN2A* gene, which encodes an inhibitor of CDK4 and CDK6, is one of the most common molecular events in human neoplasms. The major mechanisms contributing to *CDKN2A* silencing are promoter methylation, gene mutations and hemizygous or homozygous deletions. When one *CDKN2A* allele is mutated or methylated, the second allele is often deleted.[16]

The analysis of the expression of INK4 family has pointed to a down-regulation of *CDKN2A* in testicular neoplasms.[7,12] Honorio *et al*.[17] demonstrated that promoter hypermethylation of that gene is not involved in the decrease of p16INK4a protein expression. In contrast, some studies have found promoter mutation, a half of analyzed TGCTs had *de novo* promoter methylation and approximately half of TGCTs showed hypermethylation of *CDKN2A* exon 1α. All that correlated with a decreased level of *CDKN2A* mRNA expression.[1,18] However, Chaubert *et al*.[18] have not detected any *CDKN2A* mutations and observed LOH of the *CDKN2A*

TABLE 2. A) Observed loss of heterozygosity (LOH) and B) distribution of observed LOH of *CDKN2A* and *RB1* genes in testicular germ cell tumors

A) observed LOH		
Patient no.	**CDKN2A**	**RB1**
20		LOH
25		LOH
31	LOH	NI
34	LOH	I
B) distribution of observed LOH		
Tumor	**CDKN2A**	**RB1**
Seminoma, Σ 18	0% (0/16)	0% (0/15)
Nonseminoma, Σ 22	11% (2/18)	10.5% (2/19)

I = informative (heterozygous); NI = not informative (homozygous)

Numbers in parentheses: the number of tumors demonstrating LOH over the number of informative tumors.

gene in only one of 29 TGCTs with a yolk sac tumor component, using seven different markers. These observations indicate that *CDKN2A* gene inactivation might be an important mechanism leading to cell deregulation in TGCTs.

Despite of promoter methylation and mutations being the most common ways of inactivating *CDKN2A* in TGCTs, various studies detected LOH at the position of the *CDKN2A* gene, varying from as low as 5.5% to as high as 42%. The LOHs of *CDKN2A* were reported mostly in nonseminomas.[5,19] Genomic region containing *CDKN2A* (9p21) is reported to be the most commonly deleted region early in the development of nonseminomas, which may be implicated in their ability to differentiate into various types, for various markers located within this region.[20]

In our study only nonseminomas demonstrated LOH (Table 2). Both LOHs of the *CDKN2A* were found in nonseminomas with a yolk sac tumor component, one sample also having an embryonal carcinoma component. Furthermore, one nonseminoma with the LOH of *CDKN2A* demonstrated LOH of *TP53* gene, and the other showed LOH of the *CDH1* gene.[21]

The *RB1* gene is often deleted or mutated to an inactive form in a variety of human tumors. Cells of embryonal testes and intratubular germ cell neoplasia (ITGCN) show no expression of pRB, whereas it is expressed in healthy testes during spermatogenesis. The lack of pRB in most TGCTs may, therefore, reflect its deregulation by normal mechanisms in testicular germ cells. However, the lack of pRB may facilitate the transition of those cells to tumor cells of ITGCN and thus contribute to molecular pathogenesis of TGCTs.[7,12] Lowered levels of pRB mRNA compared with normal testis did not reflect a grossly altered structure of the DNA coding regions, but instead relates to a potentially reversible transcriptional modulation through the promoter methylation. The pRB appears to be differentially expressed according to the differentiation status of the tumor, more differentiated cells of teratocarcinoma show positive immunohistochemical staining, less differentiated forms of TGCT such as embryonal carcinoma are stained negatively.[12,22,23]

In contrast, deletions of *RB1* gene are, along with its mutations, also reported as one of the most common alterations of the RB pathway. Various studies revealed deletions of the *RB1* gene region in testicular cancer.[5] For example, Peng *et al*.[24] used short variable number of tandem repeats in *RB1* introns 16 and 20, and found LOH in 5% of seminomas and 28% of nonseminomas analyzed within 93% of informative TGCT cases. The location of the *RB1* gene is reported to be one of the most commonly involved in allelic imbalance within TGCTs.[4] The exact alterations of the *RB1* in various forms of TGCTs needs to be further elucidated in more detail. Studies also revealed a different pattern of LOH in different histological types of nonseminomas for markers located within the genomic region containing the *RB1* gene (13q14), varying from 0% in yolk sac tumor component to 50% in choriocarcinoma.[25]

In our study, LOH of the *RB1* gene was found in nonseminomas with an embryonal carcinoma component, and both nonseminomas with LOH of *RB1* also demonstrated LOH of the *TP53* gene.[21] Interestingly, the amount of embryonal carcinoma component in TGCT, along with vascular invasion, has been proved so far to be the only clinically valid prognostic factor for the development of stage II metastatic testicular cancer.[26]

LOH of *CDKN2A*, *RB1*, *TP53* and *CDH1* in TGCTs may increase their tumorigenic potential by the increased proliferation capacity due to *RB1* loss and decreased rate of apoptosis due to *TP53* alteration.[19,21,27] It has been shown that TP53 is abundant but inactive in cells of TGCTs. In healthy testes such reversibly inactivated TP53 may play a role in switching between proliferation and apoptosis in cells undergone meiosis.[27] It was reported that, in cells that sustained lesion in the RB pathway, there was a strong selection for the loss or inactivation of wild type TP53. Alterations of *RB1* are often seen together with alterations of *TP53* in variety of different cancers.[6,10,15] It is possible that the inactivation of both *RB1* and *TP53* genes in a cell produces

a synergistic effect, which imposes a stronger selective pressure for the cellular transformation. This may also help to explain the high proliferation rate and/or invasiveness of TGCTs with embryonal carcinoma and yolk sac tumor component. A higher incidence of LOH in nonseminomas may provide a clue to their invasive behavior, because for some of the nonseminoma types there seem to be a region of preferential loss (3q27–3q28 in embryonal carcinoma), and all of the TGCTs show gain of 12p11–12p12 sequences.[20] Knowing the exact nature of genetic alterations associated with these tumors may provide novel treatment strategies.[28]

However, the low frequency of observed LOHs in this study could be a consequence of genomic instability in above mentioned nonseminomas, rather than the main cause of *CDKN2A* and *RB1* inactivation.[24]

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research article

Study of radiation induced changes of phosphorus metabolism in mice by ^{31}P NMR spectroscopy

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Background. The aim of this study was to examine whether ^{31}P NMR can efficiently detect X-ray radiation induced changes of energy metabolism in mice. Exposure to ionizing radiation causes changes in energy supply that are associated with the tissue damage because of oxidative stress and uncoupled oxidative phosphorylation. This has as a consequence decreased phosphocreatine to adenosine triphosphate ratio (Pcr/ATP) as well as increased creatine kinase (CK) and liver enzymes (transaminases AST and ALT) levels in serum.

Materials and methods. In this study, experimental mice that received 7 Gy of X-ray radiation and a control group were studied by ^{31}P NMR spectroscopy and biochemically by measuring CK and liver enzyme levels in plasma. Mice (irradiated and control) were measured at regular time intervals for the next three weeks after the exposure to radiation.

Results. A significant change in the Pcr/ATP ratio, determined from corresponding peaks of ^{31}P NMR spectra, was observed in the 7 Gy group 2 days or more after the irradiation, while no significant change in the Pcr/ATP ratio, was observed in the control group. This result was supported by parallel measurements of CK levels that were highly increased immediately after the irradiation which correlates with the observed decrease of the Pcr/ATP ratio and with it associated drop of muscle energy supply.

Conclusions. The ^{31}P NMR measurements of the Pcr/ATP ratio can in principle serve as an instantaneous and non-invasive index for assessment of the received dose of irradiation.

Key words: X-ray irradiation; ^{31}P NMR spectroscopy; creatine kinase; biological effects of radiation; radiation dosimetry

Introduction

Biochemical changes in macromolecules and with that associated tissue damage appears several ms after acute exposure to radiation. However, multiple consequences manifest in hours, years or even decades after the irradiation. Since stochastic biological effects of radiation could be detected only through carefully planned epidemiological studies, several attempts have been made to develop a successful method for detecting deterministic effects of radiation, where the rate of tissue damage is proportional to a received radiation dose.[1,2] Such methods may help determining received doses of radiation for all subjects that were at the time of exposure not equipped with radiation detection devices. This may have important applications in military use as well as in civil use: hospitals, nuclear power plants and in some industry branches.

The most promising are the methods based on the measurements of the long lived radiation induced stable radicals in the hydroxyapatite component of teeth and bones which can be measured by electron paramagnetic resonance (EPR).[3] With

the recent development of low-frequency EPR (1 GHz) the measurements *in vivo* on teeth seems to become plausible.[4]

The other challenge is to find the method by which it would be possible to measure direct biological effect that is proportional to the dose of radiation. According to Bergonié-Tribondeu's law[5], where the radiosensitivity of cells is proportional to their reproductive activity and inversely proportional to their differentiation level, only spermatogonia and erythroblasts are highly radiosensitive to radiation. Therefore, assessment of the radiation damage through methods, which detect the DNA damage[6], *i.e.*, gene aberration detection methods[7] or the FISH method[8,9], is found to be rather complicated and time consuming due to a need of gathering specific samples. Effects of radiation are associated also with a skeletal damage, which can be detected by MR microscopy.[10] Radiation has significant effect also on metabolism of living systems that is linked with changing concentrations of phosphocreatine (Pcr) and adenosine triphosphate (ATP) molecules. Pcr, also known as creatine phosphate, is an important molecule for energy storage in skeletal muscles. Pcr is used to generate ATP by transferring phosphate group to the adenosine diphosphate molecule (ADP) forming creatine for the 2 to 7 seconds following an intense anaerobic effort. ADP conversion to ATP occurs in a catalytic reaction catalyzed by creatine kinase (CK). The presence of CK in plasma is indicative of the tissue damage that may occur in powerful ischemic stress action to muscles, as for example in myocardial infarction.[11] ADP to ATP conversion is a reversible reaction and Pcr therefore acts as a spatial and temporal buffer of ATP. Pcr is first synthesized in the liver, then transported via the bloodstream and finally stored in muscle cells and the brain. Therefore, Pcr plays a particularly important role in tissues that have high, fluctuating energy demands.[12] Since irradiation impairs function of multiple organs[13] (*i.e.* liver function) it is also possible to detect radiation effects by measuring liver enzyme levels aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[14] AST and ALT are parenchymal intracellular enzymes released into systemic circulation when there is hepatocellular injury and necrosis.

The metabolic changes of tissues and organs can be efficiently monitored by NMR spectroscopy methods[15-17], in particular by phosphorous ^{31}P and carbon ^{13}C NMR spectroscopy methods. Phosphocreatine to adenosine triphosphate ratio (Pcr/ATP) as determined from corresponding spectral line peaks of ^{31}P spectra is an appropriate index to follow energy metabolism.[18,19] Until now few attempts have been made to detect effects of radiation by NMR spectroscopy. Ng *et al.* studied effects of gamma-irradiation on tumour cells by ^{31}P NMR spectroscopy.[20] They detected a dramatic decline in high-energy phosphates beginning one day after irradiation. Box *et al.* studied effects of radiation on degradation of glycine, a protein building block molecule, by ^{13}C NMR spectroscopy.[21] In addition to NMR spectroscopy methods, magnetic resonance (MR) imaging can be efficient in detecting effects of radiation as well. For example ^{19}F MR imaging was employed to detect accumulation of perfluorooctylbromide in spleen.[22] The accumulation was a consequence of macrophage dysfunction induced by irradiation.

The aim of this study was to examine relation between a received dose of ionizing irradiation and changes in metabolism that can be detected by ^{31}P NMR spectroscopy of mice for potential determination of the received dose of radiation. The study is based on assumption that exposure of whole-body to high-dose radiation for only a short time period results in development of cell death, which presumably occurs due to uncoupling of oxidative phosphorylation and increased ion flux. This results in increased CK levels in serum and consequently decreased Pcr/ATP ratio due to homeostatic mechanisms responsible for energy supply. Assuming that the radiation affects multiple tissues, including liver, muscles and central nervous system, where is the major production and storage of Pcr, we expect the decrease of Pcr in irradiated mice and no significant change in the non-irradiated control group. If the assumption is right, the Pcr/ATP ratio could be used as a biosensor for the received dose of radiation provided that other mechanisms effecting Pcr/ATP ratio are excluded.

Materials and methods

Experimental animals and irradiation

In the experiments, C57Bl/6 mice raised at the Institute of Pathology (Medical Faculty, University of Ljubljana, Slovenia) were used. Mice were maintained at 21°C with natural day/night light cycle in a conventional animal colony. At the beginning of the experiments, mice, that were 16-20 weeks old, were subjected to an adaptation period of 7–10 days before experiments. Mice were divided equally between a control group (6 mice) that was not

irradiated and a group that received 7 Gy of X-ray radiation (6 mice).

For X-ray irradiation a Darpac 2000 unit (Gulmay Medical Ltd, Shepperton, UK), operated at 220 kV, 10 mA, and with 0.55 mm Cu and 1.8 mm Al filtration was used. In experiments whole-body of mice was irradiated at a dose rate 2.2 Gy/min with single doses of 7 Gy. During whole body irradiation mice were anaesthetised with intraperitoneal injection of acepromazine (Promace, Fort Dodge Animal Health, Iowa, USA; 0.05 mg/mouse), ketamine hydrochloride (Bioketan, Vetoquinol, Paris, France; 2.5 mg/mouse) and xylazine hydrochloride (Rompun 2%, Bayer AG, Leverkusen, Germany; 0.25 mg/mouse).

Animal studies were carried out according to the guidelines of the Ministry of Agriculture, Forestry and Food of the Republic of Slovenia (permission No 34401-60/2007/8), and in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, Bethesda, MD). Protocol was approved by Veterinary administration of the Republic of Slovenia (34401-60/2007/8).

^{31}P NMR Spectroscopy

Metabolic changes in both mice groups were measured using ^{31}P NMR spectroscopy of the whole animal at the specific time of day for several days after the prime dose of radiation. The first measurement on irradiated mice was done immediately after the irradiation and then every other day for the next 14 days; no mice died within that period. The rest of the measurements on the control group were performed in five day intervals until three weeks after the experiment onset. NMR experiments were performed on a 2.35 T (100 MHz proton frequency) horizontal bore Oxford superconducting magnet (Oxford Instruments Ltd., UK) connected to a Tecmag Apollo spectrometer (TecMag, Huston TX, USA). ^{31}P NMR signal was detected by a Bruker 4 cm double-tuned surface coil (Bruker, Ettlingen, Germany). For MRI, mice were fist anaesthetised using the same procedure as for X-ray irradiation. After that they were placed in the MRI magnet in the centre of the surface coil to focus signal acquisition on muscles and internal organs. A special care was taken in reproducibility of the animal placement (in the standard ventral position) relative to the surface coil. The coil was then tuned to proton signal for the purpose of magnet shimming which was done using the proton NMR signal. After the shimming was completed the coil was tuned to ^{31}P and the ^{31}P NMR signal acquisition started. The signal was acquired by the standard 1D acquisition sequence consisting of one 90° excitation pulse followed by the signal acquisition. The acquisition parameters were: acquisition size 4096 points, spectral width 10 kHz, acquisition time 200 ms, repetition time 2.2 s. The signal was averaged 1200 times so the total experiment time was 44 min. The spectra were reconstructed using 10 Hz exponential line broadening to decrease the signal noise. During the experiment the animals were coated with a layer of a cotton wool to prevent them dying from hypothermia.

Measurement of creatine kinase and transaminases

The activities of creatine kinase (CK) and transaminases (AST and ALT) were measured in plasma of the irradiated mice with an automated biochemistry analyser RX Daytona (Randox, Crumlin, UK). Blood samples (200 μl) were collected from the orbital sinus by heparinised glass capillary before and after irradiation at different time points (10 min and 2, 4, 7, 9, 11 days). To prevent degradation of creatine kinase blood samples were centrifuged (3000 rpm, 10 min) in 10 min after dispossession. 100 μl of plasma samples were drawn in 1 ml tube and stored at -80°C until the analysis was performed.

Statistical analysis

Measured Pcr/ATP ratios of the irradiated and the control mice group were analyzed for statistically significant difference by the two-tailed Student t-test (MS Excel 2007).

Results

Typical ^{31}P NMR spectra of irradiated mice immediately after the irradiation, after 4 days and after 10 days are depicted in Figure 1 bottom row. For comparison, spectra of the control group acquired at identical time points are shown as well (Figure 1, top row). As expected, changes were significant only in spectra of irradiated mice, while in the control group, in which mice were not exposed to radiation, all spectra are alike and were changing with time significantly less. In Figure 1 it can clearly be seen that metabolic changes due to the irradiation

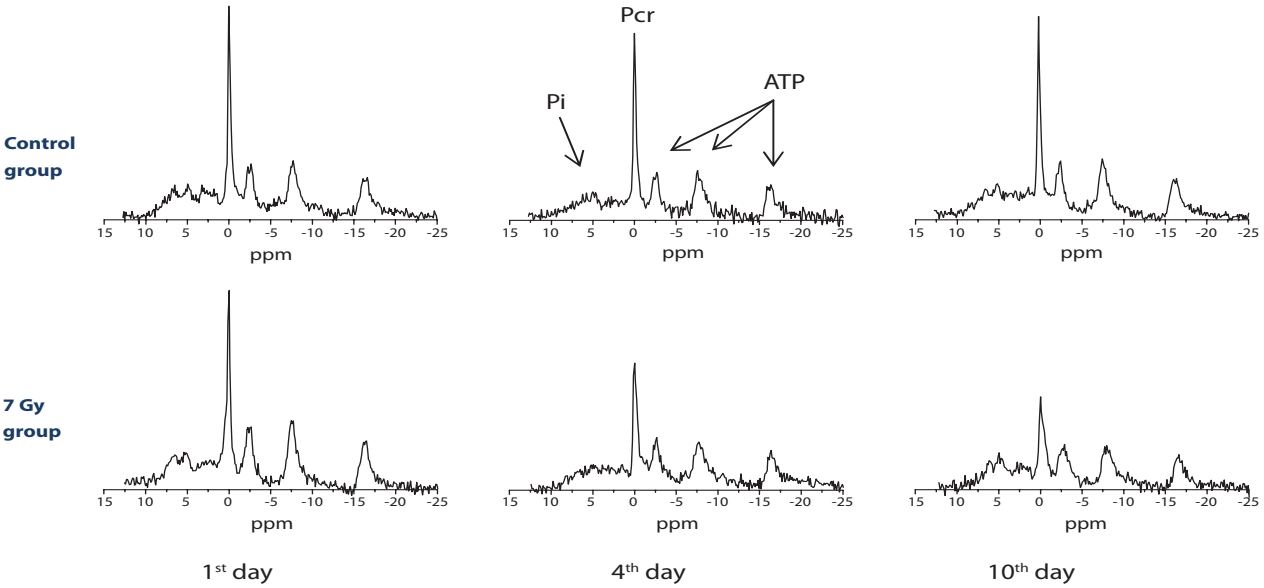

FIGURE 1. Typical ^{31}P NMR spectra of X-ray irradiated mice at different times after the irradiation: immediately, after 4 days and after 10 days for the mice group that received 7 Gy of X-ray radiation (bottom row) and the control group that was not irradiated (top row).

are associated mainly with the reduced Pcr peak, while no significant difference was observed in heights of the average ATP peak and the inorganic phosphate peak (Pi). Therefore, the ratio between heights of the Pcr and the average ATP peak is a convenient measure for metabolic activity and can be used for following effects of radiation on energy metabolism.

In Figure 2 dependence of the Pcr/ATP ratio as a function of time after the exposure to radiation for the mice group that received 7 Gy of X-ray radiation and the control mice group is depicted. In the control group, the Pcr/ATP ratio was practically constant all times, while the Pcr/ATP ratio in the irradiated group was initially identical to the Pcr/ATP ratio of the control group and then started decreasing until the animal death or partial recovery. The decrease was most significant within the first 7 days after the irradiation. After that time approximately half of the irradiated mice died and the other half never recovered completely, which can be seen by somewhat reduced Pcr/ATP ratio (reduction was approximately 20%) of the irradiated group compared to the same ratio of the control group for 7 or more days after the irradiation. Statistical analysis of the Pcr/ATP ratio by the paired t-test showed significant difference between the irradiated and the control mice group ($P = 0.023$).

Measurements of CK, AST and ALT levels in plasma of the irradiated mice as a function of time after radiation are shown in Figure 3. These measurements clearly indicate elevated CK levels immediately after the irradiation with almost tenfold increase of the CK level 10 min after the irradiation. The CK level then relatively fast returned to the normal level which was reached two days after the irradiation. Levels of both transaminases (ALT and AST) were elevated as well, however the increase was lower; the increase was approximately threefold for AST and 1.5-fold for ALT.

Discussion

Results of this study clearly indicate an existing relation between changes of energy metabolism and effects of radiation. These were detected instantly by *in vivo* ^{31}P NMR spectroscopy as well as with laboratory biochemical analysis of CK, AST and ALT levels in plasma, which was more time consuming. As expected, both methods were able to reveal metabolic changes associated with radiation effects. In ^{31}P NMR the change was observed in the reduced Pcr/ATP ratio, while biochemical analysis of plasma revealed increased CK and less pronounced increase of AST and ALT levels. The spectra reveal the level of Pcr and ATP through the whole body (muscle and internal organs). The decrease in the Pcr/ATP ratio supports our assumption, that metabolism of Pcr in post-radiation time is elevated due to a higher Pcr level in serum, which represents a substrate of CK. Uncoupling oxidative phosphorylation after the irradiation

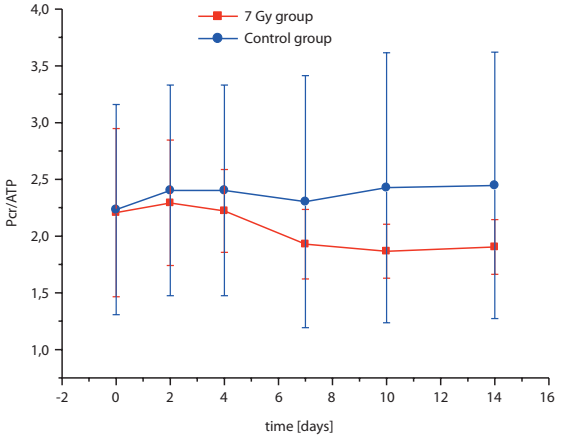

FIGURE 2. Pcr/ATP ratio as function of time after the irradiation for the mice group that received 7 Gy of X-ray radiation (squares) and the control mice group (circles). In the 7 Gy group the decrease of Pcr/ATP ratio is significant due to extensive radiation induced energy metabolism changes.

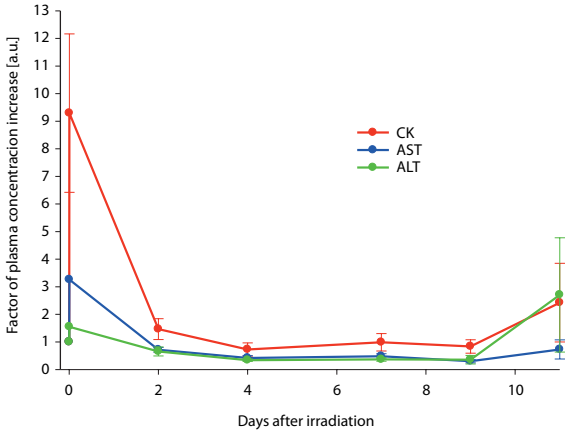

FIGURE 3. Relative creatine kinase (CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in plasma of mice that received 7 Gy of X-ray radiation as a function of time after the radiation exposure. Immediately after the exposure the CK level increase is almost tenfold while the increase of both transaminases (AST and ALT) was not as big, however, still significant.

due to cell death (or ascites cell mitochondria), creates a stressful environment with a lack of ATP.[23] Therefore, its rapid replenishment could be achieved by resynthesis from Pcr and ADP, catalyzed by CK. Cell death results also in a decreased Pcr synthesis in liver and in a decreased Pcr storage in muscles due to rhabdomylosis-like effect of radiation, which can be seen in lover Pcr/ATP in irradiated group compared to the control group 20 or more days after the irradiation (Figure 2). The Pcr/ATP ratio decreased due to reduced intracellular creatine levels and therefore lower Pcr synthesis.[24] It is expected that the decrease in the Pcr/ATP ratio is radiation-dose dependant, meaning that metabolism of Pcr would be affected even more if the radiation dose would be higher. In the irradiated mice group, in the first few days after the irradiation the ATP level was replenished by short-term mechanisms of the phosphate group transfer from Pcr to ADP. After that time, the ATP replenishment became due to severe radiation damage, which causes uncoupling of oxidative phosphorylation[25] (*i.e.* liver damage) no longer possible thus resulting in the animal death with approximately 50% probability in 10 days after the irradiation.

The results of ^{31}P NMR spectroscopy were confirmed biochemically by measuring CK levels in plasma. Parallel measurements of Pcr/ATP ratios and CK levels in plasma showed correlation between the ^{31}P NMR spectroscopy and biochemical methods of assessment of effects of radiation; *i.e.*, both methods showed initially increased CK ratios and decreased Pcr/ATP levels that returned to normal values during the recovery. Elevation of CK is an indication of acute muscle damage (*i.e* trauma, rhabdomyolysis, myocardial infarction, myositis etc.), which was in our study induce by X-ray radiation.[26] In addition, increased levels of transaminases (AST and ALT) indicate a liver damage which supports our assumption that irradiation affected metabolism of multiple organs. While CK levels and levels of both transaminases returned to normal within two days after the irradiation, Pcr/ATP ratios remained decreased significantly longer (10 or more days). As long as CK levels in plasma are elevated ATP synthesis *de novo* is extremely slow which explains different time dynamics of the return for CK and Pcr levels to normal.

Limitations of our study are associated with the credibility of CK and Pcr/ATP peaks. For ^{31}P NMR measurements surface coils were used. These have a sensitive region above the coil within a range approximately identical to the coil's radius. Therefore a proper positioning of a mouse relative to the coil is important for acquisition of the NMR signal from always identical body parts. A failure to do so may result in significantly different spectra and consequently inaccurate determination of the Pcr/ATP ratio. In addition CK levels were measured non-selectively for all different CK isoenzymes. However, it is expected that most of CK originated mainly from skeletal muscles since the muscles represent the major storage for CK.

Due to the limited access to the X-ray radiation source the study was performed using only one dose of radiation (7 Gy, plus the control group that did not receive any radiation). Unfortunately this is not enough to determine a possible relation

between the received dose and the Pcr/ATP ratio change. For that, similar experiments should be repeated for other intermediate doses (between 0 Gy and 7 Gy), which is our plan for future experiments. Although the chosen dose of 7 Gy is relatively high (50% mortality rate of mice), determination of such radiation exposure is important. At such high dose of radiation dose-dependent radiation-induced multi-organ involvement (RIMOI) and radiation-induced multi-organ failure (RIMOF) occur. Both RIMOI and RIMOF contribute to the clinical outcome and prognosis of radiation accident victims.[27,28]

Conclusions

The NMR method for detection of radiation induced metabolic changes in living organisms was verified biochemically by analysing CK levels in plasma. The accuracy of the NMR method is inferior to standard dosimetry methods. However, its advantage is that the method is instantaneous and the radiation dose can still be determined even if the subject was not carrying a radiation detection device at the time of exposure. To determine possible relation between the Pcr/ATP ratio and the received dose of radiation prospective studies are still needed.

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research article

Prophylactic cranial irradiation in patients with small-cell lung cancer: the experience at the Institute of Oncology Ljubljana

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Background. Prophylactic cranial irradiation (PCI) has been used in patients with small-cell lung cancer (SCLC) to reduce the incidence of brain metastases (BM) and thus increase overall survival. The aim of this retrospective study was to analyze the characteristics of patients with SCLC referred to the Institute of Oncology Ljubljana, their eligibility for PCI, patterns of dissemination, and survival.

Patients and methods. Medical charts of 357 patients with SCLC, referred to the Institute of Oncology Ljubljana between January 2004 and December 2006, were reviewed to determine characteristics of patients chosen for PCI. The following data were collected: age, gender, performance status (PS), extent of the disease, smoking status, type of primary treatment with outcome, haematological and biochemical parameters, PCI use, and finally brain metastases (BM) status at diagnoses and after treatment.

Results. PCI was performed in 24 (6.7%) of all patients. Six (25%) patients developed brain metastases after they were treated with PCI. Brain was the only site of metastases in 4 patients, two progressed to multiple organs. Median overall survival of patients with PCI was 21.9 months, without PCI 12.13 months (p = 0.004). From the collected data there were good prognostic factors: age under 65 years, limited disease (LD), performance status, normal levels of lactate dehydrogenase (LDH) and normal levels of C-reactive protein levels (CRP). Other prognostic factors did not show statistical significant values.

Conclusions. Survival of patients with LD, who have had PCI, was significantly better than those who had not. We decided to perform PCI in patients with LD, in those with complete or near complete response, and those with good performance status (≥ 80). We did not use PCI in extended disease (ED). The reason for that shall be addressed in the future. Doses for PCI were not uniform, therefore more standard approach should be considered.

Key words; small-cell lung cancer, brain metastases, prophylactic cranial irradiation

Introduction

Small-cell lung cancer (SCLC) expresses aggressive behaviour. Combined treatment with chemotherapy and radiotherapy provides response rates between 50-85% in limited disease (LD). Local recurrence rate decreases with combined treatment; however, brain metastases (BM) become the most common site of relapse. Brain metastases are present in about 20% of patients at the time of diagnosis, but in autopsy findings the rate reached over 50%.[1,2] As in other cancers, in clinical practice BM are diagnosed with computer tomography (CT), less common with magnetic resonance imaging (MRI)[3,4]; and all are treated with radiotherapy.[5]

In the early 1970s, prophylactic cranial irradiation (PCI) has been proposed to improve overall survival, because it is well known that central nervous system is relatively refractory to chemotherapy due to the blood-brain barrier. In the 1980s and 1990s there were many prospective studies conducted to investigate the use of PCI; however, only after the publication of two meta-analysis reporting improvement, both, in overall survival and dis-

ease free survival, PCI became a part of the standard treatment in SCLC. The first meta-analysis by Auperin *et al.* in 1999 reported the 5.4% increase in the rate of survival at three years as well as the increased rate of disease-free survival.[6] Meert *et al.* in meta-analysis in 2001 composed 12 randomized trials and reported a hazard ratio of 0.48 for the incidence of brain metastases after PCI.[7]

Recent studies suggest that patients in extensive disease setting could also benefit from PCI.[8,9]

The aim of this analysis was to review the use of PCI, to analyze the characteristics of patients with SCLC, referred to the Institute of Oncology Ljubljana, eligibility for PCI, patterns of dissemination, and survival.

Patients and methods

Cancer Registry of Republic of Slovenia reported 574 newly diagnosed patients with SCLC in the period between 2004 and 2006.[10-12] Three hundred fifty seven patients (62.19%), reviewed in this analysis, were referred for further treatment to the Institute of Oncology Ljubljana, mainly from University Clinic of Respiratory and Allergic Diseases Golnik and University Clinical Centre Maribor. One patient refused all types of further diagnostic procedures and treatments and was excluded from further evaluation.

The following data were collected: gender, age, extent of disease, performance status, smoking status, presence of other malignancies, starting serum levels of haemoglobin (Hb), lactate dehydrogenase (LDH) and C-reactive protein (CRP), type of treatment, response to treatment, PCI information, pattern of dissemination, BM status at diagnoses and after the treatment.

LD included patients with lesions confined to ipsilateral hemitorax, and regional and supra-clavicular lymph nodes. Extended disease (ED) was characterized by an evident and/or proven metastases.

Irradiation was performed at the Institute of Oncology Ljubljana; however, chemotherapy was delivered either at Institute of Oncology Ljubljana (189 patients), University Clinic of Respiratory and Allergic Diseases Golnik (123 patients) or at University Clinical Centre Maribor (29 patients). Twenty one referred patients received no treatment due to poor performance status at presentation at the Institute or due to deterioration of disease during the waiting time for therapy.

Treatment responses were evaluated according to the data available in medical charts as judged

TABLE 1. Characteristics of patients

Number of patients	356	%
Gender		
Male	270	75.84
Female	86	24.15
Age (years)	61.86	
Clinical stage	(40-83)	
Limited disease	167	46.10
Extended disease	188	52.80
No data available	1	0.2
Performance status (Karnofsky)		
>80	71	19.9
60-80	196	55.05
<60	29	8.14
No data available	60	16.85
Lactate dehydrogenase (LDH)		
Normal (≤ 4.23 μkat/L)	158	44.38
Elevated (> 4.23 μkat/L)	102	28.65
No data available	96	26.96
C-reactive protein levels (CRP)		
Normal (≤ 15 mg/L)	122	34.26
Elevated (> 15 mg/L)	132	37.07
No data available	102	28.65
Haemoglobin (Hb)		
< 120 (g/L)	86	24.15
≥ 120 (g/L)	186	52.24
No data available	84	23.59
Smoking status		
Non smokers	8	2.24
Smokers	163	45.78
Ex smokers	84	23.59
No data available	101	28.37
Other malignancies	36	10.11
synchronic	6	1.6
metachronic	30	8.4
Brain metastases (BM) as the only site	66	18.53
BM at diagnoses	37	10.39
BM after primary treatment	29	8.14

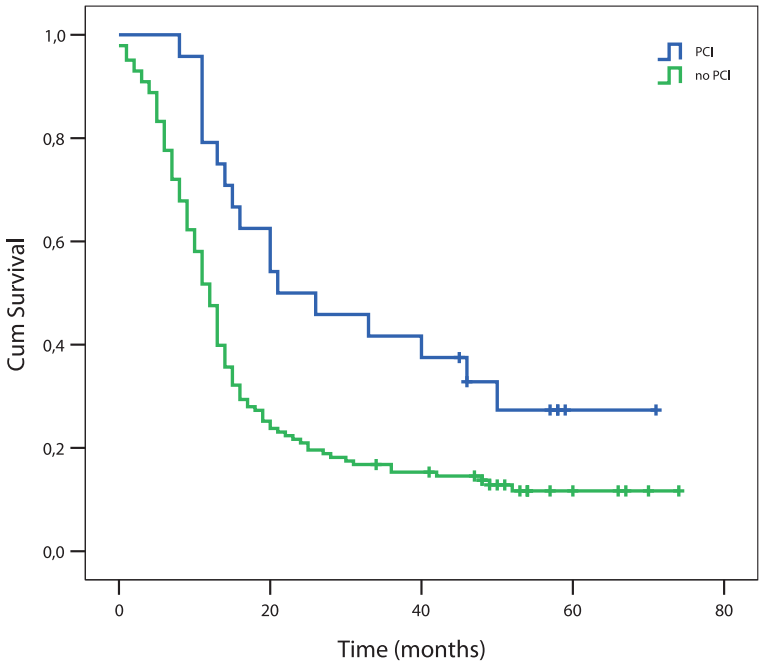

FIGURE 1. Survival of patients with prophylactic cranial irradiation (PCI) and without PCI (p = 0.004).

by radiation oncologist, based either on X-ray or CT examination during the follow-up. Some of the complete responses (CR) were also confirmed bronchoscopically.

PCI patients were irradiated on Cobalt unit with 1.25 MV or on linear accelerator with 5 or 6 MV photon beams for 5 days per week, once daily. The irradiated field involved whole brain using two opposed lateral fields.

As established the biologic effectiveness of radiation schedules depends on total dose and dose per fraction. The Equivalent Dose in 2-Gy fraction (EQD2) was calculated with the equation as derived from the linear-quadratic model

$EQD2 = D \times [(d + \alpha/\beta)/2\ \mathrm{Gy} + \alpha/\beta)]$,

where D = total dose, d = dose per fraction, α = linear (first-order dose-dependent) component of cell killing, β = quadratic (second-order dose dependent) component of cell killing, α/β -ratio = the dose where both components are equal. In analysis α/β-ratio of 10 Gy was used to calculate the biological effectiveness of radiation for tumor-cells and α/β -ratio of 3 Gy was used for normal tissue.[13]

Statistics

Statistical analysis was performed using personal computer and software statistical package SPSS, version 13 (SPSS Inc., USA).

The overall survival time was defined as the time from diagnosis to death or until the end of follow up period on April 1st 2010. The number of surviving patients was confirmed at this date.

Time to progression to brain was defined as time from diagnosis to confirmation of brain metastases by image diagnostics. For patients with PCI time to development of brain metastases was calculated also for period after completion of PCI to confirmation of brain metastases by image diagnostic.

Survival was calculated according to Kaplan-Meier's method and differences were confirmed by the log-rank test. Independent variables that appeared statistically significant on univariate analysis were tested by multivariate Cox regression analysis model.

Results

Between January 2004 and December 2006 institutions referred 357 patients with SCLC for further treatment to the Institute of Oncology; 356 were evaluable. Characteristics of patients are detailed in Table 1.

Median age at diagnosis was 61.86 years (40-83); majority were male (76%).

LD was present in 46% of patients, ED in 53%. Performance status, expressed in numbers of the Karnofsky scale, could be collected for majority of patients; however, for 17% patients only descriptions of status could be found in medical records. Majority of patients were smokers (46%). For ex-smokers (24%) qualified patients who stopped smoking at least one year prior to diagnosis. Only 8 (2%) patients were non-smokers; for 28% of patients data could not be retrieved from the medical records. Thirty six (10%) patients have had second malignancy, 6 synchronously and 30 before SCLC. Majority have had head and neck tumours (13), non-SCLC (6), skin tumours including melanoma (6), breast tumours (3), lymphoma (2), prostate carcinoma (2) and other types (3). Two hundred twenty six (63.48 %) patients have had CT or MR imaging during their diagnostic work up procedure – there were 15 (4.2%) without it; for 113 (31.74%) patients, data were not available.

The type of treatment and outcome are presented in Table 2. Majority of patients were treated with chemotherapy and irradiation. Chemotherapy as the only treatment was delivered mainly to patients with ED and 13 patients were irradiated only. Four patients underwent surgery and completed chemotherapy. Treatment resulted in 9 complete

TABLE 2. Treatment characteristics and outcome

	CR	PR	SD	PD	unknown	All
Chemotherapy	1	22	33	22	67	145
Chemotherapy and radiotherapy	6	64	37	13	53	173
Radiotherapy	0	3	1	0	9	13
Surgery and chemotherapy	2	1	0	0	1	4
No therapy						21

CR = complete response, PR = partial response; SD = stable disease; PD = progressive disease

responses (CR), 90 partial responses (PR), 71 stable diseases (SD) and 35 progressive diseases (PD). For 150 patients evaluation was not appropriately recorded.

Metastases to brain as the only site of dissemination was present in 37 patients (10.39%) at the time of diagnoses. Twenty-nine patients (8.14%) progressed after primary treatment.

Radiotherapy oncologists proposed PCI to 30 patients, whom they considered eligible, but 6 have refused it. 24 patients (6%) received PCI (20 male and 4 female), mean age of patients with PCI was 53.54 years. Characteristics of patients who received PCI are presented in Table 3. All patients with PCI had LD, statistical significant better performance status, were younger and smokers or ex smokers, only one patient had previous other malignancy.

Dose schedules of PCI were not uniform and are presented in Table 4. No trends in difference of BM frequency with increased biological equivalent dose (calculated as EQD2) received at PCI could be detected.

After PCI 6 (25%) patients developed brain metastases, in 4 patients brain was the only site of metastases, in 2 patients the disease progressed to multiple organs. In 4 out of 6 patients additional cranial irradiation was performed; in 2 patients the disease progressed while waiting for radiotherapy.

Brain was the first site of metastases in 29 patients with LD SCLC; among them 4 patients have had PCI and 25 patients were without PCI, including also 3 patients that have refused PCI. BM were present in 37 patients at the time of diagnosis (ED), 48 patients developed BM later. Overall incidence of BM in our population was therefore 32%.

The mean time to development of BM as a single site of progression for patients with PCI was 32.7 months (14.59-58.62). Mean time to development of BM as single site of progression for 25 other patients with LD who did not have PCI was 10.75 months (0.72-30.1). The difference was statistically significant ($p<0.001$).

The median overall survival (OS) for all 356 patients with SCLC included in analyses was 9.4 months (95% CI; 8.37 – 10.44)

The median OS of 167 patients presented with LD SCLC was 13.34 months (95% CI; 12.17-14.51). Median OS of patients with PCI was 21.9 months (95% CI; 6.31-37.48), for those without PCI was 12.13 months (95%CI; 10.69-14.51). The difference was statistically significant (log rank, $p=0.004$) (Figure 1). On our cut-off date on April 1st 2010 there were 28 patients still alive, 7 of them have received PCI.

Univariate analysis including all patients with SCLC showed statistically significant better survival in patients with age < 65 years, PS > 80, normal LDH and CRP levels, those with PCI and LD and, surprisingly, smokers. In multivariate analysis only LD ($p<0.0001$, HR = 0.49, 95 % CI 0.332-0.722) and PS ($p = 0.03$, HR = 0.63, 95 % CI 0.419-0.973) were identified as independent prognostic factors. Since PCI was only performed in patients with LD, separate analysis was performed for this population. In univariate analysis age < 65 years, PS > 80 and PCI showed statistically significant better survival. Multivariate analysis identified only age ($p=0.001$) and PS ($p=0.008$) as independent prognostic variables.

Discussion

PCI has been used in patients with LD SCLC to reduce the incidence of BM and increase overall survival, however reports suggest it should be used also in patients with ED SCLC. In our institution only patients with LD received PCI (14.37%). Retrospective reports in the literature mention about 8%.[14]

Standard treatment consists of combination of chemotherapy and thoracic irradiation of the site of primary tumour.[15] Combined treatment was delivered to 129 (77.24%) patients with LD SCLC, al-

TABLE 3. Characteristics of patients with prophylactic cranial irradiation

Number of patients		%
	24	6.7
Gender		
Male	20	83.33
Female	4	16.66
Age (years)	53.54 (43-73)	
Performance status (Karnofsky)		
≥ 90	6	25
80	16	66.66
Data not available	2	8.3
Smoking status		
Non smokers	0	0
Smokers	16	66.66
Ex smokers	4	16.66
No data available	4	16.66
Other malignancies	1	4.1
synchronic	0	0
metachronic	1	4.1
Lactate dehydrogenase (LDH)		
Normal (< 4.23 μkat/L)	14	58.33
Elevated (> 4.24 μkat/L)	2	8.3
Data not available	8	33.33
C-reactive protein levels (CRP)		
Normal (< 15 gr/L)	10	41.66
Elevated (> 15 gr/L)	8	33.33
Data not available	6	25
Haemoglobin (Hb)		
< 120 (g/L)	14	58.33
> 120 (g/L)	3	12.5
Data not available	6	25
Response to primary treatment		
CR	5	20.83
PR	17	70.83
Data not available	2	8.33
Brain metastases	6	25
As only site of progress	4	16.66
In multiple organ progress	2	8.3

CR = complete response, PR = partial response

so the majority of PCI patients in our review were given this treatment; one patient received only chemotherapy and was referred from another institution and one patient underwent only surgery and chemotherapy prior to PCI.

PCI is eligible in patients who achieve complete or near complete response after treatment of primary tumour. In our review only 69 (41.3%) patients in LD group met this criteria; however, data for 60 patients from the same group of LD were not available – the majority of them completed treatment in other institutions and were evaluated there. In group of patients with PCI 5 CR and 17 PR (near CR) were observed, for 2 patients appropriate data were not available in medical records.

None of our patients with ED SCLC received PCI, although 30 had PR responses, however, there were no CR. There are reports that suggest considering PCI also in patients who respond to first line chemotherapy.[16]

Patients who received PCI were younger than SCLC population studied. Radiation oncologists have chosen for PCI patients with the Karnofsky performance status (PS) of 80 or higher. This is in accordance with performance status patient's selection in prospective studies.[17] The majority of patients were heavy smokers as was expected in population of patients with SCLC.[18] Heavy smokers have comorbidities and therefore usually lower performance status, making them less likely candidates for radical treatment and also for PCI.[19] Bremnes *et al*. reported gender, extent of disease, PS, Hb levels and LDH to be independent prognostic factors.[20] In our analyses only age < 65 years and PS were independent factors of survival in multivariate analysis.

Doses of PCI in our review were not uniform. Meta analysis suggested trend towards increased reduction of BM rate with increased dose, however, prospective study exploring high versus low dose in PCI found no reduction in total incidence of BM, but there was increased mortality with higher doses.[6] Therefore a dose of 25 Gy was suggested to be the standard care in LD SCLC.[16,21] All our patients received biological equivalent doses higher than 25 Gy, but no increased mortality nor difference in frequency of BM according to the biological equivalent dose could be detected. The number of analysed PCI patients was small; therefore no conclusions could have been made.

According to our review 4 patients refused PCI. Details of this refusal were not described in our medical records. We could assume that the fear of possible side effects might have been one of the

TABLE 4. Irradiation doses that were applied as prophylactic cranial irradiation

	Dose schedule	EDQ2 α/β=10	EDQ2 α/β=3	Number of patients treated	Number of patients alive
1	14 x 2.0 Gy = 28.0 Gy	28.0	28.0	3	0
2	15 x 2.0 Gy = 30.0 Gy	30.0	30.0	2	2
3	17 x 2.0 Gy = 35.0 Gy	35.0	35.0	1	0
4	12 x 2.2 Gy = 26.4 Gy	26.84	27.45	3	1
5	13 x 2.2 Gy = 28.6 Gy	29.07	29.74	1	1
6	14 x 2.2 Gy = 30.8 Gy	31.31	32.03	1	1
7	12 x 2.5 Gy = 30.0 Gy	31.25	33.0	4	2
8	14 x 2.5 Gy = 35.0 Gy	36.45	38.5	5	1
9	10 x 3.0 Gy = 30.0 Gy	32.5	36.0	4	0

EDQ2 = Equivalent Dose in 2-Gy fraction

reasons. Several studies reported neurological impairment or abnormalities potentially related was PCI.[9,22-26] Acute toxicity consisted mostly of alopecia, headache, fatigue, nausea and vomiting and was usually manageable on outpatient basis. Long term toxicities such as memory loss, intellectual impairment, demenca, ataxia or seizures could be of great concern.

The incidence of BM as the first site of relapse at 5 years have been reported to be 37% in a group of patients not receiving PCI and 20% in PCI group.[17] However, patients in the study reported had only CR and included also a proportion of ED SCLC. Recent retrospective report indicated 25% incidence of development of BM after PCI, however, number of patients was again small.[27] The same proportion of patients developed BM also in our series.

There are still doubts among radiation oncologists about using PCI, although even cost effectiveness and quality of life studies beside studies confirming improvement in BM control, OS and DFS have been published.[28] There are decision making tools and practice guidelines available, but judgment of radiation oncologist should prevail specially in cases of near CR.[29-31]

Conclusions

Our analysis confirmed increased median survival time and decreased incidence for BM in patients with PCI.

Our policy of treatment was to perform PCI in patients with LD and good performance status, the two variables that independently showed better survival. Adding PCI in these patients setting further increased survival. Possibilities of using PCI also in ED SCLC in our institution should be further explored in the future. Doses for PCI were not uniform therefore more standard approach should be considered.

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research article

Gonadal function in patients treated for Hodgkin´s disease in childhood

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Background. The long-term survival of patients treated for Hodgkin`s disease (HD) in childhood is high and the chief concern is now being directed toward the late effects of the treatment, including the endocrine dysfunction.
Patients and methods. Testicular and ovarian functions were assessed in 64 long term survivors (24 females, 40 males) treated for HD in childhood in Slovenia between 1972 and 1994. At diagnosis they were 3-16 years old and had gonadal evaluation 4-27 years later at the age of 13-34. Fifty-four (84%) patients received chemotherapy (ChT), 49 in combination with radiation therapy (RT), 10 received RT alone. Gonadal function was assessed by the clinical examination and measurement of serum concentrations of estradiol and testosterone. Serum levels of LH and FSH were determined in the basal state and after the stimulation.
Results. Primary hypogonadism (PH) was found in 30 (47%) patients. Twenty-four of 40 (60%) males had PH with evidence of damage of germinal epithelium, 4 of them had evidence of damage of Leydig cells (LC) and 10 had evidence of dysfunction of LC as well. PH was found in 6 of 24 (25%) females. Conclusions. After therapy for HD PH was more frequent in males than in females. Not only RT but also alkylating agents and procarbazine alone caused damage of LC. Age of patient at the time of treatment was not an important risk factor for gonadal toxicity. Pelvic RT in combination with ChT is the most important risk factor of the development PH both, in males and females.

Key words: gonadal function; late effects; childhood cancer; Hodgkin's disease

Introduction

The long-term survival of patients after the treatment of childhood cancer, especially Hodgkin`s diesease (HD), has greatly improved in the last few decades due to the effective treatment, especially multiagent chemotherapy (ChT).[1] The chief concern is now being directed toward the late effects of the treatment[2], which influence on patient's quality of life and become more and more important in cancer treatment.[3,4] Endocrine glands, gonads in particular, are very susceptible to damaging effects of anticancer therapy.[5] The damaging effect of both ChT and radiotherapy (RT) on gonads is well known.[6] In a study of 2283 long-term survivors of childhood cancer Byrne and colleagues found that RT below the diaphragm depressed fertility in both sexes for about 25%, ChT with alkylating agents with or without RT below the diaphragm depressed fertility by 60% in men, but in women alkylating agents therapy administered alone had no apparent effect on fertility.[7]

The aim of this study was to define the influence of cancer treatment on the gonadal status of 64 young adults treated for HD during childhood and adolescence in Slovenia.

Material and methods

Patients

Between 1972 and 1994, 104 patients were treated for HD during childhood (0-16 years of age) in Slovenia. Twenty-four patients had died, 4 were lost to follow-up. Seventy-six ptatients are regularly followed at the outpatient Clinic for Late Effects at the Institute of Oncology, Ljubljana. Twelve pa-

TABLE 1. Chemotherapy in 54 patients treated for Hodgkin's disease

	N° of patients				
	Alone	In combination with			Total
		LOPP	ABV(D)	COPP(A)	
MOPP	11	2	10 ♣	1	24
LOPP	14		1	1	16
MOPP/ABV hybrid	8				8
COPP(A)	3				3
OPPA	1			2 ♥	3
Total N° of patients	37	2	11	4	54

♣ 4 patients received also LOPP, 1 patient COPPA

♥ 1 female, missdiagnosed as having non-Hodkin's lymphoma, received chemotherapy following protocol BFM 90 as first treatment

LOPP = chlorambucil, vincristine, procarbazine, prednison; ABV(D) = doxorubicin, bleomycin, vinblastine, (dacarbazine); COPP(A) = cyclophosphamide, vincristine, procarbazine, prednisone, (doxorubicin); MOPP = mechlorethamine, vincristine, procarbazine, prednisone; OPPA = vincristine, procarbazine, prednison, doxorubicin

TABLE 2. Gonadal function according the type of treatment in 40 males

Type of treatment	N° of patients				
	Gonadal function				Total
	PH	SIG	SH	Normal	
Pelvic RT + ChT	8			1 ♦	9
Pelvic RT alone	2			0	2
≥ 6 c (AAP) ChT with nonpelvic RT	13	1		4	18
≥ 6 c (AAP) ChT, no RT		1		1	2
≤ 5 c (AAP) ChT with nonpelvic RT	1 ♣	1		2	4
Nonpelvic RT alone			1	4	5
Total N° of patients	24	3	1	12	40

♣ pt received 3 cycles (c) of LOPP

♦ RT to the iliacal region only

PH = primary hypogonadism; SIG = subclinical impairment of gonadal function; SH = secondary hypogonadism; RT = radiotherapy; ChT = chemotherapy; AAP = ChT, containing alkylating agents and procarbazine (P) (MOPP, MOPP-ABV hybrid, MOPP/ABVD, LOPP, COPP(A) and OPPA)

tients refused endocrinological evaluation, so 64 patients (24 females, 40 males) were included in our analysis. They were treated for HD at the age of 3-16 (median 13) years and had endocrinological evaluation 4-27 (median 10) years after the end of the treatment at the age of 13-34 (median 21) years. All patients were pubertal or postpubertal when studied (only two patients were younger than 16 years).

At diagnosis, 13 patients were in stage I (12 above the diaphragm), 23 in stage II (21 above the diaphragm), 25 in stage III and 3 in stage IV (2 involvement of the lung, one of the liver). Seven patients (5 boys, 2 girls) suffered from relapse. Forty-nine patients were treated with ChT and RT, 10 with RT and 5 with ChT as the only treatment modality. Fifty-four patients had combination ChT with MOPP [mechlorethamine, vincristine, procarbazine, prednisone], MOPP-ABV [mechlorethamine, vincristine, procarbazine, prednisone-doxorubicin, bleomycin, vinblastine] hybrid, MOPP/ABVD [mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine, dacarbazine], LOPP [chlorambucil, vincristine, procarbazine, prednisone], COPP(A) [cyclophosphamide, vincristine, procarbazine, prednisone, (doxorubicin)] and OPPA [vincristine, procarbazine, prednisone, doxorubicin][8-11] (Table 1). Of the 59 patients treated with RT, 27 (19 boys, 8 girls) had RT above the diaphragm with 20-40 (median 30) Gy, 17 (8 boys and 9 girls) RT to the upper abdomen with 24-49 (median 30) Gy and 15 (11 boys, 4 girls) RT to the pelvis with 22-45 (median 30) Gy.

Twenty-eight (12 girls and 16 boys) patients had also staging laparotomy with splenectomy.

Assessment of gonadal function

The patient's data, regarding both, the diagnosis and the treatment, were collected from medical files, information concerning quality of life including attained educational level, marital status, employment and social life, past and present menstrual histories, the course of puberty and fertility histories were ascertained by the interview. The general physical examination was performed, height, weight and clinical abnormalities as well as Tanner stages of pubic hair and genital development were recorded. Each patient's blood samples were analysed for basal concentrations of total testosterone (RIA, IMUNOTECH), estradiol (DELFIA-LKB) and prolactin (DELFIA-LKB). Concentrations of luteinizing hormone (LH) (DELFIA-LKB) and follicle stimulating hormone (FSH) (DELFIA-LKB) were determined before and 10, 20, 30, 60 minutes after *i.v.* administration of gonadotropin releasing hormone (50 mcg/m^2) (LH-RH). Semen analyses were performed in 6 men.

Primary hypogonadism (PH) was defined as basal serum FSH and/or LH level above the normal upper limit and exaggerated response after the stimulation with LH-RH. In men, elevated basal serum FSH levels indicated germinal epithelium damage (GE-DA), while elevated LH levels (with/without reduced total testosterone levels) indicated Leydig cells (LC) damage (LC-DA). Normal basal values of LH and/or FSH and the exaggerated response after LH-RH stimulation were considered as a subclinical impairment of the gonadal

function (SIG). The exaggerated response of FSH after LH-RH was considered as a dysfunction of germinal epithelium (GE-dys), while the exaggerated response of LH after LH-RH were considered as a dysfunction of LC (LC-dys). Low serum basal FSH and LH levels with the poor response after *i.v.* bolus of LH-RH was considered as secondary hypogonadism (SH).

Results

Males

We found PH in 24 of 40 males (60%); in 20 of 35 males (57%) who had primary treatment and in 4 of 5 males (80%) treated for the relapse (Table 2). All 24 males had the evidence of GE-DA, four of them had the evidence of LC-DA (low level of total testosterone in one) and ten had the evidence of LC-dys as well. Twenty-two of 24 males with PH had received combination ChT (all but one ≥ 6 cycles of AA and procarbazine (P) containing ChT) and RT (to the pelvis in 8), 2 had had pelvic RT only (Table 2). Patients with LC-DA or LC-dys had received somewhat higher cumulative doses of P (med. 7.4 g/m^2) than those who had a normal LC function (med. 6.5 g/m^2), while cumulative doses of alkylating agents, proportion of patients having received pelvic RT and ages at diagnosis did not differ among the two groups. Semen analyses were performed in 6 of 24 (25%) males with PH and all were azoospermic. Five males of the 24 with PH have children.

Three patients had SIG: one had isolated GE-dys, the second LC-dys and the third GE-dys in combination with LC-dys, all after the treatment with combined ChT (MOPP/ABVD x 6, MOPP x 4 and LOPP x 6) without pelvic RT. One of them has children. One patient had evidence of SH. He had been treated with RT to the neck and mediastinum (40 Gy) (Table 2).

Of 11 males who had had pelvic RT (9 to the iliacoinguinal region, 2 to the iliacal region), 9 in combination with ChT, 10 had PH. ChT alone was less gonadotoxic, causing PH in 14 of 29 (48%) males than ChT in combination with pelvic RT (PH in 8 of 9 (89%) males). Only one of these patients, who had received RT to the iliacal region only in combination with two cycles of MOPP, had normal gonadal function (Tables 2, 3).

The endocrinological evaluation was normal in 12 males. Seven of them had received ChT and RT, four RT only and one ChT only (Table 3).

Among 7 males having received 6 cycles of MOPP without pelvic RT only one had normal endocrine tests. He had received 6 cycles of ABVD as well. Among 10 males having received 6 cycles of LOPP without pelvic RT 4 had normal gonadal function.

Three patients had received 1 or 2 cycles of MOPP or OPPA and had normal testicular function (Table 2).

Age at diagnosis, follow-up time and age at endocrine evaluation were similar in the group of patients with PH and in the group of patients without endocrinological deficiences. The only difference between the groups was the treatment modality (Tables 2, 3).

Females

We found PH in 6 of 24 (25%) females (Table 4), 3 of them had low levels of estrogen as well. All 6 had been treated with ChT and RT. Two of them had been treated with ChT (COPPA×6 and LOPP×6) and unilateral pelvic RT (24 and 30 Gy), one has primary amenorrhea, the other has irregular menstrual periods and one child. Four females with PH had received ChT (two 6 cycles of MOPP, one 6 cycles of LOPP, one ChT following protocol BFM 90 and 3 cycles of (C)OPP(A)) and nonpelvic RT, 3 upper abdominal. Two of these 4 patients have regular menstrual periods and children, one has irregular menses and one is in early menopause after having given birth to 2 children.

We found SIG in one female treated with 4 cycles of MOPP and neck RT. She has irregular menstrual periods and gave birth to one child (Table 4).

Seventeen females had normal gonadal function with regular menstrual periods; 14 of them had had ChT, 13 in combination with RT (2 pelvic), 3 had had nonpelvic RT only (Table 4, 5).

Among 6 females having received 6 or more cycles of MOPP ChT without pelvic RT, 4 had normal gonadal function (one even after 8 cycles of MOPP, 3 after ChT containing 6 cycles of ABVD as well). One female had normal gonadal function after 3 cycles of MOPP plus 3 cycles of LOPP. Of 2 females having received 6 cycles of LOPP without pelvic RT one had normal gonadal function (Table 5).

All of 5 females having received 6 cycles of MOPP/ABV hybrid regimen (in combination with unilateral pelvic RT in 2) had normal gonadal function (Table 5).

The group of females with PH and the group with a normal gonadal function did not differ regarding age at diagnosis, follow-up time or age at

TABLE 3. Therapy for Hodgkin's disease in twelve males with normal endocrine tests

Type of treatment		No of patients with normal gonadal function	Total N° of patients with the same type of treatment
ChT	**RT**		
MOPP/ABVD ×6	none/nonpelvic	1	7 ♣ ♥
LOPP × 6	nonpelvic	4	10 ♣
MOPP × 2	iliacal region (30 Gy)	1	1
MOPP × 1	nonpelvic	1	1
NONE	nonpelvic	4	5 ♠
OPPA × 2	nonpelvic	1	1
TOTAL		12	25

♥ also patients receiving 6 cycles of MOPP only

♣ 1 patient had subclinical impairment of gonadal function

♠ 1 patient had secondary hypogonadism

ChT = chemotherapy; RT = radiotherapy; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; LOPP = chlorambucil, vincristine, procarbazine, prednison; OPPA = vincristine, procarbazine, prednisone, doxorubicin

TABLE 4. Gonadal function according the type of treatment in 24 females

Type of treatment	N° of patients			
	Gonadal function			Total
	PH	SIG	Normal	
Pelvic RT + ≥ 4 c (AA) ChT	2		2	4
≥ 6 c (AA) ChT with nonpelvic RT	4	0	7	11
≥ 6 c (AA) ChT, no RT	0	0	3	3
≤ 5 c (AA) ChT with nonpelvic RT	0	1	2	3
Nonpelvic RT alone			3	3
Total N° of patients	6	1	17	24

PH = primary hypogonadism; SIG = subclinical impairment of gonadal function; RT = radiotherapy; ChT = chemotherapy; AA = ChT, containing alkylating agents (MOPP, MOPP-ABV hybrid, MOPP/ABVD, LOPP, COPP(A) and OPPA)

endocrine evaluation; they differ only by the mode of the treatment. Females with PH had received slightly larger cumulative doses of P (med. 7 g/m^2) than those with a normal gonadal function (med. 5.5 g/m^2). Females with PH had had abdominal RT in higher proportion (5 of 6 (83%) (pelvic RT in 2 of 6 (40%)) than females with normal gonadal function (abdominal RT in 8 of 17 (47%) (pelvic in 2 of 17 (12%)). ChT in combination with pelvic RT was more gonadotoxic, causing PH in 2 of 4 (50%) females, than ChT alone (PH in 4 of 20 (20%) females).

None of female patients had evidence of SH.

Discussion

Our study is a population based study. As to our knowledge there is no international population based study of gonadal dysfunction after the treatment of HD in childhood. The study populations of most studies, dealing with this topic, are selected according to the type of treatment, age, gender or institution.

Several studies showed that in men basal FSH levels and FSH response to LH-RH correlated well with the sperm production.[12-16] An increased FSH response to LH-RH can be the first manifestation of testicular damage[15], although normal FSH levels do not rule out the possibility of azoospermia.[14,17,18] In our study semen analyses in 6 patients with a high basal FSH level showed azoospermia.

Our findings are in concordance with data from other studies establishing that MOPP or MOPP-like combinations, such as MVPP (mechlorethamine,vinblastine, procarbazine and prednisone) and COPP induce azoospermia in 90-100% of patients with a 10-20% chance of recovery even 10 years after treatment.[17,19-24] In our study 1 of 7 males had a normal gonadal function after receiving 6 cycles of MOPP. The recovery of spermatogenesis following MOPP therapy appears to

TABLE 5. Therapy in 17 females with normal endocrine tests

Type of treatment		N° of patients with normal gonadal function	Total N° of patients with the same type of treatment
ChT	**RT**		
MOPP × 8	nonpelvic	1	3 ♣
MOPP/ABV hybrid × 6	nonpelvic	3	3
MOPP/ABV hybrid × 6	pelvic-unil.(24Gy)	1	1
MOPP/ABVD ×6	none	2	2
MOPP/ ABV×6+ABVD×6+LOPP×6	pelvic-unil.(22Gy)	1	1
MOPP/ABVD × 6 + LOPP × 3	none	1	1
MOPP × 3 + LOPP × 3	nonpelvic	1	1
LOPP × 3 +ABV × 2	nonpelvic	1	1
COPPA × 6	nonpelvic	1	1
LOPP × 6	nonpelvic	1	2
COPP × 2 + OPPA × 2	nonpelvic	1	1
None	nonpelvic	3	3
Total		17	20

♣ 2 patients with primary hypogonadism received 6 cycles of MOPP

ChT = chemotherapy; RT = radiotherapy; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; LOPP = chlorambucil, vincristine, procarbazine, prednison; COPP = cyclophosphamide, vincristine, procarbazine, prednisone; OPPA = vincristine, procarbazine, prednisone, doxorubicin;

be dose-related with 3 courses of MOPP representing a limiting gonadal exposure for the recovery, suggesting only a partial killing of germinal stem cells.[25] Indeed, in our study we found a normal gonadal function in two males after having received 1 and 2 cycles of MOPP ChT. We found ChT according to the protocol LOPP less damaging for testicular function than MOPP, causing GE-DA in 5 of 10 males having received 6 cycles, a finding not published elsewhere to our knowledge.

Four males had evidence of LC-DA, 12 had LC-dys. All but two of them had evidence of GE-DA as well. Only 1 of 4 males with LC-DA and 4 of 12 males with LC-dys had had pelvic RT, the others had received ChT with nonpelvic RT, indicating the adverse effect of chemotherapeutic agents on Leydig cells. This is supportive to the observations of Romerius and colleagues[26] and Mustieles and colleagues.[12] The possible explanation for a high incidence of the dysfunction of LC in males with damage of germinal epithelium (in 10 of 20) is coexistence of compensated LC failure with the germ cell depletion observed in males not treated for malignancies.[27]

Besides AA and P, pelvic RT turned out to be very gonadotoxic. Ten of eleven males, who had had pelvic RT, had PH. Two of those had had RT only, inverted Y, with doses of 40 Gy respectively, without special shielding of testes. It is well known that a cumulative dose of 200 cGy in multiple fractions may cause azoospermia and that is the dose of scattered radiation that the testes could receive from an inverted Y field.[28]

Five of 24 males with GE-DA fathered children indicating that they are not azoospermic but possibly oligospermic and fertile. Hoorweg-Nijman and colleagues found elevated levels of FSH compatible with normospermia.[16] FSH levels may provide an estimate of possible impaired spermatogenesis, however only the semen analysis is confirmatory assessment of the male gonadal function.

We have no explanation for SH in male treated with RT above the diaphragm (not including hypophysis).

We found PH in 6 of 24 (25%) females. Only one of them is amenorrhoic (after 6 cycles of COPPA). There are data of adverse effects of ChT that is in use for HD, on ovarian function in adult females, but very little on ovarian function in girls. In the study of Ortin and colleagues 2 of 18 girls were amenorrhoic after having received 6 or more cycles of MOPP.[29] In our study none of 6 girls is amenorrhoic after 6 or more cycles of MOPP, but 2 have evidence of the ovarian damage while retaining fertility.

Ionizing radiation is toxic to the ovaries. The dose of 20Gy is necessary for inducing ovarian failure in girls, but only one third of this dose will produce the same effect in women over 40 years.[30] After the abdominal irradiation in childhood with doses of 20-30 Gy, the ovarian failure was found in 17 of 18 females.[31] Four females in our series

had had unilaterally pelvic RT. Half of them had evidence of PH, but all had received ChT with AA and P as well. After RT of paraaortic lymph nodes the estimated ovarian dose is about 6 % of the prescribed dose (in the range of 100 cGy) and this dose of radiation can cause transient disturbances of menstrual cycle. Haie-Mader and colleagues analyzed the ovarian function in 134 females who had ovarian transposition during the treatment for HD or gynecological cancer and showed that the age over 25 years, MOPP ChT and total dose to the ovaries higher than 5 Gy are important risk factors for the ovarian castration.[32]

Four females in our study had elevated basal and peak FSH levels while retaining menstrual periods. Four of 6 with PH even gave birth to children. Sherman and Korenman stated that increased FSH concentration with regular menstrual cycles might be consistent with the deficient production of inhibin or an inhibin-like hormone by the partially damaged ovary.[33] It might announce the risk of premature menopause in these females, which occurred in one of our patients. Byrne and colleagues found out that the treatment for cancer during adolescence carries a substantial risk of early menopause.[34] In a study of Sklar and colleagues risk factors for nonsurgical premature menopause in survivors of childhood cancer were attained age, exposure to increasing doses of radiation to the ovaries, increasing alkylating agents score and a diagnosis of HD.[35]

It seems that in males with HD therapy is not the only cause of hypogonadism. Vigersky and colleagues found a low sperm count or sperm motility in about one-third of male patients with HD before starting ChT.[36] Rueffer and colleagues found in their study semen abnormalities in 70% of patients before the onset of the treatment for HD.[37] Unlike in males it seems that there is no adverse effect of Hodgkin's disease on the female gonadal function. In a study of Chapman and colleagues, namely, histories and pretreatment ovarian biopsy specimens indicated the normal fertility before the therapy for HD.[21]

Conclusions

After the therapy for HD hypogonadism is more frequent in males than in females.

Six or more cycles of MOPP causes PH in more than half patients. This kind of treatment is more toxic for males than for females. Six cycles of LOPP seems less gonadotoxic than 6 cycles of MOPP. MOPP/ABV hybrid regimen is not gonadotoxic for females.

Not only RT but also alkylating agents and procarbazine alone cause damage of Leydig cells.

Elevated levels of FSH are compatible with the normal fertility in males and females.

The age of patient at the time of the treatment doesn't emerge as an important risk factor for gonadal toxicity, caused by therapy.

Pelvic RT in combination with ChT is the most important damaging factor causing the gonadal dysfunction both, in males and females.

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case report

Intensity modulated radiotherapy (IMRT) in bilateral retinoblastoma

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Background. External beam radiotherapy (EBRT) for retinoblastoma has traditionally been done with conventional radiotherapy techniques which resulted high doses to the surrounding normal tissues.
Case report. A 20 month-old girl with group D bilateral retinoblastoma underwent intensity modulated radiotherapy (IMRT) to both eyes after failing chemoreduction and focal therapies including cryotherapy and transpupillary thermotherapy. In this report, we discuss the use of IMRT as a method for reducing doses to adjacent normal tissues while delivering therapeutic doses to the tumour tissues compared with 3-dimensional conformal radiotherapy (3DCRT). At one year follow-up, the patient remained free of any obvious radiation complications.
Conclusions. Image guided IMRT provides better dose distribution than 3DCRT in retinoblastoma eyes, delivering the therapeutic dose to the tumours and minimizing adjacent tissue damage.

Key words: retinoblastoma; radiotherapy; intensity modulated radiotherapy

Introduction

Retinoblastoma is the most common intraocular malignant tumour encountered in children. In most patients, retinoblastoma remains confined to the eye. However, in advanced cases, retinoblastoma can secondarily invade the orbit and metastasize to the central nervous system and other distant organs. Untreated retinoblastoma is nearly always fatal. Therefore, the early diagnosis and treatment is critical in saving lives of retinoblastoma patients and preserving a visual function of the affected eyes. Retinoblastoma occurs with an estimated frequency of 1/14000-1/34000 live births.[1] In the United States, approximately 200 to 300 new cases are diagnosed each year. About 2/3 of the patients have unilateral and 1/3 have bilateral disease. More than 90% of the patients are diagnosed before the age of 5 years.[2] Bilateral patients are generally discovered in the first year of life and unilateral ones are diagnosed later in the second year.[1,3]

Chemoreduction has changed the approach to the management of retinoblastoma. The dogma of enucleating the worse eye and irradiating the least affected eye in bilateral disease has largely been replaced by chemoreduction as a first step for both eyes. For the unilateral retinoblastoma chemoreduction is appropriate for those with Group A to C disease, but much less successful for those children with Group D or E retinoblastoma, which is usually treated by enucleation.

External beam radiation therapy (EBRT) is used less often today. It is used for moderately advanced tumours, multiple tumours, especially those with vitreous or subretinal seeds that fail chemoreduction. The external beam radiation dose is 35-45 Gy delivered over 4-5 weeks. An anterior lens-sparing, relative lens-sparing or modified lateral beam technique can be used. The anterior lens-sparing technique compared to the modified lateral beam technique leads to a higher tumour recurrence rate because the anterior retina is undertreated. On the

TABLE 1. Comparison of doses for 3DCRT and IMRT plan of our patient

	3DCRT			IMRT		
	Mean (cGy)	Max. (cGy)	Vol/dose	Mean (cGy)	Max. (cGy)	Vol/dose
R. Lens	3304	3676		2763	3134	
L. Lens	2657	3299		2639	3270	
R. Cornea	3228		V26.5<78%	2609		V26.5<70.6%
L. Cornea	2874		V26.5<67%	2909		V26.5<50.6%
R. Optic nerve		3830			4147	
L. Optic nerve		3841			4063	
R. Lac. Gland	3807		V34<99%	2527		V34<5%
L. Lac. Gland	3741		V34<100%	2456		V34<0%
Orbital Bones	2204		V20<56.8%	1965		V20<49.7%

V20 (volume received above 20 Gy), V34 (volume received above 34 Gy), V26.5 (volume received above 26.5 Gy)

other hand, the relative lens-sparing and modified lateral beam techniques yield similar eye conservation rates with subsequent salvage therapy. Much higher doses (from 50 Gy to 100 Gy) have been used in the past decades and it is quite possible that some second cancers have been due to the high radiation dose. The external beam radiation therapy can lead to significant complications such as facial hypoplasia from orbital bone atrophy, radiation cataract, and retinopathy.

The aim of this study was to compare the dose distribution of intensity modulated radiotherapy (IMRT) with the conventional external beam radiotherapy in terms of target and normal tissue doses in a recurrent bilateral retinoblastoma patient.

Case report

An 8 month-old girl was referred to the Department of Ophthalmology, Ankara University Faculty of Medicine with the complaint of strabismus in the left eye. The examination under anaesthesia revealed bilateral group D retinoblastoma in both eyes. There was an exudative retinal detachment in both eyes with extensive subretinal seeds. There was no evidence of systemic involvement on bone marrow biopsy, spinal tap, and cranial MRI. The patient was initially treated with 6 cycles of intravenous carboplatin, etoposide and vincristine chemotherapy. Initially, the tumours in both eyes responded well to chemotherapy with resolution of SRF. The patient received several cryotherapy and transpupillary thermotherapy applications to recurrent and new tumours in both eyes over a period of approximately 12 months. However, the massive recurrence developed both eyes at 12 month follow-up and it was felt that either EBRT or enucleation was necessary at this point. The family opted for EBRT. The patient was seen in the Department of Radiation Oncology, Acibadem University, Istanbul for IMRT. A thermoplastic mask was prepared for the immobilization under anaesthesia and thereafter she underwent Computerized Tomography (CT) imaging with 1-mm slices for treatment planning purposes. Target tumour volumes and organs at risk (OAR) such as orbital bone, cornea, lens, lacrimal gland and optic nerve were delineated.

Gross tumour volume (GTV)[4] dose was not specified in this case, only the recurrent tumours in both eyes were delineated as tumour in order to not to lower the dose in those areas; clinical tumour volume (CTV) was defined as both right and left retina and planning target volume (PTV) was generated from CTV plus 1 mm margin. Dose to OAR was defined according to previously reported data.[5-9]

Comparison of 3DCRT and IMRT

In order to provide dose constraints for OAR we performed 4 different IMRT plans and a conformal plan. Of these IMRT plans the best isodose distribution and the dose volume histogram were provided with a noncoplanar 4-field technique (Figure 1); when compared to a conformal plan there was no significant difference for cornea, lens and optic nerve doses. The patient was treated with 4-field noncoplanar IMRT plan to a total dose of 40 Gy, 2 Gy per fraction under general anaesthesia. According to our department's image guided ra-

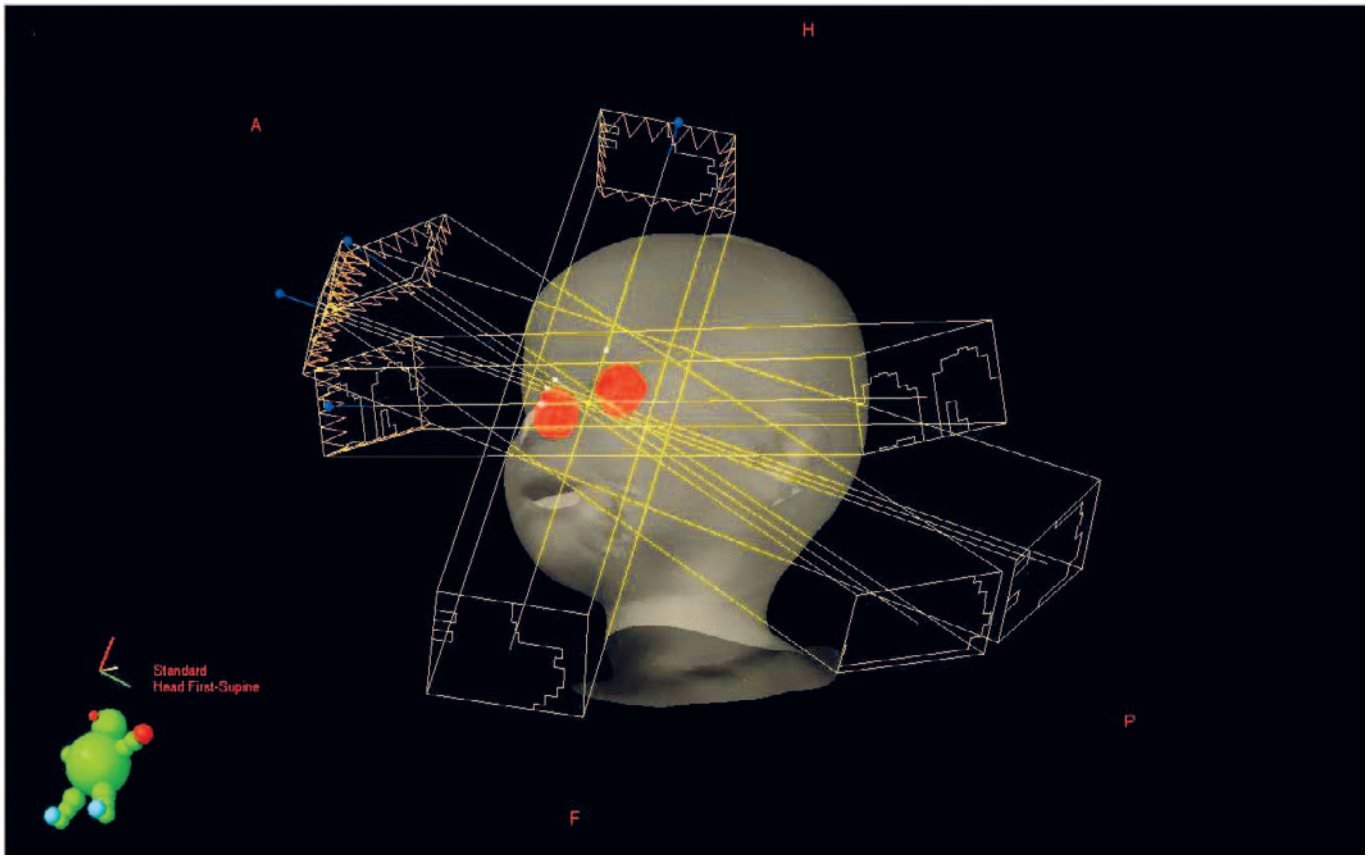

FIGURE 1. Four-field noncoplanar IMRT plan

diotherapy (IGRT) protocol, daily kilovoltage images were taken from anteroposterior and lateral fields before each treatment and corrections were done by matching pretreatment images with digitally reconstructed radiographs.

Radiation doses to the orbital bones and lacrimal glands were apparently lower while the tumour dose was higher in the IMRT plan. As a result of using multiple non coplanar beams; there were low dose areas in brain, brainstem and hypophysis with IMRT plan whereas no dose with 3DCRT, but these doses were below 5 Gy which was a safe dose for the affected areas. The comparison of doses between conformal and IMRT plan is detailed in Table 1.

At one year follow-up, the patient remained free of any obvious radiation complications.

Discussion

Retinoblastoma is a radiosensitive tumour. There is a wide spectrum of techniques used for retinoblastoma ranging from single fields to complex fields such as anterior lens sparing technique, lateral oblique fields, multiple non coplanar arcs, single anterior electron fields, stereotactic radiotherapy, conformal and intensity modulated radiotherapy plans. Even protons were used to perform homogeneous dose coverage of retina while sparing the lens and bony anatomy.[5,10-13] IMRT for retinoblastoma was first reported by Krasin *et al*.[5] Subsequently, Reisner *et al.* published a comparative analysis of external radiotherapy techniques with IMRT in a case report of unilateral retinoblastoma.[8] Previous reports on IMRT planning for retinoblastoma revealed greater sparing of the surrounding bony orbit and lacrimal gland as in our study.

High doses affecting bony orbital structures may cause growth arrest of orbital fossa and facial asymmetry.[7] IMRT leads to lower doses in orbital bones, while not reducing retinal doses. In our bilateral IMRT plan, doses in both orbital bones were higher when compared to unilateral cases of Reisner *et al*.[8] These relatively high doses can be explained by the location of recurrent tumours; which were in the posterior poles of both eyes. Plans were done in order to have an optimal dose

in these regions. In cases where the tumour is located medially or anteriorly, a lower dose may be delivered to the orbital bones using IMRT.

Dry-eye syndrome, because of lacrimal gland exposure to radiation, is also another important and irreversible complication for this patient group threatening life quality. One of the main advantages of IMRT is to reduce lacrimal gland dose without lowering retinal doses. Our patient's mean lacrimal gland doses were less than 30Gy. Dry eye is quite unlikely to develop with these radiation doses as reported by Parson *et al*.[6]

The optic nerve is also affected in the radiotherapy of retinoblastoma. Doses exceeding 54 Gy may lead to the development of radiation optic neuropathy leading to irreversible visual impairment. Reisner *et al.* reported maximum doses as high as 48 Gy for the optic nerve dose with several techniques including their IMRT planning.[8] In our setting the optic nerve received a maximum dose of 40-41 Gy which is a safe dose for optic neuropathy. The reduction in the optic nerve dose may prevent visual problems in the future life of the patient.

Corneal injury after EBRT has also been reported previously. The critical dosage was considered 50 Gy as the 50% risk at 5 years for cornea.[14] Reisner *et al.* considered V26.5 for the evaluation of corneal injury probability based on the study of Jiang *et al*.[9,10] Our plan delivered less than 50 Gy to the cornea region (mean dose for right and left cornea was 32 Gy and 28.7 Gy respectively) but the V26.5 dose was relatively higher especially on the right side, where a tumour was located more anteriorly.

The lens is the most radiosensitive tissue in the eye.[15] Lens preservation was always been an important target in radiotherapy planning for the treatment of tumours around the eye region. Doses exceeding 12 Gy usually results cataract. Lens sparing techniques with EBRT also caused cataract in 28% of patients.[16] However, a good outcome after the cataract surgery with phacoemulsification was reported even in young ages.[17] Therefore, we preferred to achieve therapeutic doses in the entire to avoid the recurrence of the tumour rather than delivering subtherapeutic doses to the retina in an effort to preserve the lens from the cataract development.

Technologic developments improved outcomes enormously in the last 10 years for EBRT. The capability of protecting normal tissue around tumour became available. IMRT with image guidance, so called IGRT-IMRT, is the superior technique that allows us to do the best and safe treatment. Outcomes of IMRT were successful with the more common cancers including prostate, head and neck, breast cancers in terms of the increased local control and normal tissue protection. Even with lung cancer, where a significant organ and tumour movement may be a problem in radiotherapy, IMRT proved to be successful. The outcomes of IMRT in rarer tumours such as retinoblastoma are not widely known because of the paucity of publications in this area.

It has been concluded that any genotoxic therapy can induce second neoplasms after long latent times and the risk is slightly higher with radiotherapy but the side effects of radiotherapy have less impact on the patients' quality of life when compared with other therapies.[18] In the pediatric setting the risk could be significant due to a higher inherent susceptibility of tissues. However, as the risk of secondary cancers as sarcomas, related with IMRT estimated to be 2% compared with 1% for 3DCRT, the use of protons became actual to reduce risk of radiation-induced carcinogenesis.[19] The efficacy of IMRT in reducing the acute and late toxicity in children with nasopharyngeal carcinoma (NPC) was reported by two centres recently.[20,21] Louis *et al.* found no difference with IMRT in terms of late toxicity such as hypothyroidism, xerostomia, hearing loss, and dental disease.[20] On the other hand Laskar *et al.* concluded that IMRT significantly reduces and delays the onset of the acute toxicity compared to EBRT, resulting in the improved tolerance and treatment compliance for children with NPC.[21] However, the number of studies with IMRT in pediatric tumours was very limited and other centre experience should be awaited.

In conclusion; image guided IMRT provides better dose distribution than 3DCRT in retinoblastoma eyes, delivering the therapeutic dose to the tumours and minimizing adjacent tissue damage. In terms of avoiding radiation complications including dry eye syndrome, facial deformity, cataract, radiation retinopathy and radiation papillopathy, IMRT planning should always be taken into consideration for patients that are referred for radiotherapy.

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research article

Linear array measurements of enhanced dynamic wedge and treatment planning system (TPS) calculation photon beam and comparison with electronic portal imaging device (EPID) measurements

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Introduction. Enhanced dynamic wedges (EDW) are known to increase drastically the radiation therapy treatment efficiency. This paper has the aim to compare linear array measurements of EDW with the calculations of treatment planning system (TPS) and the electronic portal imaging device (EPID) for 15 MV photon energy.

Materials and methods. The range of different field sizes and wedge angles (for 15 MV photon beam) were measured by the linear chamber array CA 24 in Blue water phantom. The measurement conditions were applied to the calculations of the commercial treatment planning system XIO CMS v.4.2.0 using convolution algorithm. EPID measurements were done on EPID-focus distance of 100 cm, and beam parameters being the same as for CA24 measurements.

Results. Both depth doses and profiles were measured. EDW linear array measurements of profiles to XIO CMS TPS calculation differ around 0.5%. Profiles in non-wedged direction and open field profiles practically do not differ. Percentage depth doses (PDDs) for all EDW measurements show the difference of not more than 0.2%, while the open field PDD is almost the same as EDW PDD. Wedge factors for 60 deg wedge angle were also examined, and the difference is up to 4%. EPID to linear array differs up to 5%.

Conclusions. The implementation of EDW in radiation therapy treatments provides clinicians with an effective tool for the conformal radiotherapy treatment planning. If modelling of EDW beam in TPS is done correctly, a very good agreement between measurements and calculation is obtained, but EPID cannot be used for reference measurements.

Key words: enhanced dynamic wedge; linear array; EPID

Introduction

Mechanical wedge filters (hard wedges) are often used in the treatment planning as compensators of dose inhomogeneities in the photon therapy. Nowadays, they are often replaced by Enhanced Dynamic Wedge (EDW). EDW is a technical solution of Varian Medical Systems, but also other manufactureres have solutions which achieve the same result (Elekta- omni wedge, Siemens- virtual wedge). The EDW technique achieves wedge-shaped dose distributions by the computer-controlled movement of one of the collimator jaws under the simultaneous adjustment of dose rate and speed of the moving jaw. The relationship between the number of delivered monitor units and the position of the moving jaw is governed by lookup tables referred to as "Segmented Treatment Tables"

TABLE 1. EDW profile measurements CA 24 in build up versus EPID

4x4 cm², 15deg (field edge 2 cm)			10x10 cm², 30deg (field edge 5 cm)			15x15 cm², 45deg (field edge 7.5 cm)			20x20 cm², 60deg, (field edge 10 cm)		
Position of detector in relation to Central axis (mm)	CA 24	EPID	Position of detector in relation to Central axis (mm)	CA 24	EPID	Position of detector in relation to Central axis (mm)	CA 24	EPID	Position of detector in relation to Central axis (mm)	CA 24	EPID
-50	1.03	3.01	-100	1.83	6.17	-120	3.86	10.00	-140	6.98	16.08
-45	1.87	3.53	-95	2.55	6.78	-115	4.33	10.87	-135	7.76	17.06
-40	1.9	3.97	-90	2.82	7.47	-110	5.13	11.87	-130	8.67	18.67
-35	2.84	4.49	-85	3.37	8.27	-105	5.66	13.18	-125	9.87	20.40
-30	4.78	5.32	-80	3.71	9.20	-100	6.31	14.49	-120	11.56	22.07
-25	12.02	7.37	-75	4.36	10.13	-95	7.37	15.71	-115	14.08	24.09
-20	50.2	47.84	-70	4.85	11.14	-90	9.49	17.28	-110	21.05	25.99
-15	93	99.39	-65	6.61	12.39	-85	14.53	19.16	-105	65.42	30.55
-10	100.19	100.74	-60	10.25	13.92	-80	39	22.52	-100	160.61	92.80
-5	100.12	100.44	-55	25.45	16.75	-75	107.34	59.80	-95	185.95	166.63
0	100	100.00	-50	79.05	52.91	-70	130.84	124.18	-90	186.12	166.80
5	99.59	99.65	-45	108.59	107.10	-65	133.61	125.23	-85	181.62	164.32
10	98.68	99.00	-40	111.69	108.19	-60	132.46	124.01	-80	176.63	160.58
15	94.37	96.90	-35	111.59	107.67	-55	130.4	122.30	-75	171.42	156.95
20	67.12	44.70	-30	110.35	106.74	-50	127.98	120.69	-70	166.64	152.97
25	19.13	7.28	-25	108.99	105.73	-45	125.24	118.90	-65	161.35	149.40
30	6.51	5.32	-20	107.33	104.52	-40	122.26	116.85	-60	156.44	145.25
35	2.93	4.58	-15	105.6	103.27	-35	119.87	114.80	-55	151.61	141.50
40	2.38	4.06	-10	103.94	102.38	-30	117.16	112.61	-50	146.82	137.41
45	1.87	3.58	-5	101.19	101.13	-25	113.98	110.34	-45	141.25	133.43
50	1.85	3.10	0	99.98	100.00	-20	111.23	108.03	-40	136.55	129.28
			5	99.28	99.19	-15	108.43	106.11	-35	131.67	125.48
			10	98.76	98.43	-10	105.69	104.02	-30	127.09	121.50
			15	98.32	97.38	-5	102.07	101.92	-25	122.26	117.46
			20	97.72	96.61	0	99.91	100.00	-20	117.6	113.55
			25	96.96	95.88	5	98.5	98.43	-15	112.98	110.32
			30	96.11	95.04	10	97.11	97.03	-10	108.93	106.80
			35	94.97	93.95	15	95.96	95.37	-5	103.32	103.23
			40	93.17	92.74	20	94.61	93.98	0	99.93	100.00
			45	88.98	90.27	25	93.34	92.84	5	96.96	97.06
			50	70.98	38.82	30	91.98	91.58	10	94.28	94.41
			55	22.68	14.97	35	90.57	90.22	15	91.59	91.76
			60	9.09	12.63	40	89.04	88.83	20	89.04	89.16
			65	5.97	11.22	45	87.5	87.47	25	86.52	86.63
			70	5	10.21	50	85.97	85.68	30	83.75	84.44
			75	4.13	9.20	55	84.05	84.20	35	81.32	82.19
			80	3.34	8.31	60	82.11	82.15	40	78.55	79.71
			85	3.29	7.59	65	79.78	80.18	45	76.2	77.46
			90	2.65	6.86	70	76.51	76.87	50	73.56	74.99
			95	2.35	6.13	75	63.15	34.00	55	70.96	72.62

4x4 cm², 15deg (field edge 2 cm)			10x10 cm², 30deg (field edge 5 cm)			15x15 cm², 45deg (field edge 7.5 cm)			20x20 cm², 60deg, (field edge 10 cm)		
Position of detector in relation to Central axis (mm)	CA 24	EPID	Position of detector in relation to Central axis (mm)	CA 24	EPID	Position of detector in relation to Central axis (mm)	CA 24	EPID	Position of detector in relation to Central axis (mm)	CA 24	EPID
			100	1.63	5.65	80	26.21	16.24	60	68.4	70.32
						85	10.32	14.27	65	65.96	67.95
						90	7.25	12.92	70	63.53	65.59
						95	4.92	11.79	75	61.05	63.17
						100	4.19	10.74	80	58.53	60.81
						105	4.04	9.86	85	56.34	58.67
						110	3.48	9.04	90	54.11	56.08
						115	3.01	8.25	95	49.82	52.97
						120	2.74	7.64	100	43.59	24.67
									105	21.59	14.52
									110	8.34	13.08
									115	5.9	11.99
									120	4.91	11.24
									125	4.5	10.43
									130	3.84	9.63
									135	3.38	9.11
									140	3.14	8.70

(STT). The EDW provides seven wedge angles (10°, 15°, 20°, 25°, 30°, 45°, and 60°) for both symmetric and asymmetric field sizes. The upper independent jaws, assigned to as Y1 and Y2, can travel from a full open position to 10 cm across the central axis, thus allowing field sizes up to 30 cm along the wedged direction. Two wedge orientations are available: Y1-IN and Y2-OUT, indicating the moving jaw. The EDW needs only one reference STT for each photon energy. This so called "Golden" STT represents the full field width of 30 cm and a wedge angle of 60°. Intermediate wedge angles can be derived by means of weighted averaging of an "open field STT" and the Golden STT (ratio of tangens method). The individualized treatment STT is then obtained by the truncation to the desired field size and normalization so that the final number of monitor units is the total number of monitor units needed to deliver a certain dose to the reference point. These individualized STTs are created automatically by the linac computer, as the operator types in the energy, wedge angle, monitor units, etc. In order to deliver a dynamically wedged field, the length of the treatment field is divided into 20 segments, and the speed of the moving jaw and the dose rate within each segment are controlled based on a calculated segmented treatment table (STT) generated by the linear accelerator computer.

The implementation of dynamic wedges in the various radiation therapy planning (RTP) systems has already been described.[1,2] As with any other commissioning activity, great care must be taken to ensure that enhanced dynamic wedges are correctly modelled in the treatment planning system. To directly verify the computational accuracy of a treatment planning system, measurements need to be made with the accelerator setup to the same identical specifications as already planned.[3]

This work was aimed to verify EDW (described in details in literature)[4] in the treatment planning system (TPS) and use patient set up equipment to compare dosimetrical and calculation results with electronic portal imaging device (EPID) measurements. In addition, comparison with hard wedges was also presented.

The electronic portal imaging device is very sophisticated gadget, accessory at the stand of the accelerator, which has an amorphous silicon detector remaining resistant to irradiation after the application of very high doses, and has certain dosimetrical characteristics which were also investigated here but also well described in literature.[5-10]

TABLE 2. Open field profiles in 3 cm build up vs EPID profiles in direction perpendicular to the movement of Y jaw, 10x10 cm2 field

Crossline (mm)	Open	15deg EDW	30 deg EDW	45deg EDW	60deg EDW
-110	1.3	2.8	2.8	2.9	2.9
-105	1.3	3.1	3.1	3.2	3.2
-100	1.5	3.2	3.2	3.2	3.3
-95	1.7	3.8	3.8	3.8	3.9
-90	2.0	4.3	4.3	4.3	4.4
-85	2.2	5.1	5.1	5.1	5.2
-80	2.7	6.0	6.0	6.0	6.1
-75	3.3	6.7	6.8	6.8	6.9
-70	4.0	7.8	7.9	7.9	8.0
-65	5.4	9.3	9.3	9.3	9.4
-60	9.2	11.0	11.0	11.0	11.1
-55	26.1	13.9	14.0	14.0	14.0
-50	71.2	51.0	51.5	51.6	49.7
-45	96.5	97.1	97.3	97.1	97.0
-40	100.9	99.2	99.3	99.2	99.1
-35	102.2	100.1	100.2	100.1	100.0
-30	102.3	100.5	100.6	100.5	100.4
-25	101.9	100.6	100.6	100.6	100.5
-20	101.8	100.5	100.6	100.6	100.5
-15	101.1	100.7	100.7	100.6	100.6
-10	100.5	100.5	100.6	100.6	100.5
-5	99.7	100.4	100.4	100.4	100.3
0	100.0	100.0	100.0	100.0	100.0
5	100.6	100.2	100.4	100.3	100.3
10	101.2	100.2	100.2	100.2	100.2
15	101.5	100.1	100.2	100.2	100.2
20	101.9	100.0	100.1	100.0	100.0
25	102.5	100.0	100.1	100.1	100.0
30	102.9	99.8	100.0	99.9	100.0
35	102.6	99.6	99.7	99.7	99.7
40	100.5	98.8	98.8	98.8	98.9
45	96.2	96.6	96.7	96.6	96.8
50	74.1	48.4	46.2	48.3	50.1
55	22.5	13.4	13.4	13.5	13.6
60	8.3	10.8	10.9	11.0	11.0
65	5.1	9.2	9.2	9.3	9.4
70	4.1	7.8	7.9	8.0	8.0
75	3.1	6.7	6.8	6.8	6.9
80	2.6	5.8	5.8	5.8	6.0
85	2.3	5.1	5.1	5.2	5.3
90	1.9	4.4	4.5	4.5	4.6
95	1.6	3.9	3.9	4.0	4.1
100	1.6	3.4	3.5	3.5	3.5
105	1.4	3.1	3.1	3.2	3.2
110	1.2	2.9	2.9	2.9	3.0

Materials and methods

Linear array CA24 measurements

The measurement of enhanced dynamic wedge profiles using a linear chamber array requires the integration of the dose during the entire exposure at each point of measurement. It was done by the CA 24 Scanditronix Welhofer, and two electrometers, MD 240 and CU 500E, connected to the PC and OmniPro 6.2A software. The linear array CA 24 consists of 23 ionization chambers, the volume of each is 0.147 cm^3, diameter 0.6 cm and active length 0.33 cm. The each two neighbouring chambers are placed on 2 cm distance, and their long axes are parallel to the central axis of the beam. They are mounted to the holder of the Blue water phantom. The main feature of this linear array is that the profiles are measured directly in the water, under the same conditions as measurements of the open field profiles or mechanical wedged field profiles.

The beam data was collected according to the guidelines provided by Varian[5,6]. This consists of measurements of cross profiles and depth dose curves for the maximum (60°) and at least one intermediate wedge angle, in addition to measurements of the output factors.

The calculated percentage depth dose curves (PDDs) and profiles were compared with measured data for 15 MV photons at a Varian Clinac 2100C. Square field sizes ranging from 4*x*4 cm^2 to 20*x*20 cm^2 were evaluated with measurements of PDDs and profile curves on few depths (build up, 5 cm, 10 cm, and 20 cm).

EPID measurements

The features of EPID are described well in the literature.[7-13] Portal imager aS1000 was positioned on a source to skin distance (source-EPID surface distance- SSD) 100 cm (not on standard 140 cm). The standard calibration procedure was then applied under this condition.

The EDW fields of 4 cm x 4 cm, 10 cm x10 cm, 15 cm x 15 cm, and 20 cm x 20 cm were imaged (with the usage of EPID portal dosimetry mode) for the wedge angles of 15 deg, 30 deg, 45 deg and 60 deg, with the collimator orientation and movement as for CA 24 measurements. The collimator orientation for all measurements was 90 degrees and Y1-IN wedge orientation (*Y1* being the dynamic jaw).

Linearity of the pixel response with dose was checked, followed by field measurements.

TABLE 3. WF measured for the angle of 60°, and field sizes 4x4 cm2, 10x10 cm2, 15x15 cm2, 20x20 cm2, 30x30 cm2 using the energy of 15M

X(cm)	Y1 (cm)	Y2(cm)	Measured WF	TPS WF	Hard wedge WF
4	2	2	0.892	0.882	0.431
10	5	5	0.713	0.689	0.437
15	7.5	7.5	0.596	0.575	0.444
20	10	10	0.499	0.483	n/a
30	20	10	0.343	0.345	n/a

The image acquired by EPID, which results from each EDW field irradiation, is 2D image, with the different pixel values and is closely related to the intensity map of the EDW field. The pixel values carry information about the intensity of the signal within the pixel area. Pixels lying on lines crossing the central axis pixel are creating in plane and cross plane profiles. One profile is in the direction of the moving jaw, creating the wedged distribution, and another one is the perpendicular to the direction of the moving jaw. Other pixels are lying off axis, and can be used to create 3D image of a wedged field.

In order to extract useful information about the profiles, the central axis pixel value is assigned value 100. All other pixels got then a relative value, depending on the ratio of the original pixel value on central axis, and elsewhere in plane and cross plane profiles. The series of relative pixel values on both profiles creates profiles comparable to other methods of measurements.

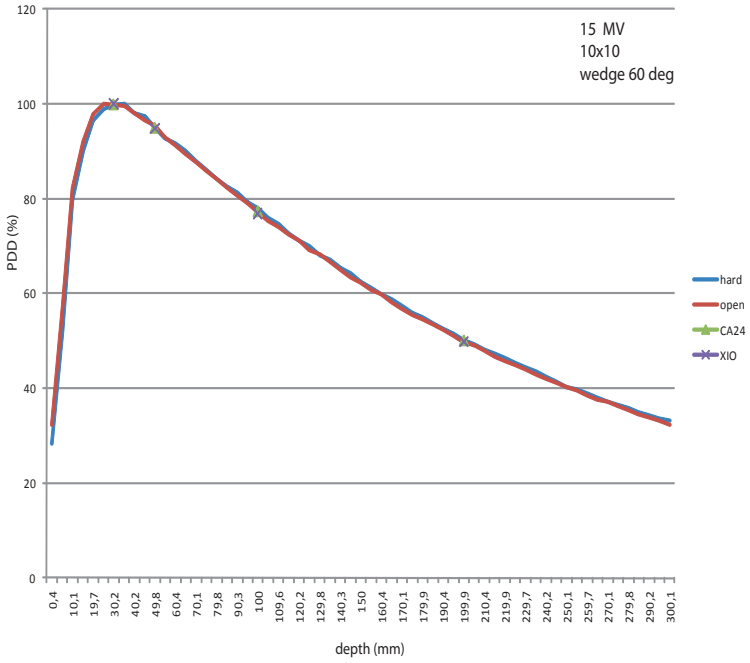

FIGURE 1. PDD of 10 cm x 10 cm field, 15 MV, wedge 60 deg.

External beam treatment planning calculations

The treatment planning system used for this purpose was XIO CMS v. 4.2.0, convolution algorithm. Virtual phantom of the size of the big Blue phantom (used for measurements in water), was defined in the TPS, and the electron density of water assigned to the inner space of the phantom. The EDW beam was created with the collimator and gantry orientation as in water and EPID measurements, and appropriate field size, wedge angle, weight point definition, normalization, etc, imitating the measurements under real conditions in water. The resulting calculated plan was analyzed taking into consideration the depth dose curve and profiles on determined depths (build up, 5 cm, 10 cm and 20 cm). Dose values were read from the Dose Profile in the menu of the treatment planning space of XIO, on 5 mm distance along the profile of the field.

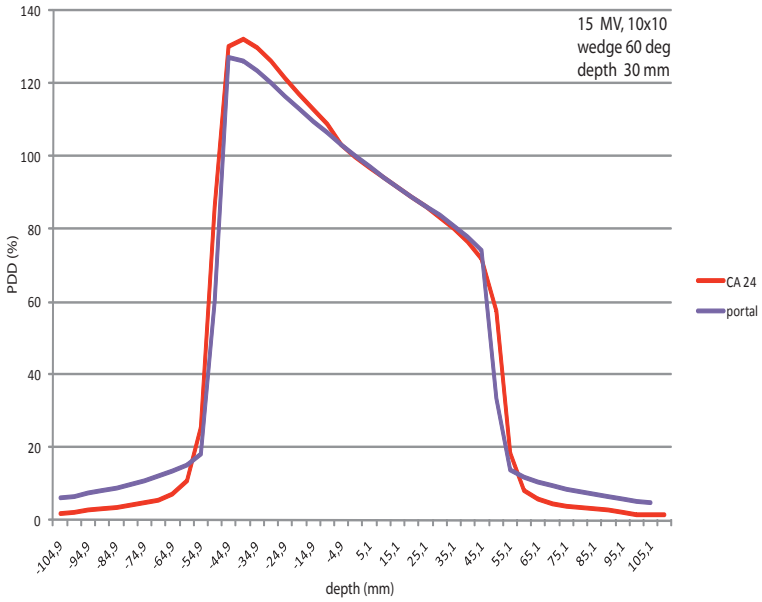

FIGURE 2. EPID profile *vs* CA24 profile, 10 cm x10 cm field, wedge 60 deg.

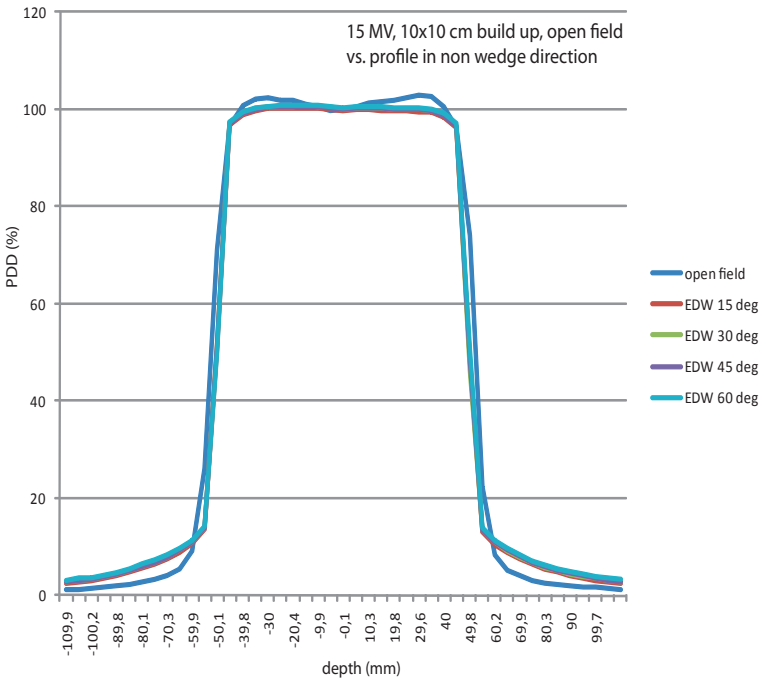

FIGURE 3. Open field profiles overlap with the EDW profiles in non wedged direction (example is 10 cm x10 cm field).

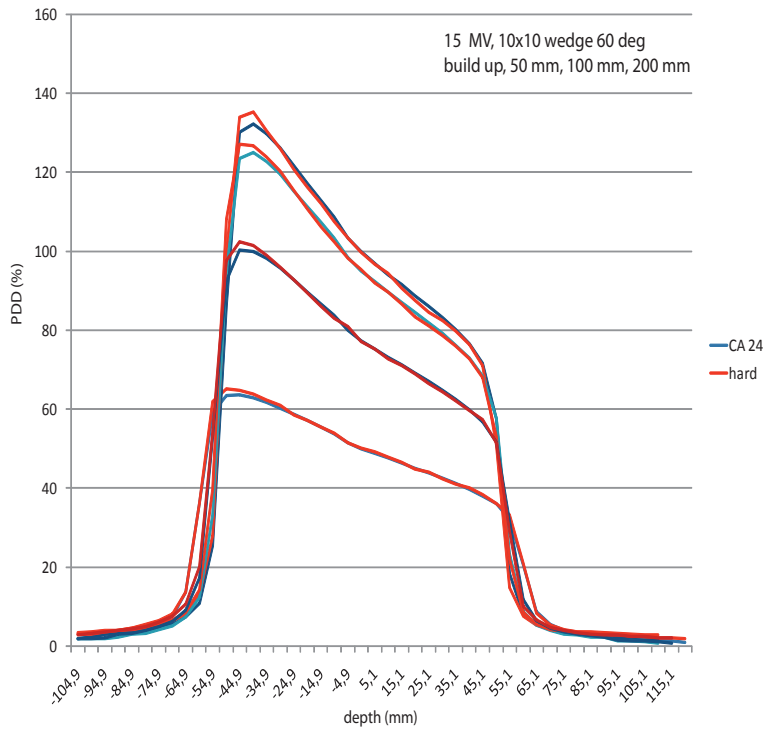

FIGURE 4. CA 24 profiles in comparison with hard wedge profiles, 10 cm x10 cm field, 60 deg wedge.

These calculated profiles, as well as the profiles obtained by CA 24, and EPID, were compared to the profiles of hard wedges obtained using Blue phantom and CC13 ionization chambers, collected upon commissioning and acceptance tests of this linear accelerator.

Hard wedges measurements and open field measurements

The measured data of open fields and for hard wedges, collected during commissioning and acceptance tests of the Varian 2100C linac were used for this study. Only additional measurements for the field 4x4 cm^2 were collected during this survey for all wedge angles and depths, since Varian recommendations for commissioning do not include this field size as mandatory.

Results

Percentage depth doses

The percentage depth dose curves of the open fields (measured by CC13 chambers), hard wedged fields (measured also by CC13 chambers), EDW fields (measured by linear array CA 24- PDD values extracted from profiles) and calculated by XIO, were compared.

Generally speaking, the PDDs of open fields and EDW fields do not differ more than 0.5%.

PDDs of open fields have a higher surface dose than the PDDs of hard wedged fields (dose extrapolated to the surface of water- 0 cm depth) (Figure 1). This comes from the beam hardening under the mechanical wedge. The beam hardening effect is also clearly visible on the tail of the PDD curve of the mechanical wedge and gives the difference of around 2%.

PDDs generated from profiles measured by CA 24 and calculated by XIO are practically identical (result of modelling the EDW in TPS).

The PDDs with EPID could not be obtained at this stage, since only measurements in build up were possible.

Profile measurements

EPID profiles in build up compared to linear array measurements in build up

Profiles were obtained in direction of the moving jaw, showing the wedged shaped distribution.

EDW profiles obtained by EPID in comparison with the same measured by the linear array differ around 1%, max up to 2%, within the field (Table 1). At the edges of the fields, the EPID profiles were having a larger gradient (dose fall down) than the profiles obtained by other methods. This applies to all wedge angles.

A dose measured by EPID outside the field (peripheral dose) was much larger than the one measured by CA 24 linear array. This is characteristic for all angles and for all field sizes. (Figure 2)

Profiles measured by EPID in comparison to open beam profiles measured by ionization chamber

EDW profiles imaged by EPID in the perpendicular direction to the movement of the jaw, were also examined, and compared to the open field profiles, which were measured during commissioning of the machine, by CC13 ionization chambers. A very good agreement was found (Table 2, Figure 3). This is not the case with the profiles of hard wedged fields, measured also in the non-wedged direction, where the interaction of the beam with the material of the hard wedge (beam hardening effect), influences the shape of the profile (a hard wedged profile demonstrates a decrease in dose at the field edges in comparison with the EDW and open field profile in non wedged direction).

Profiles of EDW field measured by linear array in comparison of hard wedges profiles measured by ionization chambers

EDW linear array profiles to hard wedges do differ more in all cases, but that was expected due to the physical differences of two techniques (Figure 4)

Profiles of EDW field measured by linear array in comparison to the calculation of XIO CMS TPS

In most cases, the dose values on profiles differ around 0.5%, within the field, while outside the field it seems that XIO underestimates the peripheral doses by factor of 2.

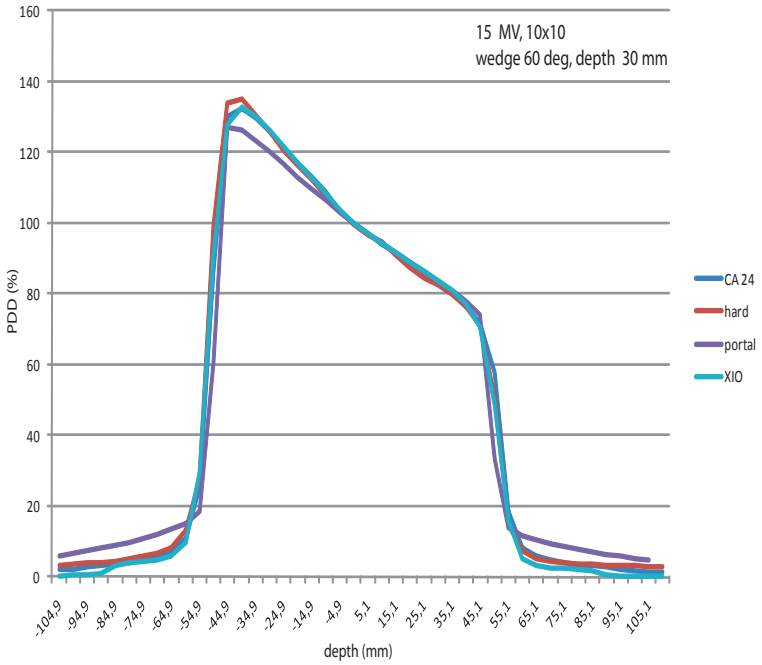

FIGURE 5. 15 MV profiles for a 10 cm x10 cm field, 60 deg wedge, build up (four methods of measurements and calculations).

EDW wedge factors

EDW wedge factors are the strong functions of the field size. This is proved by the measurements of wedge factors of EDW fields, and by the calculation of WF in the treatment planning system. This, of course, does not apply to the hard wedge whose dependence of the field size is almost negligible. This is due to the fact that mechanical wedges are always placed in the same position on the tray of the accelerator, and because the central beam always passes through the same thickness of the wedge, it does not matter what the field size is actually set (Table 3).

Discussion

For the quality assurance (QA) in radiotherapy we can use in *vivo* or *in vitro* methods with phantoms.[14] The second one can be used for for routine QA or for reference measurements. The basic conclusion of our study would be that EPID aS1000 can be used for the routine QA and for EDW verification, but not for commissioning, only for regular QA checks. The conclusion would also be that the implemented dose calculation algorithm well describes the EDW treatment.

The peripheral dose of EDW field is half the dose of the hard wedged field. The reason for that lies in scatter outside the hard wedged field, due to the interaction of the beam with the material of the mechanical wedge. Clinically, this is an advantage of EDW wedged field. The wedge angle is better preserved for EDW than for hard wedges at all depths.

The profile dose measured by EPID outside the field (peripheral dose) was much larger than the one measured by the CA 24 linear array. This is characteristic of all angles and for all field sizes. The reason for that as explained in the literature, might be due to the difference in absorption of low energy photons which appears in the material of the high Z. Spectrum of the photons is changed with the distance from the central axis, and region outside the field has only a scatter radiation. That is why the difference in profiles outside the field can be assumed to come from the difference of low energy photons of other dosimetrical methods and sensitive material of EPID detectors.

Practically, all measurement techniques of EDW give very satisfactory results in terms of the agreement within PDDs and profiles (Figure 5). Still, standard dosimetric measurements cannot be underestimated, and EPID implemented as verification tool in terms of implementation of a new technique in the department.

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doi:10.2478/v10019-010-0018-8

Sledenje bolnikov po zdravljenju raka debelega črevesa in danke

Velenik V

Izhodišča. Čeprav je sledenje bolnikov po radikalnem zdravljenju raka debelega črevesa in danke običajno, so mnenja o njegovi vrednosti nasprotujoča. Zaradi pomanjkanja prepričljivih kliničnih podatkov so predlagani različni načini sledenja. Smernice v državah in regijah se razlikujejo tudi zaradi različne zdravstvene politike, razpoložljivih denarnih sredstev in dvoma o učinkovitosti sledenja.

Zaključki. Rezultati metaanaliz kliničnih raziskav sicer dokazujejo izboljšanje preživetja bolnikov, ki smo jih intenzivno sledili, vprašanje optimalne pogostnosti kliničnih pregledov in preiskav pa ostaja neodgovorjeno. Intenzivni nadzor bolnikov je težak, za bolnika je lahko neprijeten in nevaren ter predstavlja resno finančno obremenitev zdravstvenemu sistemu. Dosegljivi podatki pa kažejo, da sledenje bolnikov ne zmanjšuje kakovosti življenja bolnikov. Potekajoče velike prospektivne multicentrične raziskave bodo lahko odgovorile na nekatera vprašanja, ki nastajajo ob sledenju bolnikov z rakom debelega črevesa in danke.

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Uporaba fluorescentnih tarčnih molekul v slikovni diagnostiki raka

Paganin-Gioanni A, Bellard E, Paquereau L, Ecochard V, Golzio M, Teissié J

Izhodišča. Glavi izziv pri zdravljenju raka sta izboljšanje zgodnjega odkrivanja in presejanje z uporabo tarčnih molekul. Takšno zgodnje odkrivanje raka zahteva specifično vezavo na rakave celice, na tumorske označevalce, ki naj bi v idealnem primeru bili prisotni na površini tumorske celice. Tarčno označevanje tumorskih celic z molekulami, ki jih lahko slikovno zaznamo, omogoča odkrivanje tumorskih celic.

Zaključki. Fluorescentna slikovna diagnostika je novejša tehnologija, ki se komplementarno uvršča med diagnostične metode v onkologiji. Omogoča zaznavanje tumorskih označevalcev z visoko prostorsko in časovno resolucijo pri malih živalih in v kliničnih študijah. V pregledu smo se osredotočili na novejše temeljne raziskave priprave testov in aparatur, ki jih uporabljamo za zgodnje odkrivanje raka s fluorescentnimi slikovnimi tehnikami.

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Odsotnost spodnje vene kave z nadaljevanjem poteka vene azygos/hemiazygos. Žilna nepravilnost pri prašičjem živalskem modelu.

Jeromel M, Pavčnik D

Izhodišča. Prašiče pogosto uporabljamo kot živalski model za proučevanje prirojenih srčno-žilnih napak, ki se pojavljajo pri človeku. Napake na živalskem modelu lahko nastanejo spontano ali pa jih ustvarimo umetno. Defekt prekatnega pretina, odprt Botallov vod in defekt preddvornega pretina so stanja, ki jih lahko na takem modelu ustvarimo umetno. Odsotnost spodnje vene kave z nadaljevanjem poteka vene azygos/hemiazygos je redka žilna nepravilnost.

Prikaz primera. Odsotnost spodnje vene kave z nadaljevanjem poteka vene azygos/hemiazygos smo slučajno odkrili, ko smo na prašičjem živalskem modelu proučevali zapiranje defekta preddvornega pretina. Ob posegu smo uporabljali perkutani femoralni pristop. Odsotnost spodnje vene kave smo potrdili z venografijo in z obdukcijo.

Zaključki. Po pregledu literature je mnenje avtorjev, da je pričujoči prispevek prvi te vrste, ki opisuje odsotnost spodnje vene kave z nadaljevanjem poteka vene azygos/hemiazygos pri prašiču.

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doi:10.2478/v10019-010-0016-x

Direktno vstavljanje koronarnih žilnih opornic zmanjša sevanje in količino kontrastnega sredstva

Caluk J, Osmanović E, Baraković F, Kusljugić Z, Terzić I, Caluk S, Sofić A

Izhodišča. Z vstavljanjem koronarnih žilnih opornic omogočimo revaskularizacijo. Uporabljamo dva načina: pred vstavitvijo žilne opornice dilatiramo žilo z balonom ali pa direktno vstavimo žilno opornico. Če zdravnik, ki opravlja poseg, lahko zmanjša čas uporabe fluoroskopa, lahko s tem tudi zmanjša izpostavljenost sevanju bolnika kot tudi medicinskega osebja. Prav tako lahko z zmanjšano količino kontrastnega sredstva zmanjša nevarnost nefrotoksičnosti, ki je najpomembnejši možni stranski učinek njegove uporabe. Namen klinične raziskave je bil primerjati čas fluoroskopije, količino uporabljenega kontrastnega sredstva in ceno pri obeh načinih vstavljanja koronarnih žilnih opornic.

Bolniki in metode. V prospektivni klinični raziskavi smo 70 bolnikov s koronarno boleznijo randomizirano zdravili s koronarno balonsko dilatacijo in vstavljanjem žilne opornice ali pa z direktnim vstavljanjem žilne opornice.

Rezultati. Čas fluoroskopije in količina kontrastnega sredstva sta bila pri direktnem vstavljanju žilnih opornic statistično značilno zmanjšana. Prav tako je bila cena pri direktnem vstavljanju žilnih opornic statistično značilno manjša kot pri posegu z balonsko dilatacijo.

Zaključki. Svetujemo, da direktno vstavimo koronarne žilne opornice pri vseh perkutanih koronarnih posegih, če ugotovimo primerne pogoje. Če je direktna vstavitev koronarne žilne opornice neuspešna, moramo narediti predhodno balonsko dilatacijo žile.

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Slikovne preiskave pri sumu na travmatsko psevdoanevrizmo torakalne aorte

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Izhodišča. Namen raziskave je bil predstaviti izsledke slikovnih preiskav pri bolnikih s sumom na travmatsko psevdoanevrizmo torakalne aorte, ki je nastala po prometni nesreči.

Bolniki in metode. V 22 letih smo odkrili 8 travmatskih psevdoanevrizem torakalne aorte pri 7 (87,5%) moških in 1 (12,5%) ženski. V času prometne nesreče je bil najmlajši bolnik star 21 let in najstarejši 55 (srednja starost 33,8 let), v času ugotovljene psevdoanevrizme pa je bila starost od 26 do 55 let (srednja starost 38,7 let). Pri vseh bolnikih smo rentgensko slikali prsne organe in naredili CT preiskavo, pri 6 (75%) bolnikih intravenozno digitalno subtrakcijsko angiografijo (*i.v.* DSA) in pri 1 (12,5%) MRI. Pri CT preiskavi smo intravenozno vbrizgali 120 ml kontrasta in pri DSA 60 ml.

Rezultati. Pri 8 (100%) bolnikih, ki so imeli prometno nesrečo in pri katerih je rentgensko slikanje prsnih organov pokazalo povečan aortni gumb in mediastinum, smo s CT preiskavo, *i.v.* DSA in MRI odkrili travmatsko psevdoanevrizmo torakalne aorte. Čas od nesreče do ugotovitve psevdoanevrizme je bil od 7 dni do 18 let (srednja vrednost 2,0 leta). Premer ugotovljene psevdoanevrizme je bil od 4,5 do 9,2 cm (srenja vrednost 5,5 cm). Pri 7 (87,5%) bolnikih je bila psevdoanevrizma v predelu istmusa aorte in pri 1 (12,5%) v predelu descendentnega predela torakalne aorte. Z rentgenskim slikanjem smo ugotovili robno kalcifikacijo aorte pri 4 (50%) bolnikih, s CT preiskavo pa pri 5 (62,5%). Intraluminalno trombozo smo našli s CT preiskavo pri 2 (25%) travmatiziranih bolnikih.

Zaključki. Pri topih poškodbah prsnega koša moramo pomisliti na možnost travmatske psevdoanevrizme aorte, še zlasti, če rentgensko slikanje prsnih organov pokaže sumljive znake. Pri ugotavljanju psevdoanevrizme aorte je metoda izbora večrezinska CT preiskava.

Radiol Oncol 2010; 44(3): 164-167.
doi: 10.2478/v10019-010-0014-z

Radiološka ocena von Hippel-Lindeaujeve bolezni: slikovne značilnosti in pregled literature

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Izhodišča. Von Hippel-Lindaujev a bolezen je dedna avtosomska dominantna onkološka bolezen, ki prizadene več organskih sistemov. Ugotovimo jo s kliničnimi, radiološkimi in genetskimi preiskavami. Ocenjujemo, da je prevalenca bolezni 1 bolnik na 36000 prebivalcev. Tumorji pri tej bolezni so lahko benigni ali maligni.

Prikaz primera. Opisujemo MR značilnosti bolezni pri družini z 10 otroki. Von Hippel-Lindaujevo bolezen smo odkrili pri materi in 5 otrocih.

Zaključki. Radiološke preiskave so zelo pomembne za zgodnjo diagnozo in zdravljenje asimptomatskih bolnikov z von Hippel-Lindaujevo boleznijo. Zgodnja diagnoza je pomembna, ker omogoča zgodnje zdravljenje in na ta način lahko vplivamo na preživetje bolnikov ter na njihovo kakovost življenja. Pri presejalnih preiskavah bolnikov, ki so dedno obremenjeni, je važna multidisciplinarna obravnava.

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Izguba heterozigotnosti *CDKN2A* (*p16INK4a*) in tumor supresorskih genov *RB1* pri germinalnih tumorjih testisov

Vladušić T, Hrašćan R, Pećina-Šlaus N, Vrhovac I, Gamulin M, Franekić J, Krušlin B

Izhodišča. Germinalni tumorji testisov so najpogostejši malignomi pri mladih odraslih moških. Biološko se razlikujeta dve najpogostejši histološki entiteti seminomski in neseminomski tumorji. Protein pRB in njegov regulatorni protein *p16INK4a* sta udeležena pri poti nastanka proteina RB, ki je pogosto okvarjena pri germinalnih tumorjih testisov. Namen študije je bil določiti pogostnost izgube heterozigotnosti *CDKN2A (p16INK4a)* in *RB1* tumor supresorkih genov *RB1* pri germinalnih tumorjih testisov.

Materiali in metode. 40 germinalnih tumorjev testisov (18 seminomov in 22 neseminomov) smo z verižno polimerazno reakcijo analizirali na polimorfizme genov.

Rezultati. Izgubo heterozigotnosti *CDKN2A* smo dokazali pri dveh (6%) od 34 (85%) primerov germinalnih tumorjev testisov. Opisane spremembe smo našli pri dveh (11%) od 18 (82%) neseminomskih tumorjih. Izgubo heterozigotnosti *RB1* pa smo dokazali pri dveh (6%) od 34 (85%) primerih vseh germinalnih tumorjev testisov. Te spremembe so bile opažene pri dveh (10.5%) od 19 (86%) neseminomskih tumorjih. Obe izgubi heterozigotnosti *CDKN2A* smo dokazali pri neseminomskih tumorjih s komponento jajčne vrečke, obe izgubi heterozigotnosti RB1 pa smo dokazali pri neseminomskih tumorjih s komponento embrionalnega karcinoma.

Zaključki. Povišana incidence izgub heterozigotnosti *CDKN2A (p16INK4a)* in tumor supresorskih genov *RB1* je lahko razlog za večjo invazivnost germinalnih tumorjev testisov.

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Raziskava sprememb metabolizma fosforja z ^{31}P jedersko magnetno resonanco pri poskusnih obsevanih z rentgenskimi žarki

Serša I, Kranjc S, Serša G, Nemec-Svete A, Lozar B, Sepe A, Vidmar J, Šentjurc M

Izhodišča. Cilj raziskave je bil proučiti, ali lahko z ^{31}P jedrsko magnetno resonanco (JMR) učinkovito odkrijemo spremembe energetskega metabolizma povzročene z rentgenskimi žarki pri poskusnih miših. Izpostavljenost ionizirajočemu sevanju povzroči spremembe v oskrbi z energijo. Spremembe so povezane s poškodbami tkiva zaradi oksidativnega stresa in oksidativne fosforilacije. Posledice obsevanja so vidne v zmanjšanju razmerja med fosfokreatinom in adenozin trifosfatom (Pcr/ATP), kot tudi v povečani koncentracji kreatin-kinaze (CK) in jetrnih encimov (transaminaz AST in ALT) v serumu.

Material in metode. V raziskavi so bile poskusne miši razdeljene na skupino, ki je prejela 7 Gy rentgenskega sevanja in na kontrolno skupino. Metabolizem obeh skupin smo spremljali z ^{31}P JMR spektroskopijo in biokemijsko z merjenjem ravni CK in jetrnih encimov v plazmi. Meritve obeh skupin miši so bile opravljene v rednih časovnih intervalih v naslednjih treh tednih po obsevanju.

Rezultati. V skupini obsevanih miši smo dva ali več dni po obsevanju iz izmerjenih višin vrhov ^{31}P JMR spektrov opazili bistveno spremembo razmerja Pcr/ATP, medtem ko v kontrolni skupini miši nismo opazili nobene pomembne spremembe razmerja Pcr/ATP. Ta rezultat podpirajo tudi opravljene vzporedne meritve ravni CK. Raven CK je bila izrazito povečana takoj po obsevanju, kar se dobro ujema z opaženim zmanjšanjem razmerja Pcr/ATP in z njim povezanim upadom mišične oskrbe z energijo.

Zaključki. ^{31}P JMR meritve razmerja Pcr/ATP lahko služijo kot takojšen in neinvaziven pokazatelj prejete doze sevanja.

Radiol Oncol 2010; 44(3): 180-186.
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Preventivno obsevanje glave pri bolnikih z drobnoceličnim rakom pljuč: izkušnje na Onkološkem Inštitutu Ljubljana

Stanič K, Kovač V

Izhodišča. Preventivno obsevanje glave (PCI) uporabljamo pri bolnikih z drobnoceličnim rakom pljuč za znižanje incidence možganskih metastaz in podaljšanje preživetja. Namen retrospektivne raziskave je bila analiza značilnosti bolnikov z drobnoceličnim rakom pljuč, napotenih na Onkološki inštitut Ljubljana, njihova primernost za PCI, mesta širjenja bolezni in preživetje.

Bolniki in metode. Pregledali smo dokumentacijo 357 bolnikov z drobnoceličnim rakom pljuč, ki so bili med januarjem 2004 in decembrom 2006 napoteni na Onkološki inštitut Ljubljana, da bi ugotovili, kakšni bolniki so bili izbrani za PCI. Beležili smo naslednje podatke: razširjenost bolezni, starost, spol, telesno zmogljivost, kadilski status, način in rezultat primarnega zdravljenja, nekaj hematoloških in biokemičnih parametrov, uporabo PCI ter status možganskih metastaz ob diagnozi in po zdravljenju.

Rezultati. Preventivno obsevanje glave je imelo 24 (6,7%) izmed vseh bolnikov. Po PCI je pri 6 (25%) bolnikih prišlo do možganskih zasevkov, pri 4 bolnikih je bilo to edino mesto razsoja, pri dveh je bolezen napredovala v več organov. Srednje preživetje bolnikov, ki so imeli PCI, je bilo 21,9 mesecev, tistih brez pa 12,13 mesecev (p=0,004). Dobri prognostični dejavniki so bili: starost pod 65 let, omejena oblika bolezni, telesna zmogljivost in normalne vrednosti laktatne dehidrogenaze ter C-reaktivnega proteina. Drugi prognostični dejavniki niso bili statistično značilni.

Zaključki. Preživetje bolnikov z drobnoceličnim rakom pljuč, ki smo jim profilaktično obsevali glavo, je bilo statistično značilno boljše od tistih brez PCI. Za takšno obsevanje smo se odločali pri bolnikih, ki so imeli omejeno bolezen, popoln ali skoraj popoln odgovor na zdravljenje in dobro telesno zmogljivost. PCI nismo uporabljali pri bolnikih z razširjeno boleznijo, to področje bi bilo potrebno še raziskati. Doze obsevanja niso bile enotne, potrebno bi bilo oblikovati bolj standarden pristop.

Radiol Oncol 2009; 44(3): 187-193.
doi:10.2478/v10019-010-0034-8

Okvara spolnih žlez po zdravljenju Hodgkinove bolezni v otroštvu

Zadravec Zaletel L, Bratanič N, Jereb B

Izhodišča. Preživetje bolnikov, zdravljenih v otroštvu zaradi Hodgkinove bolezni (HB), je visoko. Pričakovana življenjska doba mladih bolnikov je dolga, zato so raziskave poznih posledic zdravljenja raka v otroštvu, vključno okvar žlez z notranjim izločanjem, v ospredju zanimanja.

Preiskovanci in metode. Delovanje spolnih žlez smo ocenili pri 64 mladostnikih (24 ženskah in 40 moških), ki so se zdravili zaradi HB v otroštvu v Sloveniji med leti 1972 in 1994. Ob postavitvi diagnoze so bili stari 3-16 let, spolne žleze smo ocenili 4-27 let kasneje v starosti 13-34 let. 54 (84%) preiskovancev je prejemalo kemoterapijo (KT), 49 v kombinaciji z obsevanjem (RT), 10 mladostnikov je imelo le RT. Delovanje spolnih žlez smo ocenili s kliničnim pregledom in merjenjem serumske koncentracije estradiola in testosterona ter serumske koncentracije LH in FSH v bazalnem stanju in po stimulaciji.

Rezultati. Primarni hipogonadizem smo ugotovili pri 30 (47%) preiskovancih. 24 od 40 (60%) moških je imelo okvaro kličnega epitelija testisa, pri štirih od teh smo ugotovili tudi okvaro Leydigovih celic, pri desetih pa njihovo disfunkcijo. Primarni hipogonadizem smo ugotovili pri 6 od 24 (25%) žensk.

Zaključki. Po zdravljenju HB v otroštvu se je primarni hipogonadizem pogosteje pojavil pri moških kot pri ženskah. Okvare Leydigovih celic ni povzročila le RT, temveč tudi alkilirajoči agensi in prokarbazin. V naši raziskavi starost bolnikov v času zdravljenja ni bil pomemben dejavnik tveganja za okvaro spolnih žlez. RT medenice v kombinaciji s KT je bil najpomembnejši dejavnik tveganja za razvoj primarnega hipogonadizma tako pri moških kot pri ženskih.

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doi:10.2478/v10019-010-0013-0

Radioterapija z modulirano intenziteto žatkovnega snopa (IMRT) pri obojestranskem retinoblastomu

Atalar B, Ozyar E, Gunduz K, Gungor G

Izhodišča. Teleradioterapijo uporabljamo tudi za zdravljenje retinoblastomov. S konvencionalnimi tehnikami obsevanja se težko izognemo obsevanju zdravih okolnih tkiv.

Prikaz primera. Pri 20 mesečni deklici, ki je imela obojestranski retinoblastom skupine D, smo uporabili radioterapijo z modulirano intenziteto žatkovnega snopa (IMRT). Za obsevanje obeh očes smo se odločili ob ponovitvi bolezni. Deklica je bila že zdravljena s kemoterapijo pa tudi s krioterapijo in transpupilarno termoterapijo. Z izračuni smo primerjali, kakšno sevalno dozo na okolana zdrava tkiva je deklica prejela z IMRT tehniko obsevanja in kakšno bi prejela, če bi se odločili za 3-dimenzionalno konformalno radioteraijo. Po letu dni nismo opazili nobenih izrazitejših sevalnih zapletov.

Zaključki. Slikovno vodena IMRT tehnika obsevanja retinoblastoma omogoča boljšo razporeditev doze kot 3-dimenzionalna konformalna radioteraija. Pri obsevanju tumorja poškodujemo okolna zdrava tkiva v najmanjši možni meri.

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doi: 10.2478/v10019-010-0037-5

Merjenja dinamičnih klinov na linearnem pospeševalniku energije 15 MV z uporabo linearnega niza detektorjev in z napravo za elektronsko portalno slikanje ter primerjava z izračunom načrtovalnega sistema za obsevanje

Petrovic B, Grzadziel A, Rutonjski L, Slosarek K

Izhodišča. Znano je, da dinamični klini (EDW) znatno izboljšajo učinkovitost zdravljenja z obsevanjem. Namen te raziskave je primerjati meritve EDW, opravljene z linearnim nizom detektorjev, z meritvami, opravljenimi z napravo za elektronsko portalno slikanje (EPID) ter primerjava obeh z izračunom načrtovalnega sistema za obsevanje (TPS). Vse meritve EDW in izračuni so narejeni za žarkovni snop z energijo 15 MV.

Materiali in metode. Z linearnim nizom ionizacijskih celic smo v fantomu *»Blue water«* izmerili žarkovne snope različnih velikosti in z različnimi klinastimi filtri. Z načrtovalnim sistemom za obsevanje XIO CMS v.4.2.0 smo omogočili pogoje pri meritvah in s konvolucijsko metodo izračunali dozo žarkovnih snopov.

Rezultati. Izmerili smo krivulje globinskih doz (PDD) ter dozne profile žarkovnih snopov. Meritve žarkovnih snopov z EDW so se od izračunov s XIO CMS TPS razlikovale za približno 0,5%. Profili v smeri, ki je bila pravokotna na smer klina, se skorajda niso razlikovali od profilov odprtega polja. Krivulje PDD za vse meritve EDW se niso razlikovale za več kot 0,2%, PDD odprtega polja pa je bila skoraj enaka krivuljam PDD polj z EDW. Preverili smo tudi faktorje prepustnosti klina za 60° dinamični klin in odkrili razlike do 4%. EPID meritve se od meritev z linearnim nizom razlikovale do 5%.

Zaključki. Implementacija EDW v radioterapiji zagotovi učinkovito orodje za načrtovanje konformne radioterapije. S pravilnim modelom EDW lahko dobimo zelo dobro ujemanje med meritvami in izračuni. EPID pa ni primeren za referenčne meritve.

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.

Thoracic oncology

October 7 – 9, 2010
The 2nd International Thoracic Congress Dresden will be held in Dresden, Germany.
E-mail profmanegold@t-online.de

Oncology

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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

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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

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E-mail hjk3425@skku.edu

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E-mail ostorosgyula@freemail.hu

Thoracic oncology

December 9 – 11, 2010
The ASCO/ASTRO/IASLC/University of Chicago Multidisciplinary Symposium in Thoracic Oncology will be held in Chicago, IL, USA.
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Clinical oncology

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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

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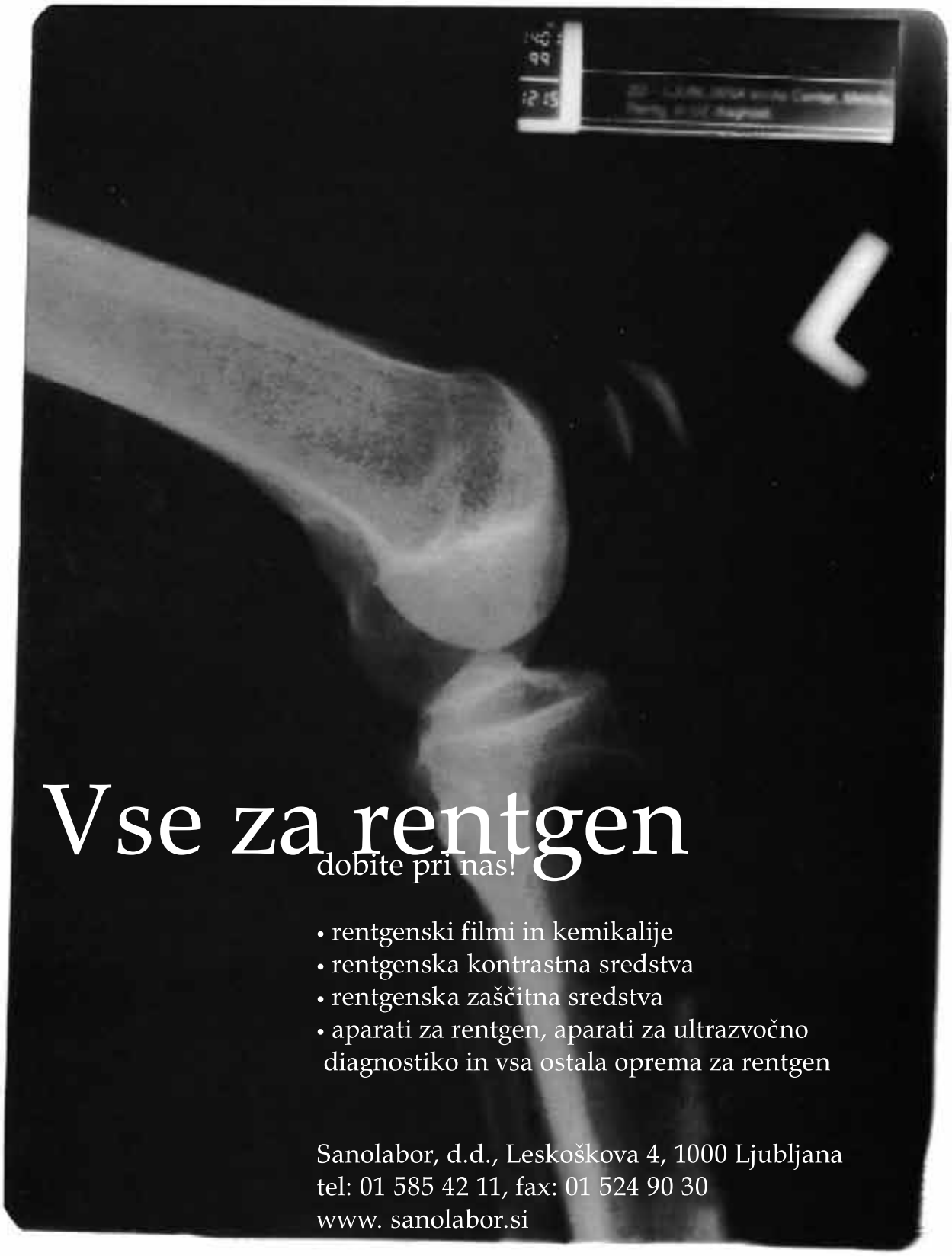

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1. Povzetek glavih značilnosti zdravila Iressa (gefitinib). Junij 2009.

Sestava: Filmsko obložene tablete vsebujejo 250 mg gefitiniba. **Indikacije:** zdravljenje odraslih bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim rakom z aktivacijskimi mutacijami EGFR-TK **Odmerjanje in način uporabe:** Zdravljenje z gefitinibom mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil proti raku. Priporočeno odmerjanje zdravila IRESSA je ena 250-mg tableta enkrat na dan. Tableto je mogoče vzeti s hrano ali brez nje, vsak dan ob približno istem času. **Kontraindikacije:** preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov, dojenje **Opozorila in previdnostni ukrepi:** Pri 1,3 % bolnikov, ki so dobivali gefitinib, so opažali intersticijsko bolezen pljuč (IBP). Ta se lahko pojavi akutno in je bila v nekaterih primerih smrtna. Če se bolniku poslabšajo dihalni simptomi, npr. dispneja, kašelj in zvišana telesna temperatura, morate zdravljenje z zdravilom IRESSA prekiniti in bolnika takoj preiskati. če je potrjena IBP, morate terapijo z zdravilom IRESSA končati in bolnika ustrezno zdraviti. čeprav so bile nepravilnosti testov jetrnih funkcij pogoste, so jih redko zabeležili kot hepatitis. Zato so priporočljive redne kontrole delovanja jeter. V primeru blagih do zmernih sprememb v delovanju jeter je treba zdravilo IRESSA uporabljati previdno. Če so spremembe hude, pride v poštev prekinitev zdravljenja. Zdravilo IRESSA vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze2galaktoze ne smejo jemati tega zdravila. Bolnikom naročite, da morajo takoj poiskati zdravniško pomoč, če se jim pojavijo kakršnikoli očesni simptomi, huda ali dolgotrajna driska, navzea, bruhanje ali anoreksija, ker lahko vse te posredno povzročijo dehidracijo. **Medsebojno delovanje zdravile:** Induktorji CYP3A4 lahko povečajo presnovo gefitiniba in zmanjšajo njegovo koncentracijo v plazmi. Zato lahko sočasna uporaba induktorjev CYP3A4 (npr. fenitoina, karbamazepina, rifampicina, barbituratov ali zeliščnih pripravkov, ki vsebujejo šentjanževko/Hypericum perforatum) zmanjša učinkovitost zdravljenja in se ji je treba izogniti. Pri posameznih bolnikih, ki imajo genotip slabih metabolizatorjev s CYP2D6, lahko zdravljenje z močnim zaviralcem CYP3A4 poveča koncentracijo gefitiniba v plazmi. Na začetku zdravljenja z zaviralcem CYP3A4 je treba bolnike natančno kontrolirati glede neželenih učinkov gefitiniba. Pri nekaterih bolnikih, ki so jemali varfarin skupaj z gefitinibom, so se pojavili zvišanje internacionalnega normaliziranega razmerja (INR) in/ali krvavitve. Bolnike, ki sočasno jemljejo varfarin in gefitinib, morate redno kontrolirati glede sprememb protrombinskega časa (PC) ali INR. Zdravila, ki občutno in dolgotrajno zvišajo pH v želodcu npr. zaviralci protonske črpalke in antagonisti H2, lahko zmanjšajo biološko uporabnost gefitiniba in njegovo koncentracijo v plazmi in tako zmanjšajo učinkovitost. Redno jemanje antacidov, uporabljenih blizu časa jemanja zdravila IRESSA, ima lahko podoben učinek. **Neželeni učinki:** V kumulativnem naboru podatkov kliničnih preskušanj III. faze so bili najpogosteje opisani neželeni učinki, ki so se pojavili pri več kot 20 % bolnikov, driska in kožne reakcije (vključno z izpuščajem, aknami, suho kožo in srbenjem). Neželeni učinki se ponavadi pojavijo prvi mesec zdravljenja in so praviloma reverzibilni. Ostali pogostejši neželeni učinki so: anoreksija, konjunktivitis, blefaritis in suho oko, krvavitev, npr. epistaksa in hematurija, intersticijska bolezen pljuč (1,3 %), navzea, bruhanje, stomatitis, dehidracija, suha usta, nepravilnosti testov jetrnih funkcij, bolezni nohtov, alopecija, asimptomatično laboratorijsko zvišanje kreatinina v krvi, proteinurija, astenija, pireksija. **Vrsta in vsebina ovojnine:** škatla s 30 tabletami po 250 mg gefitiniba **Način izdajanja zdravila:** samo na recept **Datum priprave besedila:** junij 2009 **Imetnik dovoljenja za promet:** AstraZeneca AB, S-151 85, Sodertalje, Švedska Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila. **Dodatne informacije so na voljo pri:** AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, 1000 Ljubljana, telefon: 01/51 35 600.

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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 indicirano za zdravljenje bolnikov z rakom skvamoznih celic glave in vratu; v kombinaciji z radioterapijo za lokalno napredovalo bolezen in v kombinaciji s kemoterapijo na osnovi platine za ponavljajočo se in/ali metastatsko bolezen. **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

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MERCK SERONO

PM-ONC-02/09/10.04.2009

Povzetek glavnih značilnosti zdravila

Ime zdravila: Temodal 20 mg, 100 mg, 140mg, 180 mg, 250 mg, Temodal 2,5 mg/ml prašek za raztopino za infundiranje **Kakovostna in količinska sestava:** Vsaka kapsula zdravila Temodal vsebuje 20 mg, 100 mg, 140 mg, 180 mg ali 250 mg temozolomida. Ena viala vsebuje 100 mg temozolomida Po rekonstituciji 1 ml raztopine za infundiranje vsebuje 2,5 mg temozolomida. Pomožna snov: Ena viala vsebuje 2,4 mmol natrija. **Terapevtske indikacije:** Zdravilo Temodal 2,5 mg/ml je indicirano za zdravljenje: odraslih bolnikov z novo diagnosticiranim multiformnim glioblastomom, sočasno z radioterapijo (RT) in pozneje kot monoterapija in otrok, starih 3 leta in več, mladostnikov in odraslih bolnikov z malignimi gliomi, npr. multiformnimi glioblastomi ali anaplastičnimi astrocitomi, ki se po standardnem zdravljenju ponovijo ali napredujejo. **Odmerjanje in način uporabe:** Zdravilo Temodal 2,5 mg/ml smejo predpisati le zdravniki, ki imajo izkušnje z zdravljenjem možganskih tumorjev. **Odrasli bolniki z novo diagnosticiranim multiformnim glioblastomom** Zdravilo Temodal 2,5 mg/ml se uporablja v kombinaciji z žariščno radioterapijo (faza sočasne terapije), temu pa sledi do 6 ciklov monoterapije (monoterapijska faza) z temozolomidom (TMZ). **Faza sočasne terapije** TMZ naj bolnik jemlje v odmerku 75 mg/m2 na dan 42 dni, sočasno z žariščno radioterapijo (60 Gy, danih v 30 delnih odmerkih). Zmanjševanje odmerka ni priporočeno, vendar se boste vsak teden odločili o morebitni odložitvi jemanja TMZ ali njegovi ukinitvi na podlagi kriterijev hematološke in nehematološke toksičnosti. TMZ lahko bolnik jemlje ves čas 42-dnevnega obdobja sočasne terapije (do 49 dni), če so izpolnjeni vsi od naslednjih pogojev:

- absolutno število nevtrofilcev (ANC – Absolute Neutrophil Count) ≥ 1,5 x 109/l;
- število trombocitov ≥ 100 x 109/l;
- skupna merila toksičnosti (SMT) za nehematološko toksičnost ≤ 1. stopnje (z izjemo alopecije, navzee in bruhanja).

Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko.

Faza monoterapije Štiri tedne po zaključku faze sočasnega zdravljenja s TMZ in RT naj bolnik jemlje TMZ do 6 ciklov monoterapije. V 1. ciklu (monoterapije) je odmerek zdravila 150 mg/m2 enkrat na dan 5 dni, temu pa naj sledi 23 dni brez terapije. Na začetku 2. cikla odmerek povečajte na 200 mg/m2, če je SMT za nehematološko toksičnost za 1. cikel stopnje ≤ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (ANC) ≥ 1,5 x 109/l in število trombocitov ≥ 100 x 109/l. Če odmerka niste povečali v 2. ciklu, ga v naslednjih ciklih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m2 na dan v prvih 5 dneh vsakega naslednjega cikla, razen če nastopi toksičnost. Zmanjšanje odmerka in ukinitev zdravila med fazo monoterapije opravite, kot je opisano v preglednicah 2 in 3. Med zdravljenjem morate 22. dan pregledati celotno krvno sliko (21 dni po prvem odmerku TMZ). **Odrasli in pediatrični bolniki, stari 3 leta ali več, s ponavljajočim se ali napredujočim malignim gliomom:**Posamezen cikel zdravljenja traja 28 dni. Bolniki, ki še niso bili zdravljeni s kemoterapijo, naj jemljejo TMZ v odmerku 200 mg/m2 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/m2 enkrat na dan, v drugem ciklu pa se poveča na 200 mg/m2 enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Preobčutljivost za dakarbazin (DTIC). **Posebna opozorila in previdnostni ukrepi: Pljučnica, ki jo povzroča Pneumocystis carinii** Pilotno preskušanje podaljšane 42-dnevne sheme zdravljenja je pokazalo, da pri bolnikih, ki so sočasno prejemali TMZ in RT, obstaja še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s Pneumocystis carinii (PCP). **Malignosti** Zelo redko so poročali tudi o primerih mielodisplastičnega sindroma in sekundarnih malignostih, vključno z mieloidno levkemijo. Antiemetično zdravljenje Navzea in bruhanje sta pogosto povezana z zdravljenjem s TMZ. **Antiemetično zdravljenje** se lahko da pred uporabo TMZ ali po njej. **Odrasli bolniki z novo diagnosticiranim multiformnim glioblastomom** Antiemetična profilaksa je priporočljiva pred začetnim odmerkom sočasne faze in je močno priporočljiva med fazo monoterapije. **Ponavljajoči se ali napredujoči maligni gliom** Pri bolnikih, ki so močno bruhali (stopnja 3 ali 4) v prejšnjih ciklih zdravljenja, je potrebno antiemetično zdravljenje. **Laboratorijske vrednosti** Pred jemanjem zdravila morata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC ≥ 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 > 1,5 x 109/l in število trombocitov > 100 x 109/l. Če med katerimkoli ciklom ANC pade na < 1,0 x 109/l ali število trombocitov na < 50 x 109/l, morate odmerek zdravila v naslednjem ciklu zmanjšati za eno stopnjo (glejte poglavje 4.2). Stopnje odmerka so 100 mg/m2, 150 mg/m2 in 200 mg/m2. Najmanjši priporočeni odmerek je 100 mg/m2. **Pediatrična uporaba** Kliničnih izkušenj z uporabo TMZ pri otrocih, mlajših od 3 let, ni. Izkušnje z uporabo tega zdravila pri starejših otrocih in mladostnikih so zelo omejene. **Starejši bolniki (stari > 70 let)** Videti je, da je pri starejših bolnikih tveganje za nevtropenijo ali trombocitopenijo večje, kot pri mlajših. Zato je pri uporabi zdravila TMZ pri starejših bolnikih potrebna posebna previdnost. **Moški bolniki** Moškim, ki se zdravijo s TMZ je treba svetovati, naj ne zaplodijo otroka še šest mesecev po prejetem zadnjem odmerku in naj se pred zdravljenjem posvetujejo o možnostih za shranitev zmrznjene sperme. **Natrij** To zdravilo vsebuje 2,4 mmol natrija na vialo. To je treba upoštevati pri bolnikih na nadzorovani dieti z malo natrija. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študije medsebojnega delovanja so izvedli le pri odraslih. V ločeni študiji 1. faze, sočasna uporaba TMZ in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali izpostavljenosti njegovem aktivnem presnovku monometiltriazenoimidazol karboksamidu (MTIK). Analiza populacijske farmakokinetike v preskušanjih 2. faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka TMZ. Sočasno jemanje z valprojsko kislino je bilo povezano z majhnim, a statistično pomembnim zmanjšanjem očistka TMZ. Študij za določitev učinka TMZ na presnovo ali izločanje drugih zdravil niso izvedli. Ker pa se TMZ ne presnavlja v jetrih in se na beljakovine veže le v majhni meri, je malo verjetno, da bi vplival na farmakokinetiko drugih zdravil. Uporaba TMZ v kombinaciji z drugimi mielosupresivnimi učinkovinami lahko poveča verjetnost mielosupresije. **Neželeni učinki:** Pri bolnikih, ki se zdravijo s TMZ v kombinaciji z RT ali monoterapijo po RT zaradi novo diagnosticiranega multiformnega glioblastoma ali z monoterapijo pri bolnikih s ponavljajočim se ali napredujočim gliomom, so bili zelo pogosti neželeni učinki podobni; slabost, bruhanje, zaprtje, neješčnost, glavobol in utrujenost. Pri bolnikih z novo diagnosticiranim glioblastomom multiforme na monoterapiji so zelo pogosto poročali o konvulzijah, medtem ko je bil izpuščaj opisan zelo pogosto pri bolnikih z novo diagnosticiranim multiformnim glioblastomom, ki so prejemali TMZ sočasno z RT, ter pri tistih, ki so zdravilo prejemali v obliki monoterapije, pogosto pa pri tistih s ponavljajočim se gliomom. Pri obeh indikacijah so o večini hematoloških neželenih reakcij poročali pogosto ali zelo pogosto. **Imetnik dovoljenja za promet:** Schering-Plough Europe, Rue de Stalle 73, Bruselj Belgija **Način in režim izdaje zdravila: Zdravilo Temodal 20 mg, 100 mg, 140mg, 180 mg, 250 mg** se izdaja na recept (Rp/Spec), Temodal 2,5 mg/ml prašek za raztopino za infundiranje pa je namenjeno uporabi samo v bolnišnicah (H). **Datum priprave informacije:** februar 2010

Literatura: 1 Povzetek temeljnih značilnosti zdravila Temodal 2 Stupp R, et. al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised III study: 5-year analysis of the EORTC-NCIC trial

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Samo za strokovno javnost.

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 samostojno vzdrževalno zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč s stabilno boleznijo po 4 ciklih standardne kemoterapije na osnovi platine v prvi liniji zdravljenja. Zdravilo Tarceva je indicirano tudi 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 je treba zmanjševati 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: 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 treba zdravljenje z zdravilom Tarceva prekiniti, dokler ni znana diagnoza. Bolnike, ki se sočasno zdravijo z erlotinibom in gemcitabinom, je treba skrbno spremljati zaradi možnosti pojava toksičnosti, podobni intersticijski bolezni pljuč. Če je ugotovljena intersticijska bolezen pljuč, zdravilo Tarceva ukinemo in uvedemo ustrezno zdravljenje. Pri približno polovici bolnikov, ki so se zdravili z zdravilom Tarceva, se je pojavila driska (vključno z zelo redkimi primeri, ki so se končali s smrtnim izidom). 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 treba zdravljenje z zdravilom Tarceva 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. Bolniki, ki prejemajo zdravilo Tarceva, imajo večje tveganje za razvoj perforacij v prebavilih, ki so jih opazili občasno (vključno z nekaterimi primeri, ki so se končali s smrtnim izidom). Pri bolnikih, ki sočasno prejemajo zdravila, ki zavirajo angiogenezo, kortikosteroide, nesteroidna protivnetna zdravila (NSAID) in/ali kemoterapijo na osnovi taksanov, ali so v preteklosti imeli peptični ulkus ali divertikularno bolezen, je tveganje večje. Če pride do tega, je treba zdravljenje z zdravilom Tarceva dokončno ukiniti. Poročali so o primerih kožnih bolezni z mehurji in luščenjem kože, vključno z zelo redkimi primeri, ki so nakazovali na Stevens-Johnsonov sindrom/toksično epidermalno nekrolizo in so bili v nekaterih primerih smrtni. Zdravljenje z zdravilom Tarceva je treba prekiniti ali ukiniti, če se pri bolniku pojavijo hude oblike mehurjev ali luščenja kože. Zelo redko so poročali o primerih perforacije ali ulceracije roženice; opazili so tudi druge očesne bolezni. Zdravljenje z zdravilom Tarceva je treba prekiniti ali ukiniti, če se pri bolnikih pojavijo akutne očesne bolezni, kot je bolečina v očeh, ali se le-te poslabšajo. 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 učinkov, 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 *kumarinske antikoagulante*, je treba redno kontrolirati protrombinski čas ali INR. Sočasno zdravljenje z zdravilom Tarceva in *statinom* lahko poveča tveganje za miopatijo, povzročeno s statini, vključno z rabdomiolizo; to so opazili redko. 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, navzea, bruhanje, stomatitis, bolečina v trebuhu, pruritus, suha koža, suhi keratokonjunktivitis, konjunktivitis, zmanjšanje telesne mase, depresija, glavobol, nevropatija, dispepsija, flatulenca, alopecija, okorelost, pireksija, nenormalnosti testov jetrne funkcije. *Pogosti neželeni učinki* so krvavitve v prebavilih, epistaksa, keratitis, paronihija, fisure na koži. *Občasno* so poročali o perforacijah v prebavilih, hirzutizmu, spremembah obrvi, krhkih nohtih, odstopanju nohtov od kože, blagih reakcijah na koži (npr. hiperpigmentacija), spremembah trepalnic, hudi intersticijski bolezni pljuč (vključno s smrtnimi primeri). *Redko* pa so poročali o jetrni odpovedi. *Zelo redko* so poročali o Stevens-Johnsonovem sindromu/toksični epidermalni nekrolizi ter o ulceracijah in perforacijah roženice.
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:** 2.0/10. **Informacija pripravljena:** avgust 2010.

053-10-TAR

DODATNE INFORMACIJE SO NA VOLJO PRI:
Roche farmacevtska družba d.o.o.
Vodovodna cesta 109, 1000 Ljubljana.
Povzetek glavnih značilnosti zdravila
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ČAS ZA ŽIVLJENJE.

DOKAZANO PODALJŠA PREŽIVETJE PRI BOLNIKIH:

- z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč[1]
- z metastatskim rakom trebušne slinavke[1]

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

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Zamenjava opioidnega zdravljenja: pri zamenjavi peroralnih ali parenteralnih opioidov s fentanilom je treba začetni odmerek izračunati na osnovi količine analgetika, ki je bila potrebna v zadnjih 24 urah, jo pretvoriti v odgovarjajoči odmerek morfina s pomočjo razpredelnice in nato preračunati ustrezen odmerek fentanila, spet s pomočjo razpredelnice (glejte SmPC). Prvih 12 ur po prehodu na transdermalni obliž Epufen bolnik še vedno dobiva predhodni analgetik v enakem odmerku kot prej; v naslednjih 12 urah se ta analgetik daje po potrebi. Titracija odmerka in vzdrževalno zdravljenje: obliž je treba zamenjati vsakih 72 ur. Odmerek je treba titrirati individualno, dokler ni dosežen analgetični učinek. Odmerek 12,5 mikrogramov/uro je primeren za titriranje odmerka v manjšem odmernem območju. Če analgezija na koncu začetnega obdobja nošenja obliža ni zadostna, se lahko odmerek po 3 dneh zveča. Možno je, da bodo bolniki potrebovali občasne dodatne odmerke kratko delujočih analgetikov (npr. morfina) za prekinitev bolečine. Sprememba ali prekinitev zdravljenja: vsaka zamenjava z drugim opioidom mora potekati postopoma, z majhnim začetnim odmerkom in počasnim zvečevanjem. Splošno veljavno pravilo je postopna ustavitev opioidne analgezije, da bi preprečili odtegnitvene simptome, kot so navzeja, bruhanje, diareja, anksioznost in mišični tremor. Uporaba pri starejših bolnikih: starejše in oslabljene bolnike je treba skrbno opazovati zaradi simptomov prevelikega odmerjanja ter odmerek po potrebi zmanjšati. Uporaba pri otrocih: transdermalni obliži Epufen se lahko uporabljajo le pri pediatričnih bolnikih (starih od 2 do 16 let), ki tolerirajo opioide in peroralno že dobivajo opioide v odmerku, enakovrednemu najmanj 30 mg morfina na dan. Bolnik mora prvih 12 ur po prehodu na Epufen še vedno dobivati predhodni analgetik v enakem odmerku kot prej. V naslednjih 12 urah je treba ta analgetik dajati odvisno od kliničnih potreb. Titracija odmerka in vzdrževalno zdravljenje: če je analgetični učinek Epufena prešibak, je treba bolniku dodati morfin ali drugi opioid s kratkim delovanjem. Odvisno od dodatnih potreb po analgeziji in jakosti bolečine pri otroku se lahko uporabi več obližev. Odmerek je treba prilagajati korakoma, po 12,5 mikrogramov/uro. Uporaba pri bolnikih z jetrno ali ledvično okvaro: Zaradi možnosti pojava simptomov prevelikega odmerjanja je treba te bolnike skrbno spremljati in odmerek ustrezno zmanjšati. Uporaba pri bolnikih s povečano telesno temperaturo: Pri teh bolnikih bo morda treba prilagoditi odmerek. **Način uporabe:** transdermalni obliž Epufen je treba takoj po odprtju vrečke nalepiti na nerazdraženo, neobsevano kožo, na ravno površino prsnega koša, zgornjega dela hrbta ali nadlakti. Po odstranitvi zaščitne plasti je treba obliž trdno pritrditi na izbrano mesto in z dlanjo pritiskati približno 30 sekund, da se obliž popolnoma nalepi, še zlasti na robovih. Uporaba pri otrocih: pri mlajših otrocih je obliž priporočljivo nalepiti na zgornji del hrbta, ker je manjša verjetnost, da bi otrok odstranil obliž. Transdermalnega obliža se ne sme deliti, ker podatkov o tem ni na voljo. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilno učinkovino, hidrogenirano kolofonijo, sojo, arašide ali katerokoli pomožno snov. Akutna ali pooperativna bolečina, ko v kratkem časovnem obdobju ni možno titriranje odmerka in obstaja verjetnost za življenjsko ogrožajočo respiratorno depresijo. Huda okvara osrednjega živčnega sistema. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Zaradi razpolovne dobe fentanila je treba bolnika v primeru pojava neželenega učinka opazovati še 24 ur po odstranitvi obliža. Pri nekaterih bolnikih, ki uporabljajo transdermalni obliž Epufen, se lahko pojavi respiratorna depresija. Epufen je treba previdno dajati: bolnikom s kronično pljučno boleznijo, zvišanim intrakranialnim tlakom, možganskim tumorjem, boleznimi srca, jeter in ledvic, tistim z zvišano telesno temperaturo, pri starejših bolnikih in otrocih, bolnikih z miastenijo gravis. Odvisnost od zdravila: kot posledica ponavljajoče se uporabe se lahko razvijeta toleranca na učinkovino ter psihična in/ali fizična odvisnost od nje. Ostali: lahko se pojavijo neepileptične (mio)klonične reakcije. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Derivati barbiturne kisline, opioidi, anksiolitiki in pomirjevala, hipnotiki, splošni anestetiki, fenotiazini, mišični relaksanti, sedativni antihistaminiki in alkoholne pijače, zaviralci MAO, itrakonazol, ritonavir, ketokonazol, nekateri makrolidni antibiotiki, pentazocin, buprenorfin. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Zdravilo ima močan vpliv na sposobnost vožnje in upravljanja s stroji. **NEŽELENI UČINKI:** Najbolj resen neželen učinek fentanila je respiratorna depresija. Zelo pogosti (≥ 1/10): dremavost, glavobol, navzeja, bruhanje, zaprtje, znojenje, srbenje, somnolenca. Pogosti (≥ 1/100 do < 1/10): kserostomija, dispepsija, reakcije na koži na mestu aplikacije, sedacija, zmedenost, depresija, tesnoba, živčna napetost, halucinacije, zmanjšan apetit. Občasni (≥ 1/1000 do < 1/100): tahikardija, bradikardija, tremor, parestezija, motnje govora, dispneja, hipoventilacija, diareja, zastajanje urina, izpuščaj, rdečina, hipertenzija, hipotenzija, evforija, amnezija, nespečnost, vznemirljivost. Nekateri od naštetih neželenih učinkov so lahko posledica osnovne bolezni ali drugih zdravljenj. Drugi neželeni učinki: odpornost, fizična in psihična odvisnost se lahko razvijejo med dolgotrajno uporabo fentanila. Pri nekaterih bolnikih se lahko pojavijo odtegnitveni simptomi, ko zamenjajo prejšnje opiodne analgetike s transdermalnim obližem s fentanilom ali po nenadni prekinitvi zdravljenja. **NAČIN IZDAJE:** Samo na zdravniški recept. **OPREMA:** Škatle s 5 transdermalnimi obliži. **IMETNIK DOVOLJENJA ZA PROMET:** Lek farmacevtska družba, d.d., Verovškova 57, Ljubljana, Slovenija **INFORMACIJA PRIPRAVLJENA:** avgust 2009

Lek farmacevtska družba d.d., Verovškova 57, 1526 Ljubljana, Slovenija, www.lek.si

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- izboljša splošno počutje bolnikov [3,4]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA: MEGACE 40 mg/ml peroralna suspenzija

Sestava: 1 ml peroralne suspenzije vsebuje 40 mg megestrolacetata. **TERAPEVTSKE INDIKACIJE:** Zdravljenje anoreksije-kaheksije ali nepojasnjene, pomembne izgube telesne mase pri bolnikih z AIDS-om. Zdravljenje anorektično-kahektičnega sindroma pri napredovalem raku. **ODMERJANJE IN NAČIN UPORABE:** Pri aidsu je priporočeni začetni odmerek Megace za odrasle 800 mg (20 ml peroralne suspenzije) enkrat na dan eno uro pred jedjo ali dve uri po jedi in se lahko med zdravljenjem prilagodi glede na bolnikov odziv. V raziskavah bolnikov z aidsom so bili klinično učinkoviti dnevni odmerki od 400 do 800 mg/dan (10 do 20 ml), uporabljani štiri mesece. Pri anorektično-kahektičnem sindromu zaradi napredovalega raka je priporočljiv začetni odmerek 200 mg (5 ml) na dan; glede na bolnikov odziv ga je mogoče povečati do 800 mg na dan (20 ml). Običajni odmerek je med 400 in 800 mg na dan (10–20 ml). V raziskavah bolnikov z napredovalim rakom so bili klinično učinkoviti dnevni odmerki od 200 do 800 mg/dan (5 do 20 ml), uporabljani najmanj osem tednov. Pred uporabo je potrebno plastenko s suspenzijo dobro pretresti. Uporaba pri otrocih: Varnosti in učinkovitosti pri otrocih niso dokazali. Uporaba pri starostnikih: Zaradi pogostejših okvar jeter, ledvic in srčne funkcije, pogostejših sočasnih obolenj ali sočasnega zdravljenja z drugimi zdravili je odmerek za starejšega bolnika treba določiti previdno in običajno začeti z najnižjim odmerkom znotraj odmernega intervala. **KONTRAINDIKACIJE:** Preobčutljivost za megestrolacetat ali katerokoli pomožno snov. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Uporaba gestagenov med prvimi štirimi meseci nosečnosti ni priporočljiva. Pri bolnikih s tromboflebitisom v anamnezi je treba zdravilo Megace uporabljati previdno. Zdravljenje z zdravilom Megace se lahko začne šele, ko so bili vzroki hujšanja, ki jih je mogoče zdraviti, ugotovljeni in obravnavani. Megestrolacetat ni namenjen za profilaktično uporabo za preprečitev hujšanja. Učinki na razmnoževanje virusa HIV niso ugotovljeni. Med zdravljenjem z megestrolacetatom in po prekinitvi kroničnega zdravljenja je treba upoštevati možnost pojava zavore nadledvične žleze. Morda bo potrebno nadomestno zdravljenje s stresnimi odmerki glukokortikoidov. Megestrolacetat se v veliki meri izloči prek ledvic. Ker je verjetnost zmanjšanega delovanja ledvic pri starostnikih večja, je pri določitvi odmerka potrebna previdnost, prav tako je koristno spremljanje ledvične funkcije. Peroralna suspenzija vsebuje saharozo. Bolniki z redko dedno intoleranco za fruktozo, malabsorpcijo glukoze/galaktoze ali pomanjkanjem saharoza-izomaltaze ne smejo jemati tega zdravila. Peroralna suspenzija vsebuje tudi majhne količine etanola (alkohola), in sicer manj kot 100 mg na odmerek. **INTERAKCIJE:** Aminoglutetimid: poročali so o zmanjšanju koncentracije progestogena v plazmi z možno izgubo terapevtskega delovanja zaradi inducirane presnove. Sočasno jemanje megestrolacetata (v obliki peroralne suspenzije) in zidovudina ali rifabutina ne povzroča sprememb farmakokinetičnih parametrov. **NEŽELENI UČINKI:** Pogosti (≥ 1/100, < 1/10): navzea, bruhanje, driska, flatulenca, izpuščaj, metroragija, impotenca, astenija, bolečina, edem. Neznana pogostnost (pogostnosti ni mogoče oceniti iz razpoložljivih podatkov): poslabšanje osnovne bolezni (širjenje tumorja), adrenalna insuficienca, kušingoidni izgled, Cushingov sindrom, diabetes mellitus, motena toleranca za glukozo, hiperglikemija, spremembe razpoloženja, sindrom karpalnega kanala, letargija, srčno popuščanje, tromboflebitis, pljučna embolija (v nekaterih primerih usodna), hipertenzija, navali vročine, dispneja, zaprtje, alopecija, pogosto uriniranje. **Vrsta ovojnine in vsebina:** Plastenka z 240 ml suspenzije. **Režim izdaje:** Rp/Spec. **Imetnik dovoljenja za promet:** Bristol-Myers Squibb spol. s r.o., Olivova 4, Praga 1, Češka; **Odgovoren za trženje v Sloveniji:** PharmaSwiss d.o.o., Ljubljana, tel: 01 236 4 700, faks: 01 236 4 705; MGS-120609. **Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila!**

Reference: 1. Povzetek glavnih značilnosti zdravila Megace – 12. junij 2009; **2.** Register zdravil Republike Slovenije XI – leto 2008; **3.** Beller, E., 1997. Ann Oncol 8: 277-283; **4.** Čufer, T, 2002. Onkologija 9(2): 73-75; **5.** Yavuzsen, T., 2005. J Clin Oncol 23(33): 8500-8511; **6.** Bilten Recept 7(1), 22.5.2009

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Korekcijska faza: 50 i.e./kg 3 x tedensko. Odmerek prilagajamo postopno, z vsaj štiritedenskimi časovnimi presledki za 25 i.e./kg 3 x tedensko. Vzdrževalna faza: priporočen skupni tedenski odmerek je od 75 do 300 i.e./kg. ***Odrasli bolniki z zmanjšanim ledvičnim delovanjem, ki se še ne zdravijo z dializo:*** začetni odmerek je 50 i.e./kg s.c. 3 x tedensko. Odmerek prilagajamo postopno, z vsaj štiritedenskimi časovnimi presledki za 25 i.e./kg 3 x tedensko. Vzdrževalni odmerek je od 17 do 33 i.e./kg 3 x tedensko, največji tedenski odmerek ne sme presegati 200 i.e./kg 3 x tedensko. ***Odrasli bolniki na peritonealni dializi:*** Korekcijska faza: 50 i.e./kg s.c. 2 x tedensko.Vzdrževalni odmerek je od 25 do 50 i.e./kg 2 x tedensko. ***Odrasli bolniki z rakom s simptomatsko anemijo, ki se zdravijo s kemoterapijo:*** Bolnike z anemijo zdravimo do ciljne koncentracije Hb 100-120 g/l, Hb pa ne sme preseči 120 g/l. Začetni odmerek je 150 i.e./kg s.c. 3 x tedensko ali 450 i.e./kg s.c. 1 x tedensko. ***Odrasli kirurški bolniki, vključeni v program avtolognega zbiranja krvi za avtotransfuzijo:*** 600 i.e./kg i.v., 2-krat na teden v obdobju treh tednov pred kirurškim posegom. Odrasli kirurški bolniki, ki niso vključeni v program avtolognega zbiranja krvi za avtotransfuzijo: 600 i.e./kg, s.c., enkrat tedensko v obdobju treh tednov pred kirurškim posegom in na dan kirurškega posega. **Kontraindikacije:** čista aplazija rdečih krvnih celic (PRCA), nenadzorovana arterijska hipertenzija, kontraindikacije povezane s programom avtolognega zbiranja krvi, preobčutljivost za katerokoli sestavino zdravila, bolniki, pri katerih je predviden večji elektiven kirurški poseg in niso vključeni v program avtolognega zbiranja krvi s hudo koronarno, cerebrovaskularno, karotidno ali periferno arterijsko bolezen ali so nedavno preboleli miokardni infarkt ali cerebrovaskularni dogodek, bolniki, ki ne morejo prejemati ustrezne antitrombotične profilakse. **Posebna opozorila in previdnostni ukrepi:** Med zdravljenjem moramo spremljati in nadzorovati krvni tlak, če ga ne moremo urediti, moramo zdravljenje prekiniti. Potrebna je previdna uporaba zdravila pri bolnikih z epilepsijo in kronično boleznijo jeter. Prvih osem tednov zdravljenja priporočamo redno spremljanje števila trombocitov. Za optimalen odgovor na zdravljenje, je treba zagotoviti ustrezne zaloge železa. Po več mesecih ali letih zdravljenja s subkutano apliciranim zdravilom so redko poročali o PRCA, povzročeni s protitelesi. Če sumimo PRCA moramo zdravljenje takoj prekiniti. Zaradi verjetnosti navzkrižne reakcije s protitelesi, bolniku ne smemo dati drugega epoetina in mu moramo zagotoviti ustrezno zdravljenje. Pri ocenjevanju ustreznosti odmerka pri bolnikih z rakom, ki prejemajo kemoterapijo, moramo upoštevati, da minejo 2-3 tedni od začetka zdravljenja do pojava eritrocitov, nastalih pod njegovim vplivom v krvi. Kot pri vseh rastnih faktorjih obstaja verjetnost, da bi lahko spodbujali razvoj katere koli vrste rakave bolezni. Pri bolnikih, pri katerih je predviden večji elektivni ortopedski kirurški poseg, je treba ugotoviti vzrok za anemijo in ga odpraviti pred začetkom zdravljenja. Pri bolnikih s kroničnim ledvičnim odpovedovanjem je potrebna previdnost. **Interakcije:** Ni dokazov, da zdravljenje z epoetinom alfa vpliva na metabolizem drugih zdravil. Ker se ciklosporin veže na eritrocite, obstaja možnost interakcije med zdraviloma. **Neželeni učinki:** trombocitemija, PRCA, anafilaktična reakcija, hipersenzitivnost, krči, glavobol, cerebralna krvavitev, cerebrovaskularni dogodki, hipertenzivna encefalopatija, tranzitorna ishemična ataka, hipertenzija, tromboze, pljučna embolija, navzea, diareja, bruhanje, izpuščaj, angionevrotični edem, urtikarija, artralgija, mialgija, porfirija, pireksija, gripi podobni simptomi, neučinkovitost zdravila, periferni edem, reakcija na mestu injiciranja, tromboza žilnega pristopa. **Imetnik dovoljenja za promet:** Johnson & Johnson d.o.o. Šmartinska 53, 1000 Ljubljana **Režim izdajanja zdravila:** H/Rp. **Datum revizije:** 11. 12. 2009.

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POMEMBEN JE **VSAK** KORAK!

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SUTENT 12,5 mg, 25 mg, 37,5 mg, 50 mg trde kapsule
Sestava in oblika zdravila: Vsaka trda kapsula vsebuje 12,5 mg, 25 mg, 37,5 mg ali 50 mg sunitiniba v obliki sunitinibijevega malata. **Indikacije:** Zdravljenje neizrezljivega in/ali metastatskega malignega gastrointestinalnega stromalnega tumorja (GIST), če zdravljenje z imatinibijevim mesilatom zaradi odpornosti ali neprenašanja ni bilo uspešno. Zdravljenje napredovalega in/ali metastatskega karcinoma ledvičnih celic (MRCC). **Odmerjanje in način uporabe:** Terapijo mora uvesti zdravnik, ki ima izkušnje z zdravljenjem MRCC ali GIST. Priporočeni odmerek je 50 mg enkrat dnevno, peroralno vsak dan 4 tedne zapored; temu sledi 2-tedenski premor (Shema 4/2), tako da celotni ciklus traja 6 tednov. Odmerek je mogoče prilagajati v povečanjih po 12,5 mg, upoštevaje individualno varnost in prenašanje. Dnevni odmerek ne sme preseči 75 mg in ne sme biti manjši od 25 mg. Pri sočasni uporabi z močnimi zaviralci ali induktorji CYP3A4 je potrebno odmerek ustrezno prilagoditi. *Uporaba pri otrocih in mladostnikih (< 18 let):* Sutenta ne smemo uporabljati, dokler ne bo na voljo dodatnih podatkov. *Uporaba pri starejših bolnikih (≥ 65 let)*: med starejšimi in mlajšimi bolniki niso opazili pomembnih razlik v varnosti in učinkovitosti. *Insuficienca jeter*: pri bolnikih z jetrno okvaro razreda A in B po Child-Pughu prilagoditev odmerka ni potrebna; pri bolniki z okvaro razreda C Sutent ni bil preizkušen. *Insuficienca ledvic*: kliničnih študij niso izvedli. Sutent se uporablja peroralno, bolnik ga lahko vzame z ali brez hrane. Če pozabi vzeti odmerek, ne sme dobiti dodatnega, temveč naj vzame običajni predpisani odmerek naslednji dan. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Koža in tkiva. Krvavitve v prebavila, dihala, sečila, v možganih ter krvavitve tumorja. Učinki na prebavila: poleg navzee in driske tudi resni zapleti. Hipertenzija. Hematološke bolezni. Bolezni srca in ožilja: zmanjšanje LVEF in srčno popuščanje. Podaljšanje intervala QT. Venski trombembolični dogodki. Dogodki na dihalih: dispneja, plevralni izliv, pljučna embolija ali pljučni edem. Moteno delovanje ščitnice. Pankreatitis. Delovanje jeter. Delovanje ledvic. Fistula. Preobčutljivost/angioedem. Motnje okušanja. Konvulzije. Pri krvavitvah, učinkih na prebavila, hematoloških boleznih, dogodkih na dihalih, venskih trombemboličnih dogodkih, pankreatitisu in učinkih na jetra so opisani tudi smrtni izidi. **Medsebojno delovanje z drugimi zdravili:** Zdravila, ki lahko zvišajo koncentracijo sunitiniba v plazmi (ketokonazol, ritonavir, itrakonazol, eritromicin, klaritromicin ali sok grenivke). Zdravila, ki lahko znižajo koncentracijo sunitiniba v plazmi (deksametazon, fenitoin, karbamazepin, rifampin, fenobarbital, *Hypericum perforatum* oz. šentjanževka). Antikoagulanti. **Nosečnost in dojenje:** Sutenta se ne sme uporabljati med nosečnostjo in tudi ne pri ženskah, ki ne uporabljajo ustrezne kontracepcije, razen če možna korist odtehta možno tveganje za plod. Ženske v rodni dobi naj med zdravljenjem s Sutentom ne zanosijo. Ženske, ki jemljejo Sutent, ne smejo dojiti. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Sutent lahko povzroči omotico. **Neželeni učinki:** Najpogostejši neželeni učinki: pljučna embolija, trombocitopenija, krvavitev tumorja, febrilna nevtropenija, hipertenzija, utrujenost, diareja, navzea, stomatitis, dispepsija, bruhanje, obarvanje kože, disgevzija, anoreksija, zvišanje ravni lipaze. Zelo pogosti: anemija, nevtropenija, hipotiroidizem, zmanjšanje teka, motnje okušanja, glavobol, bolečina v trebuhu / napihnjenost, flatulenca, bolečine v ustih, sindrom palmarno plantarne eritrodizestezije, spremembe barve las, astenija, vnetje sluznice, edemi. **Način in režim izdajanja:** Izdaja zdravila je le na recept, uporablja pa se samo v bolnišnicah. Izjemoma se lahko uporablja pri nadaljevanju zdravljenja na domu ob odpustu iz bolnišnice in nadaljnjem zdravljenju. **Imetnik dovoljenja za promet:** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, Velika Britanija. **Datum zadnje revizije besedila:** 28.10.2009

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

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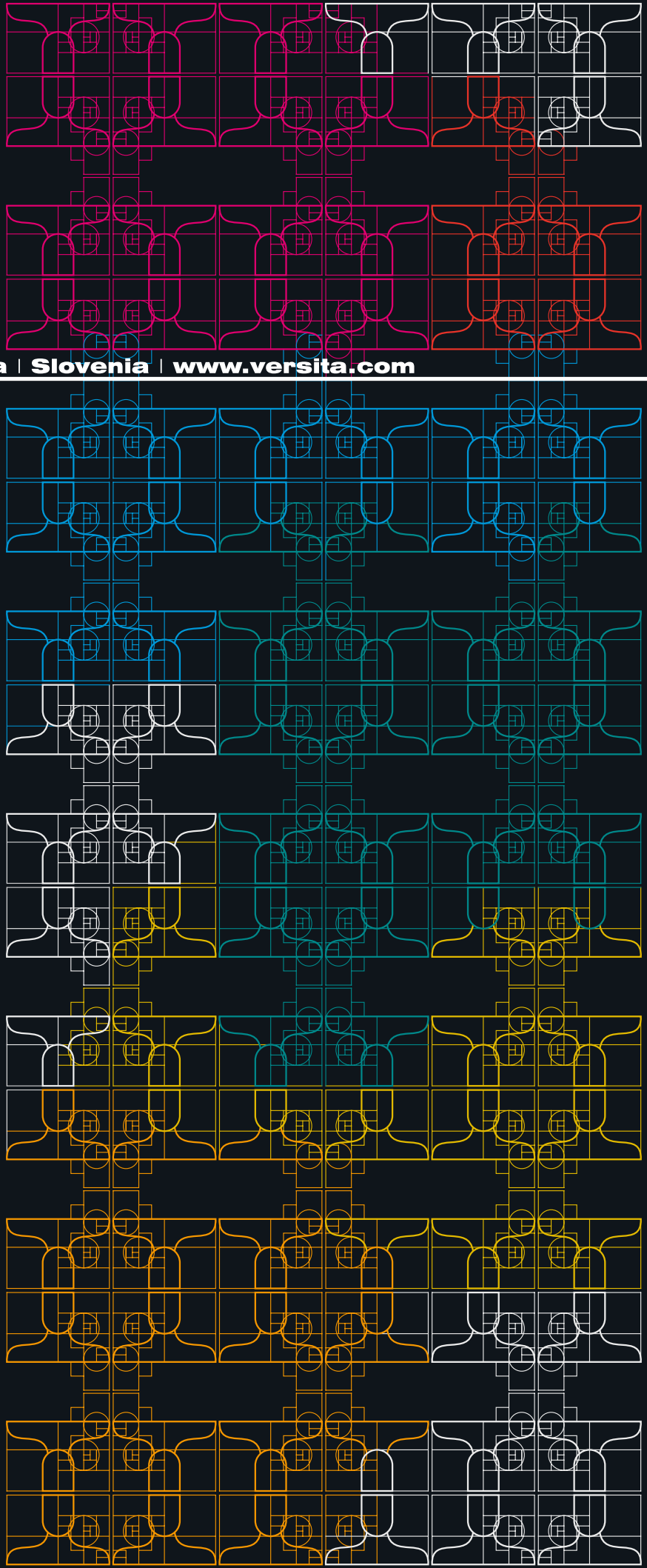

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