RADIOLOGY AND ONCOLOGY

September 2009
Vol. 43 No. 3
Ljubljana

ISSN 1318-2099

ALIMTA®
pemetreksed

Edina histološko usmerjena citostatična terapija

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

ALIMTA/Cisplatin:

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

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

*vs. Gemcitabin/Cisplatin

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

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

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

SI-AL-09-FEB-008

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September 2009
Vol. 43 No. 3
Pages 137-212
ISSN 1318-2099
UDC 616-006
CODEN: RONCEM

Aims and scope
Radiology and Oncology is a journal devoted to publication of original contributions in diagnostic and interventional radiology, computerized tomography, ultrasound, magnetic resonance, nuclear medicine, radiotherapy, clinical and experimental oncology, radiobiology, radiophysics and radiation protection.

Publisher
Association of Radiology and Oncology

Affiliated with
Slovenian Medical Association – Slovenian Association of Radiology, Nuclear Medicine Society,
Slovenian Society for Radiotherapy and Oncology, and Slovenian Cancer Society
Croatian Medical Association – Croatian Society of Radiology
Societas Radiologorum Hungarorum
Friuli-Venezia Giulia regional groups of S.I.R.M.
(Italian Society of Medical Radiology)

Reader for English
Vida Kološa

Key words
Eva Klemenčič

Secretary
Mira Klemenčič

Design
Monika Fink-Serša

Printed by
Imprint d.o.o., Ljubljana, Slovenia

Published quarterly in 600 copies

Beneficiary name: DRUŠTVO RADIOLOGIJE IN ONKOLOGIJE
Zaloška cesta 2,
1000 Ljubljana
Slovenia
Beneficiary bank account number: SI56 02010-0090006751
IBAN: SI56020100090006751
Our bank name: Nova Ljubljanska banka, d.d.,
Ljubljana, Trg republike 2,
1520 Ljubljana; Slovenia
SWIFT: LJBASI2X

Subscription fee for institutions EUR 100, individuals EUR 50

The publication of this journal is subsidized by the Slovenian Research Agency.

Indexed and abstracted by:
Science Citation Index Expanded (SciSearch®)
Journal Citation Reports/Science Edition
Scopus
EMBASE/Excerpta Medica
Open J-gate
Chemical Abstracts
Biomedicina Slovenica

This journal is printed on acid- free paper

Radiology and Oncology is available on the internet at: http://www.onko-i.si/radioloncol and http://www.versita.com

ISSN 1581-3207

RADIOLOGY AND ONCOLOGY

Ljubljana, Slovenia
September 2009
Vol. 43 No. 3

ISSN 1318-2099
UDC 616-006
CODEN: RONCEM

CONTENTS

Radiology and Oncology is covered in *Science Citation Index Expanded (SciSearch®), Journal Citation Reports/Science Edition, Scopus, EMBASE/Excerpta Medica, Open J-gate, Chemical Abstracts, Biomedicina Slovenica*

Radiol Oncol 2009; 43(3): 137-143. doi:10.2478/v10019-009-0031-y

special communication

60 years of the Slovenian Association of Radiology 1950-2010

Dušan Pavčnik

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The year 2010 is the 60th birthday as well as the diamond jubilee of the Slovenian Association of Radiology (SAR). Only a few SAR members remember the birth and early years of our association of radiology. My intention is to bring these days back. My memory is neither complete nor perfect, is also quite subjective, some time biased. To commemorate the history of SAR, we need to look at the developments of radiology before our association was created.

Radiology was born on November 8, 1895 when Wilhelm Conrad Röntgen made his significant contribution to medical science. On that day, he observed a different kind of ray was mixed with the cathode rays and was amazed to find that when he held materials between the cathode-ray tube and the fluorescent screen he could see a shadow of the bones and soft tissue in his hand on the barium platinocyanide screen. He temporarily termed the new rays as X rays.[1] Four years later, in the final year of the nineteen century, the first X-ray machine was purchased by primarius Dr. Edo Šlajmer for the general hospital in Ljubljana.[2] Drs. Alojzij Kunst, Josip Hebein, Mila Kovačeva, Ciril Cirman, Serafin Vakselj and Rudolf del Cott laid the basis for diagnostic radiology in Slovenia.[2] Primarius Dr. Alojzij Kunst, the first Slovenian radiologist, was driving force to make radiology popular among colleagues. In his lectures at the Slovenian Medical Association (Slovensko zdravniško društvo) meetings he emphasized the importance of delivering the exact diagnosis to clinicians, thereby allowing them to select proper treatment. He also served as president of the Slovenian Medical Association from 1938-1940. The first meeting of a new X-ray Society in old Yugoslavia was held in Split in 1930 and then the 1st congress of Yugoslavian radiologists took place in Belgrade in 1935.[2] Primarius Kunst, primarius del Cott and Prof. Hebein were active members of this society.

After ending the Medical Chamber of Slovenia in 1946, different professional sections of the Slovenian Medical Association became a forum for physicians to discuss professional issues and other day to day problems. The Slovenian Association of Radiology (SAR) was founded on August 8th in 1950, as Section of Radiology of the Slovenian Medical Association (Radiološka sekcija Slovenskega zdravniškega društva) on the initiative of the Slovenian Medical Association and professor Dr. Josip Hebain,

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Key words: radiology; interventional radiology; history; ultrasound; CT; MRI

Figure 1. Prof. Dr. Josip Hebain, 1950-1956.

SLOVENSKO ZDRAVNIŠKO DRUŠTVO

RADIOLOŠKA SEKCIJA

Figure 2. Section of Radiology of the Slovenian Medical Association.

Figure 3. Prof. Dr. Mira Vurnik Žumer, 1956-1957; 1962-1964.

Figure 4. Prof. Dr. Ludvik Tabor, 1957-1958; 1964-1966; 1968-1969; 1975-1982.

Figure 5. Prof. Dr. Stanko Hernja, 1959-1960.

Figure 6. Section of Radiology and Nuclear Medicine of the Slovenian Medical Association.

Figure 7. Section of Radiology of the Slovenian Medical Association.

Figure 8. Prim. Dr. Uroš Vizjak, 1966-1968.

Figure 9. Prim. Dr. Vekoslav Janežič, 1970-1971.

who was elected its first president (Figures 1, 2). In 1956, the SAR and Prof. Hebein organized the forth congress of Yugoslavian radiologists in Ljubljana. Overall, 7 invited faculty from Europe, 140 radiologists and for the first time 15 companies participated at the meeting.[2] After the meeting, the second president of the SAR, Prof. Dr. Mira Vurnik Žumer took her turn (Figure 3). Prof. Dr. Ludvik Tabor (Figure 4) was elected the third and Prof. Dr. Stanko Hernja the forth president of the SAR (Figure 5).[3-6]

Although radiology had been already separated as a discipline between diagnostic and therapeutic aspects of radiology at that time, some radiotherapists were members of the SAR.[2,7] In the mid fifties, investigation and the clinical research with radioisotopes began in Slovenia. Iodine 131 was used for thyroid diagnosis first by Dr. Jože Satler and later by Dr. Bojan Varl. In 1955, Dr. Leo Šavnik and then in 1957, Dr. Stojan Plesničar injected patients with radiopharmaceuticals for tumor radiotherapy at the Institute of Oncology in Ljubljana.[7,8] In the late fifties or early sixties nuclear medicine colleagues joined the SAR and its name changed subsequently into the Section of Radiology and Nuclear Medicine of the Slovenian Medical Association (Sekcija za radiologijo in nuklearno medicino Slovenskega zdravniškega društva) (Figure 6). By 1974, five more nuclear medicine departments appeared in hospitals in Slovenj Gradec, Celje, Maribor, Sempeter pri Novi Gorici and Ankaran that resulted in creation of an independent Section of Nuclear Medicine (Sekcija za nuklearno medicino).[8,9] Prof. Bojan Varl served as their first president.[10] After that event the SAR was renamed back to the Section of Radiology (Figure 7).

Since the beginning, SAR has served as a forum for radiologists to collectively voice common concerns and professional interests. Its purpose is to promote and develop the highest standards of radiology and to exchange professional experiences and scientific information in all fields of radiology and related sciences through patient care, education and research. SAR is governed by the President, the Executive Board and the General Assembly. The Slovenian Association of Radiology is the official educational and scientific association of Slovenian radiologists.

One of the aims of the SAR is to promote close cooperation among radiologists with other international radiological societies and, especially in neighboring countries, to promote common educational and research programs (for example Alpe Adria Radiological Group). Since the first meeting in Dobrna (Slovenia) in 1968, organized by primarius Dr. Uroš Vizjak (Figure 8), radiologists from university radiological departments of Trieste, Padua, Verona, Graz, Ljubljana and Zagreb have been meeting in one of the neighboring countries to share their scientific experiences annually.[11,12] Between the 1958 and 1961 the SAR and the Croatian Section of Radiology organized successful intersectional meetings in Pula, Maribor and Split. Primarius Dr. Mila Kovačeva organized a meeting in Maribor in 1959. Prof. Božena Ravnihar, Prof. Jože Stropnik, Prof. Stanko Hernja, Prof. Ludvik Tabor, Prof. Obrez and the SAR organized the eighth congress of the Yugoslavian radiologists in Ljubljana in 1972. Dr. Ludvik Tabor has served as secretary general of the Yugoslavian Society of Radiology for many years starting from 1968. The 1st and the 2nd Yugoslavian Congress of Radiology took place in Belgrade in 1935 and 1950, the 3rd in Zagreb in 1953, the 4th in Ljubljana in 1956, the 5th in Skopje in 1960, the 6th in Belgrade in 1964, the 7th in Pula in 1968, the 8th in Ljubljana in 1972, the 9th in Sarajevo in 1976, the 10th in Novi Sad in 1980, the 11th in Belgrade in 1984, and the 12th in Ohrid in 1988th.[13]

Figure 10. Prof. Dr. Jože Stropnik, 1971-1975.

Figure 11. Prof. Dr. Dušan Pavčnik, 1982-1995.

Figure 12. Association of Radiology of the Slovenian Medical Association.

Figure 14. Assist. Prof. Dr Živa Zupančič, 1995-2006.

Figure 15. Slovenian Association of Radiology in the late 1990s.

DRUŠTVO RADIOLOGOV
SLOVENSKO ZDRAVNIŠKO DRUŠTVO

PREDSEDNIK prof. dr. D. Pavčnik	TAJNIK dr. D. Babnik-Peskar	ČLANI UPRAVNEGA ODBORA dr. G. Brenko dr. R. Cesar dr. S. Galijaš prim. dr. T. Goranič prof. dr. V. Jevtič dr. J. Kocijančič
PODPREDSEDNIK asist. dr. Ž. Zupančič	BLAGAJNIK dr. J. Knific	dr. M. Kolenc dr. N. Mudnič dr. I. Pisanec dr. S. Rainer dr. M. Škrbec

Figure 13. Letter head with the logo in the early 1990s.

Figure 16. Assist. Prof. Dr Dimitrij Kuhelj, 2006 -2010.

Figure 17. Prof. Dr. Ivo Obrez in the late 60s.

Figure 18. Prof. Dr. Dušan Pavčnik in the early 2000s.

The SAR and its presidents have organized and hosted successful meetings in most of the Slovenian cities. Due to the old X ray equipment in Slovenian hospitals in 1960s and 1970s, the radiation protection and systematic inspection and monitoring of working environments was an important issue during the term of primarius Dr. Vekoslav Janežič (Figure 9).

The permanent expert collegium (strokovni kolegij) consisted of the X-ray department chairmen in Slovenia who were appointed in 1974 as advising body to the SAR. That body provided expert assistance to the SAR on the field of the X ray equipment selection, radiation protection, and several other professional issues and questions (Figure 10).

The Slovenian Association of Radiology has been affiliated with the Journal of Radiology and Oncology published in English quarterly, covering all technical and clinical aspects of diagnostic and interventional radiology, radiotherapy, nuclear medicine, oncology, radiobiology, radio-physics and radiation protection. The history of publishing this radiological-oncological journal in Ljubljana dates back to 1964 when the first issue of Radiologia Iugoslavica was published. Radiologia Iugoslavica was cofounded by Prof. Ivo Obrez, Prof. Stojan Plesničar, Prof. Božena Ravnihar, Prof. Ludvik Tabor and Prof. Stanko Hernja. The seat of the editorial office has always been at the Institute of Oncology Ljubljana. In 1992, its 26th volume appeared under the new name of Radiology and Oncology (Radiol Oncol).[14] More than half of editors were from the Institute of Oncology. The Editors from the SAR were: Prof. Ivo Obrez, Prof. Ludvik Tabor, Prof. Stanko Hernja, Prof. Mario Prodan, Dr. Peter Soklič, Prof. Dušan Pavčnik and Associate Prof. Igor Kocijančič. Prof. Dr. Ludvik Tabor served as the Editor in Chief from 1976-1981. Prof. Dr. Gregor Serša serves as current Editor in Chief. Recently in 2008 our journal has been indexed and abstracted by Science Citation Index Expanded (SciSearch®). The next goal for the Radiol Oncol is to obtain the impact factor, often abbreviated IF. The IF is a measure of the citation to science journals which is frequently used as a proxy for the relative importance of a journal within its field.[15]

As the technology for radiology imaging has rapidly developed so has the need to train and educate radiologists who have an expertise in the clinical and scientific aspects of radiological imaging and interventional radiology. This has always been one of the prime missions of our association. The practice of radiology has changed beyond recognition since 1950 when SAR was founded. During Prof. Pavčnik's terms from 1982-1995 the use of the ultrasound, computer tomography imaging, magnetic resonance imaging and interventional radiology have become the daily routine (Figure 11). Just the term diagnostic radiology was not accurate anymore. According to the statue of the European Association of Radiology (EAR), radiology was defined as diagnostic and interventional radiology and medical imaging. Dr. Pavčnik left for 1 year fellowship in Boston at Harvard Medical School in 1984 and Dr. Erika Brenčič became acting president and kept that position for one year. We have organized several educational meetings in Ljubljana, Kamnik, Šempeter pri Novi Gorici, Izola, Kobarid, Golnik, Slovenj Gradec, Maribor, Ptuj, Novo mesto, Brežice, Ankaran and Celje. One of the highlights was the lecture of Dr. Myron Marx from San Francisco: CT examination of eleven Egyptian mummies from the Fine Arts Museum in Boston in 1987. In 1989, the SAR and Dr. Pavčnik organized the 6th Yugoslav meeting on interventional radiology in oncology in Ljubljana. Under the combined presidency of Prof. Pavčnik and Prof. Šurlan, it turned out to be a success. Overall, 5 invited

faculty from Europe and the United States, over 150 radiologists and 43 companies participated and supported the meeting, invited faculty and its meeting book.

In 1982 the SAR had 92 members. The numbers steadily increased to 128 members in 1995 and to 148 in 2008. Apart from education and clinical work, professional issues remained an important goal. For example, primarius Dr. Jurij Zalar and primarius Dr. Bogomir Celcer started protesting against the law which would decrease our radiation vacation benefits together with vacation down to 36 days per year at the SAR meeting in Slovenj Gradec in 1988.

The 1990s were years of transition for the SAR. During this time Slovenia declared its independence. Section of Radiology became the Association of Radiology (Društvo Radiologov) that has registered at the Slovenian Medical Association. The SAR has joined the European Association of Radiology. Our first true logo, pre-current logo was an image of Slovenia's map inside the double ring of the EAR logo. It was used in the letter head of the SAR (Figures 12, 13). Despite the war, Prof. Lazlo Horvath from Hungary and Prof. Moretin from the USA participated at the 1991 SAR meetings in Ljubljana during the time of the moratorium.

The SAR congresses have been taking place since 1996. The event originally took place every four years in different locations, starting in Portorož 1996, and then followed by Ljubljana 2000, Bled 2004 and Ptuj 2008. The current name of the SAR and its logo was suggested during the term of Dr. Živa Zupančič (Figures 14, 15). The SAR and Dr. Zupančič organized the 1st, the 2nd and the 3rd Slovenian Congress of Radiology.

The Slovenian radiological community showed its appreciation for Prof. Obrez's contributions to diagnostic and interventional radiology. Dr. Dimitrij Kuhelj, the current president (Figure 16), established the eponymous Ivo Obrez Lecture at every forth year congress of the SAR. This eponymous lecture was introduced in memory of an individual who made a special contribution to radiology and to the Slovenian Association of Radiology (Figure 17). The first speaker was Prof. Dušan Pavčnik at the 4th Congress of Slovenian Radiologists in Ptuj in 2008 (Figure 18). In his lecture, early years of cardiovascular and interventional radiology, Dr. Pavčnik called the 1970s, 1980s and 1990s exciting years of our lives as diagnostic and interventional radiologists. Dr. Obrez's papers, book chapters, his lectures, inventions, including working beside him were a constant inspiration to us that changed our orientation from diagnostic angiographers to interventional radiologists. Ivo Obrez had a vision and the passion for this minimally invasive therapy.[16,17]

The SAR is one of the smallest societies of the European Society of Radiology. It has grown slowly since its foundation in 1950. Currently, the Slovenian Association of Radiology has 149 radiologists in all subspecialties.

Acknowledgement

I would like to thank Erika Brenčič, Jurij Us, Marko Demšar, Dimitrij Kuhelj, Nikolaj Sadnikar, Elizabeta Baretič Kolar, Peter Soklič, Jana Shiro, Marijan Pocajt and Maja Podkrajšek for all their assistance without which this paper would not have been possible.

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Radiol Oncol 2009; 43(3): 144-151. *doi:10.2478/v10019-009-0028-6*

review

Locally recurrent rectal cancer: treatment options

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Background. *Although the preoperative radiochemotherapy and the optimised surgical technique have improved the outcome in patients with rectal cancer, the local recurrence still remains a therapeutic problem. In up to 50% of patients the local recurrence appears without simultaneous distant metastases. This review highlights current treatment options of locally recurrent rectal cancer.*

Conclusions. *The optimal management of the isolated local recurrence remains a difficult and controversial issue. The radical surgical resection is the mainstay of the curative treatment, but an extended surgery can be associated with significant morbidity and impaired quality of life. The preoperative chemoradiation for turnout down staging increases the chance of resectability and the addition of intraoperative radiotherapy may further improve the local control and survival. Re-irradiation is feasible in patients who already received irradiation as part of the primary rectal cancer treatment.*

Key words: locally recurrent - rectal cancer; multi-modality therapy

Introduction

The local recurrence (LR) of rectal cancer occurs in up to 30% of patients who had undergone only the radical resection. The introduction of total mesorectal excision (TME) has reduced the rate of LR to <10%[1,2] and to ≤6% when TME has been combined with the preoperative radiotherapy alone or combined with chemotherapy.[3,4] Seventy-five percent of LR are detected within two years from diagnosing primary tumor.[5] From 20% to 50% of patients with LR have isolated the local recurrence without distant metastasis. LR may be accompained with pain, bleeding or constipation, depending on the type of the previous surgery. The management of the isolated locoregional recurrence is difficult and treatment options may be limited in patients who have already received a local radiation therapy for the primary rectal cancer. In the absence of the surgical intervention, the 5-year survival of these patients is less than 4% and the median survival of 8 months.[6,7]

The choice of therapy depends upon disease location, extent and prior treatment. Predictors for the outcome in patients who received radiotherapy for locally recurrent rectal cancer were performance status, stage, chemotherapy, surgery, extent of resection, histologic grading, and like in other

Received 28 May 2009
Accepted 6 June 2009

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localization haemoglobin levels both before and during radiotherapy.[8,9] Radical surgery (R0) remains the mainstay of the treatment for achieving the longterm local control and survival for locally recurrent rectal cancer (LRRC), but many times an aggressive multimodality approach is required to accomplish negative margins and a chance of cure.

Predictors of local recurrence

Many factors affect the risk of the local recurrence. The risk increases with the advanced stage[10] and adverse pathological features of primary tumour, including perineural and vascular invasion and grade.[11] LR is more likely associated with tumours located in distal rectum, the presence of obstruction or perforation and tumour fixation to adjacent structures.[12] The significance of the involvement of lateral or circumferential resection margin (CRM) as an independent prognostic factor for LR and the survival has been confirmed in a prospective randomised study on 190 patients who underwent the curative resection of rectal cancer. The rate of CRM involvement was 25%; among those with clear margins, 90% remained free of pelvic recurrence at 5 years, whereas only 23% of those with the lateral margin involvement were without LR.[13]

Recently published data from Davis *et al.* showed that there was no difference in the incidence of LR after sphincter-saving resections compared to the abdominoperineal excision, as long as the appropriate technique was used, the distal margin of clearance was at least 1 cm and CRM margins were free of tumour. By avoiding continuing the TME dissection into the pelvic floor and removing low lying tumours en block with the surrounding levator, the rate of involved CRM was reported to be 0% and the LR rate only 5%.[14] As LR after both surgical procedures most commonly arise from residual extramucosal disease, the incomplete removal of the potentially tumour-bearing mesorectum is the main cause of LR.[15] There is a different level of training and experience performing »total mesorectal excision« (TME) among surgeons, resulting in wide range of LR in published reports. A study comparing local recurrence rates after the rectal cancer resection in a group of Canadian surgeons showed that patients of surgeons who had additional training or expertise in colorectal surgery had a local relapse rate of 13%, compared with 34% in general surgeons' group whose practice included fewer of these operations.[16] Finally, the rate of LR in patents receiving preoperative or postoperative radiotherapy, either alone or combined with chemotherapy, is reduced comparing with patients treated with surgery alone. More favourable local control rates were reported in series using the preoperative approach.[14,15]

Surgery

The only chance for the curative treatment of isolated LR is provided by the radical re-resection.[17] Several studies have analyzed factors which could help to select patients with LRRC for surgery *i.e.* that might predict resectability and, consequently, prognosis. Results are controversial. However, factors most often associated with the increased chance of the radical resection were younger age, female gender, prior local excision or restorative surgery that was performed at another institution. The poorer outcome was related to the presence of pain (as a symptom of LR), lateral tumour extension, increasing number of sites of the recurrent tumour fixation in the pelvis and elevated CEA level before the re-resection.[18]

Surgical procedures available in LRRC are low anterior resection, abdominoperineal resection, pelvic exenteration and ab-

Table 1. Locally recurrent rectal cancer - external beam radiation without or with intraoperative radiation

Author	Year	Patients (n)	Therapy	Survival (%)	Local relapse (%)	Distant relapse (%)
Gunderson *et al.*[30]	1996	123	EBRT/CT→surg→IORT	5y, 20	5y, 37	5y, 72
Lowy *et al.*[31]	1996	43	EBRT/CT→surg→IOHDR	2y, 58	2y, 36	-
Farouk *et al.*[32]	1997	116	EBRT→surg	5y, 7	3y, 93	3y, 54
		64	EBRT→surg→IORT	5y, 18	5y, 27	5y, 75
Wong *et al.*[29]	1998	519	EBRT	5y, 5	5y, 93	-
Mannaerts *et al.*[33]	2001	94	EBRT	3y, 14	3y, 90	-
		19	EBRT→surg	3y, 11	3y, 86	-
		33	EBRT→surg→IORT	3y, 60	3y, 27	-
Wiig *et al.*[34]	2002	48	EBRT/CT→surg	5y, 30	5y, 70	-
		59	EBRT/CT→surg→IORT	5y, 30	5y, 50	-
Rades *et al.*[35]	2008	84	EBRT+/- CT→surg	3y, 36	3y, 67	41

Abbreviations: EBRT - external beam radiotherapy; CT - chemotherapy; IORT - intraoperative radiation.

dominosacral composite resection, and the decisions on the most appropriate one depends upon the site and extend of LR. The anastomotic recurrence without fixation to surrounding structures may be cured by the surgical resection alone in as many as 50% of cases.[19] In more extensive cases, sacrectomy with pelvic reconstruction is required to achieve a complete resection and 5-year survival rates in the range of 20-35% have been reported.[19,20] The resection with negative microscopical margins can be achieved in approximately 45% of cases (range 10-67%).[21-23] Results of surgical resection alone with positive margins left behind are poor, with less than 10% of those patients surviving 3 years and no 5-year survivors.[24] Because of the significant perioperative morbidity and the poor survival outcome extended surgery is not very popular.[25] On the other hand, untreated LR significantly reduces the quality of life which became more and more important in the treatment of oncological patients.[26,27] Furthermore, Miller *et al.* argued that the aggressive surgical treatment of LR improved survival, favourably affected quality of life and represented a cost-effective use of resources.[28]

Combined modality treatment in patients with LR undergoing curative surgery for primary rectal cancer

Despite the radical resection of LRRC, in 25% to 61% of patients another recurrence developed locally or disease progressed systemically.[25] In addition, external beam radiotherapy (EBRT) alone (*i.e.* not being accompanied with surgery) or in combination with 5- fluorouracil (5-FU) chemotherapy has only a palliative effect and offers no hope for cure. It allows a temporary symptomatic improvement in majority of patients, but the median duration of symptom relief is only a few months and the 5-year survival is usually less than 5%.[29] Because of the generally poor results achieved with the surgical resection or EBRT alone, the logical approach for LRRC seemed to be the combination of both modalities.

The effect of the preoperative chemoradiation (45-55 Gy in 5-6 weeks) with 5-fluorouracil (5-FU) chemotherapy in previously nonirradiated patients is supported by data from retrospective series (Table 1). To further increase the response rate and consequently to reduce the need for extensive surgery, improve resectability, local control and survival, other

chemotherapy agents (CPT-11, oxaliplatin, capecitabine) and targeted agents may be of benefit in the future.

According to above mentioned reports, the EBRT doses to the whole pelvis usually should not exceed 50 Gy because small bowel toxicity restricts delivery of higher dose. However, this dose is insufficient to sterilize gross residual disease after the surgery.[36] With the use of intraoperative irradiation (IORT) or high-dose rate brachytherapy (IOHDR), a boost of ionizing radiation can be given directly to the parts of tumour resection bed that are most prone for recurrence, yet avoiding irradiation of surrounding normal structures. IORT can achieve the biologic equivalent dose of 2 to 3 times that of the same dose delivered using conventionally fractionated EBRT.[30] The combination with IORT allows the reduction of the EBRT dose which – together with the physical removal of healthy normal structures from IORT field – reduces toxicity of this modality and potentially improve the therapeutic ratio. IORT has generally been delivered by accelerator-generated electron beam or high-dose rate (HDR) brachytherapy using gamma rays or beta rays emitted by the encapsulated radioactive sources inserted during the surgery, to a total dose in a range of 10–30 Gy. The treatment with IORT requires a dedicated operating suite or transfer of the anesthetized patient from the operating room to the radiotherapy suite. For the mobile HDR-IORT machine, a shielded facility is necessary. Recently, mobile IORT machines were constructed which can be used in conventional hospitals on a daily basis and shared between several operating rooms.

As the IORT facilities are available only in a very limited number of radiotherapy centres, treatment results in the literature are rare and conflicting. While Wiig *et al.*[34] showed that IORT did not modify the outcome after the surgery, regardless of the volume of residual disease, reports from some centres suggest that improved the local control and the survival can be achieved in selected patients when the combination of preoperative chemoradiotherapy, radical surgery and IORT is implemented. Five-year survival rates of 18% to 30% and local control rates of 50% to 73% were reported (Table 1).[30-35] Recently, a comparison of various treatment combinations revealed significantly improved survival, disease-free survival, and local control rates at 3 years of 60%, 43%, and 73%, respectively, when the combination of EBRT, surgery, and IORT was used.[33] The most frequently observed IORT-related toxicities were ureteral stenosis (6%) and peripheral neuropathy (16%-34%).[30,33] Similarly, a relationship between IORT dose and the incidence of Grade 2 or 3 neuropathy was also demonstrated by Gunderson *et al*., although not reaching the level of statistical significance ($\leq$ 12.5 Gy *vs.* $\geq$ 15 Gy, 7% vs. 19%; $p = 0.12$).[30]

Multimodality treatment in patients with LR who have received previous external beam radiation therapy

The anatomic location of local failure after the ''optimized'' rectal cancer surgery was studied by Syk *et al*.[37] All recurrences were found within the irradiated volume in the low pelvis, anatomically below the S1-S2 interspace, if the patients had undergone preoperative radiotherapy or if they had not.[37] Similar results were reported by Yu *et al*. with only a limited number of marginal and out-of-field failures, indicating that standard pelvic radiotherapy fields are appropriate for most rectal cancer patients. Of the in-field recurrences, nearly 80% occurred in the low pelvic and presacral regions.[38]

As a majority of patients with LR have already received the local radiation therapy in neoadjuvant or adjuvant setting during the primary rectal cancer treatment and because of fear of a high probability of severe late toxicity related to the Re-RT, patients are usually

Table 2. Locally recurrent rectal cancer - treatment of previously irradiated patients

First author	Patients (n)	Year	Therapy	Survival (%)	Local relapse (%)	Distant relapse (%)
Alektiar *et al*.[44]	74	2000	surg→ IOHDR±EBRT±CT	5y, 23	61	38
Haddock *et al*.[41]	51	2001	EBRT±CT +surg+IORT	5y, 12	5y, 66	5y, 76
Lindel *et al*.[45]	69	2001	EBRT/CT→surg→IORT	27	65	-
Mohiuddin *et al*.[46]	103	2002	EBRT/CT→surg	19	-	-
Valentini *et al*.[47]	59	2003	EBRT/CT→surg	5y, 39	5y, 47	5y, 30
Das *et al*.[48]	50	2007	EBRT/CT→surg	48	3y, 64	

Abbreviations: EBRT - external beam radiotherapy; CT - chemotherapy; IORT - intraoperative radiation; surg - surgery.

treated with the best supportive care.[39,40] This is most probably the reason why the prognosis for patients with LRRC is on average worse in previously irradiated patients than in those without prior irradiation. Two Mayo Clinic studies demonstrated a better local control and survival when the palliative resection of LR was followed by IORT; however, in previously irradiated patients both outcome measures were lower than in patients not receiving prior EBRT: at 5-years, 34% *vs* 63% and 12% *vs* 20%, respectively.[30,41] In the randomized Stockholm trial comparing the preoperative irradiation to the surgical resection alone, 15% of irradiated patients suffered a local recurrence. They were treated with a variety of combinations of surgery, RT, and chemotherapy that resulted in a median survival of 11 months and no 5-yr survivors compared to 15 months in patients from surgery only group ($p = 0.0002$).[42]

Recent data suggest that limited doses of 30 Gy external beam Re-RT are likely to be safe, even when combined with concomitantly administered chemotherapy, if the small bowel can be excluded from the irradiation field, and an additional booster dose of up to 10 Gy can be used for limited volumes.[43] Subsequent toxicity in re-irradiated patients is accaptable and resulted tumor shrinkage could be followed by surgical salvage and long-term survival in selected patients (Table 2).[41,44-48] The irradiated volume usually encompasses recurrent tumor with a 2-4 cm margin. As the late intestinal toxicity strongly depends on the fractionation pattern used, hyperfractionation RT schedules with small fraction doses are preferred.

Conclusions

Despite the improved local control in rectal cancer achieved by preoperative chemoradiotherapy and TME surgery, a substantial proportion of patients will experience the local recurrence. A complete resection is crutial for achieving a long-term local control and survival. The addition of local high-dose radiation delivered in the form of IOERT or IO-HDR brachytherapy appears to have the potential to improve the treatment outcome after the extended surgery. However, in patients with gross residual disease after the surgical procedure, the local tumour control is inadequate despite aggressive treatment combinations. For a more accurate administration of higher radiation doses, advanced EBRT techniques such as 3D-conformal RT, intensity modulated radiotherapy (IMRT) and proton beam therapy are to be employed, whereas for the precise localisation of the disease, the integration of different imaging modalities is essential. To a further increase response rate, the evaluation of new radiation sensitizing drugs or biologic modifiers during EBRT is warranted. Because of the high probability of distant metastases, chemo-

therapy should be an essential component of these aggressive treatment approaches. As LR is more common in patients with locally advanced tumours, who have already received 5-FU-based chemotherapy in the context of the primary treatment, a systemic therapy employing more effective novel agents is indicated.

Acknowledgement

The article resumes the lecture given by the author during the second edition of the international course "Oncology for surgeons" in Iasi, Romania on April 14-18, 2009.

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Radiol Oncol 2009; 43(3): 152-161. *doi:10.2478/v10019-009-0033-9*

research article

Transcatheter embolization of bronchial arteries in the treatment of haemoptysis

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Background. *Massive haemoptysis is a clinical state characterized by the expectoration of blood at a rate of 300-600 mL/24 h, thus causing life-threatening asphyxia. The aim of our study is to review use of transcatheter bronchial artery embolization (BAE) in the treatment of massive haemoptysis.*

Materials and methods. *Series of 11 patients with the clinical picture of massive haemoptysis was referred to our hospital for digital subtraction angiography and BAE within a 33 months period. There were 8 male (aged 43-69, mean age 56) and 3 female patients (aged 63-65, mean age 64). Aortography of thoracic aorta was initially performed in all patients, followed by selective angiography of bronchial and intercostal arteries, and intercostobronchial tree as indicated. A selective arterial embolization was done in 9 patients (9 primary and 3 secondary embolizations). The embolization was performed under fluoroscopy control by manual injection of the mixture of contrast solution (1 ccm) and embolization material, Embosphere (BioSphere Medical Inc., MA, USA), particle size 350-500 m.*

Results. *Bronchiectasis was the most common cause of bleeding (45.4%), while hypervascularization and intensive parenchymal opacification were the most frequent angiographic indicators of bleeding (100%), followed by tortuous and hypertrophic arteries (72.7%). Primary BAE proved successful in 81.9% and secondary BAE performed within 24 months in 33.3% of patients, whereas the tertiary (operative) treatment was required in 22.2% of patients. In 44.4% of patients, BAE was associated with only mild discomforts, like pain and cough.*

Conclusions. *BAE is a reliable and minimally invasive method in the management of massive haemoptysis. Therefore, it should be considered as the primary method of the treatment or as a procedure for the stabilization the patient before the surgery.*

Key words: massive haemoptysis; bronchial artery; embolization

Received 3 December 2008
Accepted 25 May 2009

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Introduction

Massive haemoptysis is the expectoration of blood at a rate of 300-600 mL/24 h. If left untreated, it can lead to asphyxia and death. Massive haemoptysis accounts for 5% of all haemoptysis cases and is associated with a high mortality rate (up to 75%). If massive haemoptysis is treated conservatively, mortality rate ranges from 50% to 85%.[1-4] Tuberculosis and sarcoidosis are the most common causes of massive haemoptysis. In 90% of cases, haemoptysis originates from bronchial arteries, whereas only a minor portion arises from non-bronchial (pulmonary and systemic) circulation.[2] The bronchial artery embolization (BAE) is a percutaneous transcatheter minimally invasive procedure, which has proved successful in the management of massive haemoptysis and is associated with a lower mortality rate as compared with the surgical treatment (7.1% - 18.2%).[2,5,6] The aim is to present our results in the management of haemoptysis by the use of transcatheter BAE.

Patients and methods

During 33 months, 11 patients were referred to our hospital for digital subtraction angiography (DSA) and BAE because of the clinical picture of massive haemoptysis. Bronchiectasis was the cause of haemorrhage in 5 (45.4%), lung tuberculosis in 3 (27.3%), aspergilloma in 2 (18.2%) patients, and carcinoma in 1 (9.1%) patient.

DSA was recommended by interdisciplinary consultation (pulmonologist, thoracic surgeon and interventional radiologist). DSA and BAE were preceded by lung X-ray, computed tomography of the thorax and bronchoscopy to identify the localization of bleeding and type of lesions.

Bronchoscopy proved inadequate in 5 patients because of the procedure intolerance due to the patients' poor general condition and poor visualization of the site of bleeding. An informed consent was obtained from all patients prior to the procedure. There were 8 male (aged 43-69, mean age 56) and 3 female (aged 63-65, mean age 64) patients.

Prior to DSA, patients were administered diazepams, 5 mg i.v. (Apaurin, Krka, Novo Mesto, Slovenia) for mild sedation, along with monitoring of vital functions. DSA was performed by Seldinger technique *via* common femoral artery, by using diagnostic pigtail and selective 5FR catheters of different shapes such as cobra-shaped and hook-shaped (Mikaelsson, Medikrit, Tokyo, Japan), classic J and hydrophilic guide wires 0.035 (Terrumo, Japan) and nonionic Omnipaque contrast agent (Nycomed, Princeton, NJ, USA). For thoracic aorta angiography, a contrast agent was injected by the use of the automated injector (18 ccm/20 ccm/s). On selective angiography of aortic branches, contrast medium was manually injected, adjusting the amount and pressure to fluoroscopy-visualized angiogram.

Aortography of thoracic aorta was initially performed in all patients, followed by selective angiography of bronchial and intercostal arteries, and intercostobronchial tree as indicated. The selective arterial embolization was done in 9 (81.8%) patients. In 2 (18.2%) patients, it could not be performed because the aspect of the aorta (thoracic aorta tortuosity) prevented a stable selective placement of the tip of the catheter into the target artery.

Angiography of the subclavian artery branches (thyrocervical trunk, costocervical trunk and internal thoracic artery) was performed in cases where selective angiography of bronchial and intercostal arteries yielded negative results after the detection of pathologic process and its localization determined by diagnostic imaging methods

and/or bronhoscopy. Due attention was paid to the possible detection of Adamkiewicz artery. Angiographic signs suggesting site of bleeding include hypervascularization, intensive parenchymal opacification, pronounced tortuosity, arterial aneurysms and AV fistulas. The embolization of the feeding artery was performed on the basis of pathologic angiographic characteristics pointing to the localization of bleeding. Upon placing the tip of the catheter safely into the target artery, the embolization was performed under fluoroscopy control by manual injection of mixture of contrast solution (1 ccm) and embolization material, Embosphere (BioSphere Medical Inc., MA, USA), particle size 350-500 μm.

The amount of the material injected depended on the patency and filling of the vascular bed of the target artery. The embolization was discontinued when the embolization material ceased to flow out from the catheter, indicating a significant increase in the distal resistance of the embolized artery. Control angiographies were done by manual injection of the contrast medium through the same catheter at a pressure adjusted to the new situation in the embolized artery, under the fluoroscopy control. The catheter was previously rinsed with saline. In addition to control selective angiographies of embolized arteries, angiographies of thoracic arteries were also performed to visualize the possible, previously overlooked pathologically altered arteries that may have presented additional sources of bleeding. In the patients presented, there was no need of pulmonary angiography or use of microcatheters (≤3F) during the procedure of embolization.

After the procedure, the patient's general condition (blood pressure, ECG, breathing, pain severity) and the site of puncture were monitored for 4 h. Then, the patients in good general condition were transferred to a specialized institution for lung diseases, accompanied by the medical personnel, for continuous general condition monitoring and management of underlying disease. The patients were under the regular clinical control for the next 24 months. Depending on the disease dynamics and haemoptysis recurrence patterns, the patients were treated conservatively or were referred for the secondary embolization or some other mode of the active treatment.

Results

All of the 11 angiograms showed pathologic angiographic findings. Such a finding was present on the angiograms of thoracic aorta in 2/11 (18.2%) patients with extensive bronchiectasias, and on selective angiograms of the thoracic aorta branches in the remaining 9/11 (81.8%) patients. The angiographic characteristics of pathologic haemorrhage included hypervascularization and intensive parenchymal opacification in 11/11 (100%), AV fistulas in 6/11 (54.5%), tortuous and hypertrophic arteries in 8/11 (72.7%) and aneurysms in 3/11 (27.3%) patients. The pathologic process in pulmonary parenchyma was localized on the right and left side in 6/11 (54.5%) and 5/11 (45.5%) patients, respectively.

Embolization proved successful in 9/11 (81.8%) patients. In 2/11 (18.2%) patients, it could not be performed although their thoracic aorta angiograms revealed a pathologic area in the lung parenchyma. A tortuous appearance of thoracic aorta and the pattern of bronchial artery origin prevented a safe manipulation and a stable selective access to the artery showing a pathologic finding. Although BAE was not performed in these two patients, they were included in the analysis because BAE was planned and attempted in these patients as well.

Embolization of intercostobronchial arteries and bronchial artery itself was

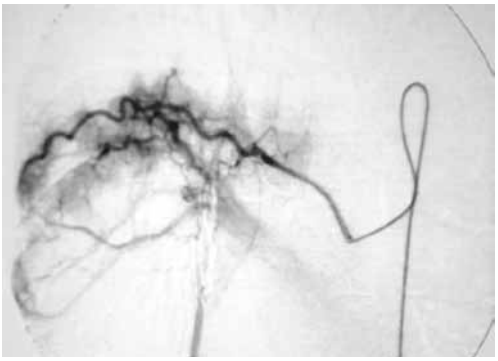

Figure 1a. Digital subtraction angiography in a patient with bronchiectasis before embolization.

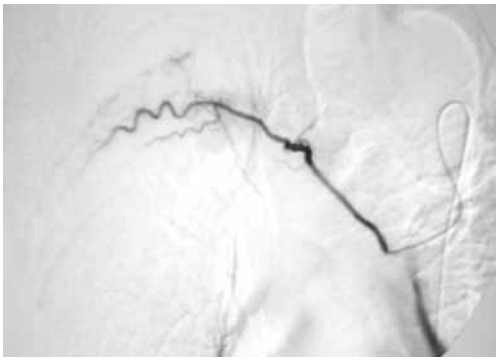

Figure 1b. Digital subtraction angiography in a patient with bronchiectasis after embolization.

done in 8/9 (88.9%) patients, whereas 1/9 (11.1%) patient underwent embolization of the thyrocervical trunk branches of the left subclavian artery (ASCL) (Table 1). In five of 8/9 (62.5%) patients submitted to selective angiography of bronchial arteries, two bronchial arteries were found on the left side and one bronchial artery on the right side – Type I according to Cauldwell's anatomic classification of the number and origin of bronchial arteries. Adamkiewicz artery as a branch of the arteries involved by the target embolization was not visualized either during or after the procedure; thus, there was no relative contraindication for BAE.

The results of the primary embolization were regularly followed-up for a mean of 21.6 (19-24) months of the procedure (Table 1). The primary procedure proved a successful mode of the treatment for massive haemoptysis in 6/9 (66.7%) patients. The cause of haemoptysis was lung tuberculosis in 3/6 (50.0%) and bronchiectasis in 2/6 (33.3%) patients (Figures 1a, b), whereas one (16.7%) patient underwent the primary embolization for microcellular bronchial carcinoma, survived for 5 months of the procedure and died from myocardial infarction. The secondary embolization was performed in 3/9 (33.3%) patients, at a mean of 3 (1-6) months of the initial procedure. In this group, bronchiectasis was the underlying disease in two patients, and aspergilloma in one patient (Figures 2a, b, c, d, e). The operative treatment of haemoptysis following two embolization procedures was required in 2/9 (22.2%) patients, *i.e.* for aspergilloma and bronchiectasis in one patient each (Table 1). During the immediate post-embolization procedure (up to 72 h), back pain and coughing were reported by 4/9 (44.4%) patients. These complaints were symptomatically treated because any major complications were ruled out by the course of symptoms and respective studies (X-ray, ECG, laboratory tests and CT).

Discussion

Bronchial arteries are direct parietal branches of the thoracic aorta, originating between 5^{th} and 6^{th} thoracic vertebra at the level of tracheal bifurcation. They supply a nutritive circulation for pulmonary tissue and blood vessels, trachea, inner lung coat, pulmonary hilar lymph nodes, oesophagus and pericardium. Most commonly used classification for describing number and origin of bronchial arteries is from Cauldwell *et al.*[7,8] According to this classification, two left bronchial arteries and one right presenting as an intercosto-

Table 1. Results of percutaneous treatment for haemoptysis

Patient No.	Aetiology	Embolization/period 1 (prim. BAE)	Embolization/period 2 (sec. BAE)	Operation	Control (months)
1	Tbc	+			20
2	Tbc	+			24
3	Tbc	-			19
4	Asp	+	+ (1 month)	+ (3 months)	22
5	Asp	+			19
6	Bron	-			23
7	Bron	+	+ (2 months)	+ (4months)	22
8	Bron	+	+ (6 months)		23
9	Bron	+			21
10	Bron	+			23
11	Ca	+			(5 - IM)†
N=11		9/11 (81.9%)	3/9 (33.3%)	2/9 (22.2%)	19-24 months

Legend: Prim BAE - primary embolization; sec BAE - secondary embolization; Tbc - lung tuberculosis; Asp - aspergilloma; Bron - bronchiectasis; Ca - microcellular carcinoma; N - total patient number; †(IM) myocardial infarction mortality

bronchial trunk (ICBT) (40%); one on the left and one ICBT on the right (21%); two on the left and two on the right (one ICBT and one bronchial artery) (20%); and one on the left and two on the right artery (one ICBT) (9.7%). There are also aberrant bronchial arteries (originating outside the level Th5 and Th6) with reported prevalence ranging from 8.3%-35%.[7,8,9] Anomalous origins include aortic arch, mammary artery, subclavian artery, brachiocephalic trunk, thyrocervical trunk, inferior phrenic artery and abdominal aorta. One should be aware of the possible presence of the aberrant bronchial arteries when there is not significant bronchial arterial supply to areas of abnormal pulmonary parenchyma or in the patients with recurrent haemoptysis despite a successful embolization.

The presence of intercostobronchial tree was found in two of our patients with lung tuberculosis (3/11) and bronchiectasis (5/11) as underlying diseases. In one patient suffering from aspergilloma of the upper lobe of the left lung, branches of the subclavian artery were the predominant source of bleeding.

Angiographic signs suggesting bleeding site include dilated and tortuous bronchial arteries, neovascularity, arterial aneurysms, peribronchial hypervascularity, AV shunting into the pulmonary artery or vein. A contrast extravasation as a specific sign of haemorrhage is rarely seen, with reported prevalence from 3.6-10.7% because the bleeding from bronchial arteries is slow and intermittent.[1,2,10,11] The comparison of the signs of bleeding and hypervascularization of the lung parenchyma were indicators of the lesion localization and haemorrhage in all patients (11/11; 100%). Besides those findings, at least one of the following pathognomonic signs was present in all our patients: AV fistulas in 6/11 (54.5%); tortuous, hypertrophic arteries in 8/11 (72.7%); and arterial aneurysms in 3/11 (27.3%) patients. We found hypervascularization of the lung parenchyma and tortuous arteries in 1 (9.1%) patient with lung carcinoma, which is in contrast to the reports on the absence of angiographic signs of haemoptysis in one-third of individuals with malignant lung diseases.[1] However, the adequate treatment of haemoptysis in lung cancer patients can

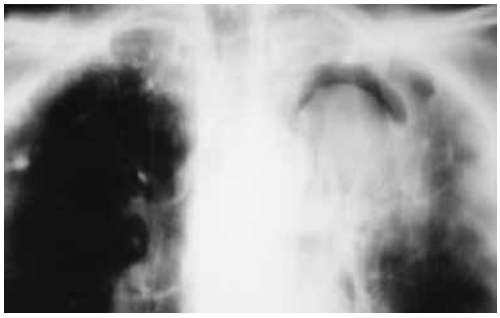

Figure 2a. X-ray/tomography of aspergilloma.

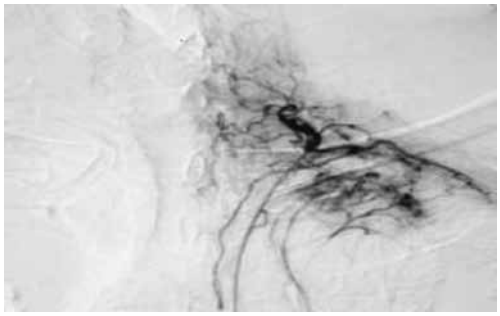

Figure 2c. Digital subtraction angiography in a patient with aspergilloma before embolization.

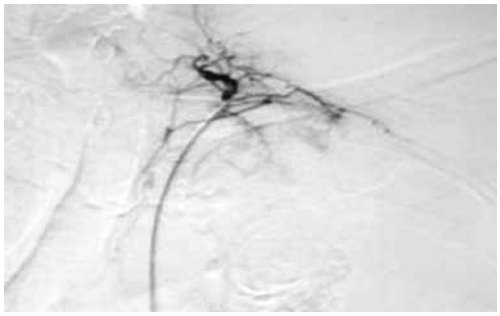

Figure 2e. Digital subtraction angiography in a patient with aspergilloma after secondary embolization.

improve their short-time survival rate, not only because of the patient's characteristics (better performance status, more females), but also because of a more suitable management of urgent conditions.[12] AV shunting is a major and reliable angiographic sign of haemoptysis on DSA, recorded in all 5/11 (45.5%) patients with bronchiectasis as the underlying disease and in one of the two (9.1%) patients with aspergilloma.

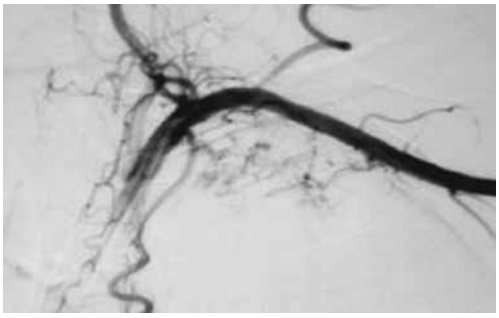

Figure 2b. Digital subtraction angiography in a patient with aspergilloma before embolization.

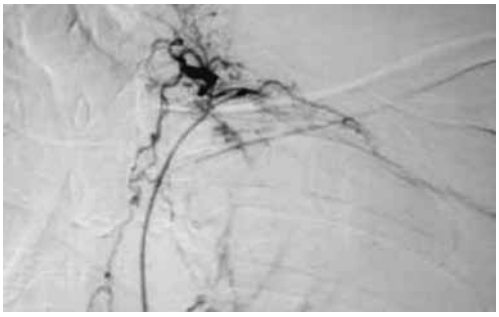

Figure 2d. Digital subtraction angiography in a patient with aspergilloma after primary embolization.

BAE has been used as a therapeutic method of the treatment for haemoptysis since 1973. It is also used as an adjuvant method to the surgical, bronchoscopic and/or conservative treatment.[1,2,13,14] BAE enables a direct bleeding control, thus obviating the need of the operative procedure, which is associated with higher mortality (17.6-19%)[15,16], longer hospital stay and higher costs of the treatment.[2,4] In addition, the embolization provides better clinical preconditions for the possible subsequent operative treatment. In BAE the rate of the technical success is high (77%-94%). A long-term success of the primary BAE is up to 80% and depends on the grade of progression of the underlying pulmonary disease causing hemoptysis.[3,14,17] In our patient group the success of the percutaneous approach in the management of haemoptysis was 81.9% (9/11 patients). In nine patients a

100% technical success was recorded. In remaining two patients the embolization was not performed due to the failure of achieving a stable position of the catheter, which is the precondition for performing a safe embolization. The stable selective placement of the tip of the catheter into the target artery could not be achieved because of significant thoracic aorta tortuosity.

In the literature, one-month clinical results of bronchial artery primary embolization range from 48% to 98%.[1,18] Such a broad range of the results of the primary embolization may be explained by pathophysiologic changes that occur after the embolization. The embolization is quite frequently followed by hypertrophy of the "adjacent" arteries. The primary procedure failure and proneness to secondary haemorrhages may be caused by the underlying disease activity, circulatory collateralization, or inadequate embolization and prevention of broad communication between the target and adjacent arteries. We presume that the possible inadequate primary embolization may have induced the recurrence in our patient with the apical localization of aspergilloma (Figure 2). Bronchiectasis and lung tuberculosis are the factors that lead to massive haemoptysis and the multiple active treatment (embolization and/or operative procedure) in 73% of patients.[1] In our patient series, bronchiectasis and lung tuberculosis contribute around 73% cases of haemoptysis, the former being found in 45.5% (5/11) of patients. In the group of patients requiring multiple BAE and/or the operative treatment, bronchiectasis was the underlying disease in two-thirds and aspergilloma in one-third of patients. Lung tuberculosis was not present in this group of patients. This is an interesting finding, considering the fact that lung tuberculosis is the underlying disease in 15.5% of all haemoptysis recurrences.[1] The variation between our results and literature data on the prevalence of lung tuberculosis can be attributed to the small patient sample, making the comparison with other reports imprecise. The small number of patients included in our study prevented any reliable comparison of our data on the high prevalence of bronchiectasis and aspergilloma as the factors for BAE or the operative treatment with the respective literature reports. However, the inappropriate treatment of the underlying disease and/or disease extension (*e.g.*, aspergilloma in the upper lobe of the left lung; Figure 2) may be objective reasons of the recurrence. This may explain the higher prevalence of multiple embolizations in our patient series (33.3%) as compared with 18.4% reported in the literature. The prevalence of lesions detected in non-bronchial arteries in patients with the unsuccessful embolization procedure recorded in our patient series (33.3%) was comparable to literature reports (25.0%-36.4%). Chronic inflammatory diseases of pulmonary parenchyma lead to the reduction of pulmonary circulation at the level of pulmonary arterioles due to the associated vasculitis and hypoxic vasoconstriction. This in turn entails the opening of precapillary anastomoses of bronchial and pulmonary arteries, which results in bronchial arterial hypertrophy. The elevation of intravascular pressure or inflammatory erosion of arterial wall in the arteries affected with such lesions usually causes ruptures and consequential haemorrhage. A good control of the underlying disease is the main factor of a long-term success and prevention of haemoptysis recurrence.[3,12] In our series, chronic inflammatory states (bronchiectasis, aspergilloma) caused the recurrence in three (33.0%) patients within 6 months of the primary procedure. The presence of the apical process in the lungs (as in our patient with aspergilloma; Table 1, patient no. 4) make the procedure of the embolization more complex and the therapeutic outcome uncertain. Such a situation requires

the successful embolization of a number of intrathoracic branches of the subclavian artery and possible collateral arteries as the potential sources of haemorrhage. In the context of bronchiectasis and aspergilloma as the reasons for the secondary treatment in three patients, the BAE procedure was more complex, as demonstrated by the need of a tertiary, operative procedure in two of these patients (one patient with aspergilloma and bronchiectasis each) (Table 1) Prior to the embolization, it is necessary to estimate the distribution pattern of radicular arteries and the origin of anterior spinal artery (artery of Adamkiewicz), involved in the vascularization of spinal medulla, since its embolization leads to spinal ischemia and transverse myelitis.[9,19] This unilateral vessel usually arises between Th9 and Th12 in 75% of cases. Anterior medullary arteries have characteristic „hairpin" configuration at angiography. In our patients, the artery of Adamkiewicz was not visualized on DSA and selective DSA, ensuring a safer approach in the procedure of the embolization. However, during BAE a due attention was paid to the possible visualization of the mentioned arteries because Uflacker *et al.* report on radicular arteries visualized during the embolization, which may be a contraindication for BAE, in 42/75 cases.[20,21] However, these authors did not consider it an absolute contraindication for BAE.

In cases of a difficult placement of the tip of a 5FR selective catheter into the target artery, the procedure of BAE can frequently be simplified and safer with the use of microcatheters. Employing a microcatheter is favourable for enabling a more selective access to the target artery and the microcatheter tip placement more distally from the possible radicular artery origin.[21] However, a safe placement of the tip of 5FR selective catheter into the target artery can be checked by vigorous yet properly dosed injection of a contrast medium, as we did in our patients. If this does not result in the catheter tip "popping up" from the target artery, the embolization can be performed without the use of microcatheter. Of course, a precondition is ruling out the origin of radicular arteries. That is why we believe, like some other authors, that microcatheters are not necessary to use on BAE in such cases.[22]

The advances in DSA technique, along with the use of microcatheters and nonionic iso-/low-osmolarity contrast agents, have enabled a more efficient and safer approach in the management of haemoptysis. The rate of haemoptysis recurrence may reach 46% after the initial embolization. According to some authors, in a high percentage (87%) it occurs consequentially to recanalization of the previously embolized arteries rather than due to arterial hypertrophy (27%).[21,23] This implies to the procedures performed with the use of temporary embolization agent, Gelfoam.[20] Polyvinyl alcohol (PVA) and Microsphere (Embosphere, Embogold) are permanent embolization agents that require the re-embolization in only 15.5% of cases.[24] The procedure success also depends on the choice and type of embolization material needed for the arterial occlusion.[1,2,8,9,18,19] Therefore, we used Embosphere (BioSphere Medical Inc., MA, USA). None of our patients was initially scheduled for the operative procedure. If not so, there would have been no reason to avoid using a temporary embolization agent, followed by the operation. We also avoided using liquid embolic agents (Absolute ethanol, glues) because they cause the occlusion of the capillary network, leading to tissue necrosis.[23-25] The choice of embolization material is among the most important steps in the procedure of BAE. This primarily refers to the material properties that determine the duration of the embolization effect, and to the size of the particles employed (350-500 μm), which taken together ensure a long-term haemoptysis control.[1,2,7,18] The size of the emboliza-

tion material particles should be in size of 350-500 μm. It is essential to avoid use of embolic less than 350 μm because it increases the risk of unintentional systemic or pulmonary embolization. Experimental studies have demonstrated a bronchopulmonary anastomosis of 325 μm in human lung.[26]

This is of utmost importance because of the width and patency of communications between bronchial arteries and pulmonary veins, and bronchial arteries and pulmonary arteries, as well as for some unexpected communications of bronchial arteries with systemic arteries, also described in other endovascular procedures.[18,23,24,27] With the use of 350-500 μm Embospheres, we achieved technically satisfactory results in 81.8% of patients, comparable to literature reports. The rate of the successful outcome of the primary embolization (66.7%) was also quite consistent with literature data.[1-3,7,13,14,17,18,20,21,28]

In addition to the proper choice of embolization material, the choice of contrast medium is also highly relevant in the procedure of BAE. Hyperosmolarity may cause transient ischemia of radicular arterial branches. Literature reports describe transverse myelitis consequential to vasotoxicity caused by the use of ionic contrast.[9,19] Therefore, we employed Omnipaque, a nonionic, low-osmolarity contrast medium, associated with the absence of neurotoxicity and reduced coughing. In spite of this, 4/9 (44.4%) patients developed cough and back pain within 72 h of the procedure. Following respective studies, these complaints were treated symptomatically and did not require additional therapy nor prolonged the expected duration of the hospital stay. This is consistent with literature reports on the rate of post-BAE pain development (24% - 91%).[10]

Conclusions

Massive haemoptysis is a clinical emergency, posing a life threat to the patient due to the potential asphyxia. The embolization of bronchial and non-bronchial arteries is a safe and efficient interventional procedure for the successful management of acute haemoptysis. Proper knowledge of the bronchial artery anatomy, their possible communications and underlying pathophysiology of massive haemoptysis are preconditions for the successful procedure performance. Advances in the angiography technique and the use of novel, sophisticated materials make the procedure of BAE safe and associated with a minimal risk for the patient. Due control of the underlying disease, that has led to parenchymal and arterial lesions, thus causing the bleeding, is an important factor to prevent the recurrent bleeding. We do hope that the general notes on the issue of haemoptysis, technique, advantages and results of BAE, and on the role of proper choice of embolization material will result in a more favourable approach to the problem of massive haemoptysis. This is expected to bring an even closer interdisciplinary collaboration of pulmonologists and interventional radiologists, to the benefit of our patients.

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Radiol Oncol 2009; 43(3): 162-169. *doi:10.2478/v10019-009-0032-x*

research article

Diagnostic evaluation and surgical management of recurrent hydatid cysts in an endemic region

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Background. *Echinococcosis is a zoonotic disease that occurs mainly in endemic areas. Recurrent hydatid cyst (RHC) and its diagnosis present insidious problems for surgeons. The aim of this study was to evaluate the diagnosis and surgical management of RHC in Turkey, where the disease is endemic.*

Methods. *We conducted a comprehensive study of 146 patients with abdominal hydatid cysts that were managed surgically between 1997 and 2007. Among those patients, RHC arose in 14 (9.5%) of cases.*

Results. *The female to male patient-ratio was 6 to 8 and median age was 47.4 years. Patients' symptoms included abdominal pain, nausea, fever, and jaundice. Cysts reoccurred in patients sporadically between 4 months and 22 years. Abdominal US, CT, and MRI were utilized for the diagnosis in 14 (100%), 11 (78.5%), and 2 (14.2%) patients respectively, demonstrating the RHC of the liver and concomitant cysts (splenic region, mesentery of the colon and perivesical) in all cases, respectively. The recurrent cysts (with a mean diameter of 12 cm) were removed using partial pericystectomy, introflexion, and total cystectomy surgical techniques. Postoperative morbidity occurred in 14% of patients.*

Conclusions. *Especially in endemic countries like Turkey, RHC should be included in the differential diagnosis of cystic masses in abdominal organs that were previously treated for hydatid cysts. Surgery still remains the treatment of choice for RHC with early management and proper perioperative evaluation contributing to a high cure rate.*

Key words: hydatid; cyst; recurrence

Introduction

Hydatid disease due to *Echinococcus granulosus* is endemic in particular regions of the world including the Mediterranean countries, the Middle East, Eastern Europe, South America, Australia and New Zealand. The clinical presentation of hydatid disease depends on the size and site of the lesion and the accessibility of the organ involved in the clinical examination.[1]

As there is no effective medical therapy for recurrent hydatid cyst (RHC), surgery is still the first-choice treatment.[2] Administering pre- and post-operative courses of anti-helmintic drugs and using

Received 31 March 2009
Accepted 1 July 2009

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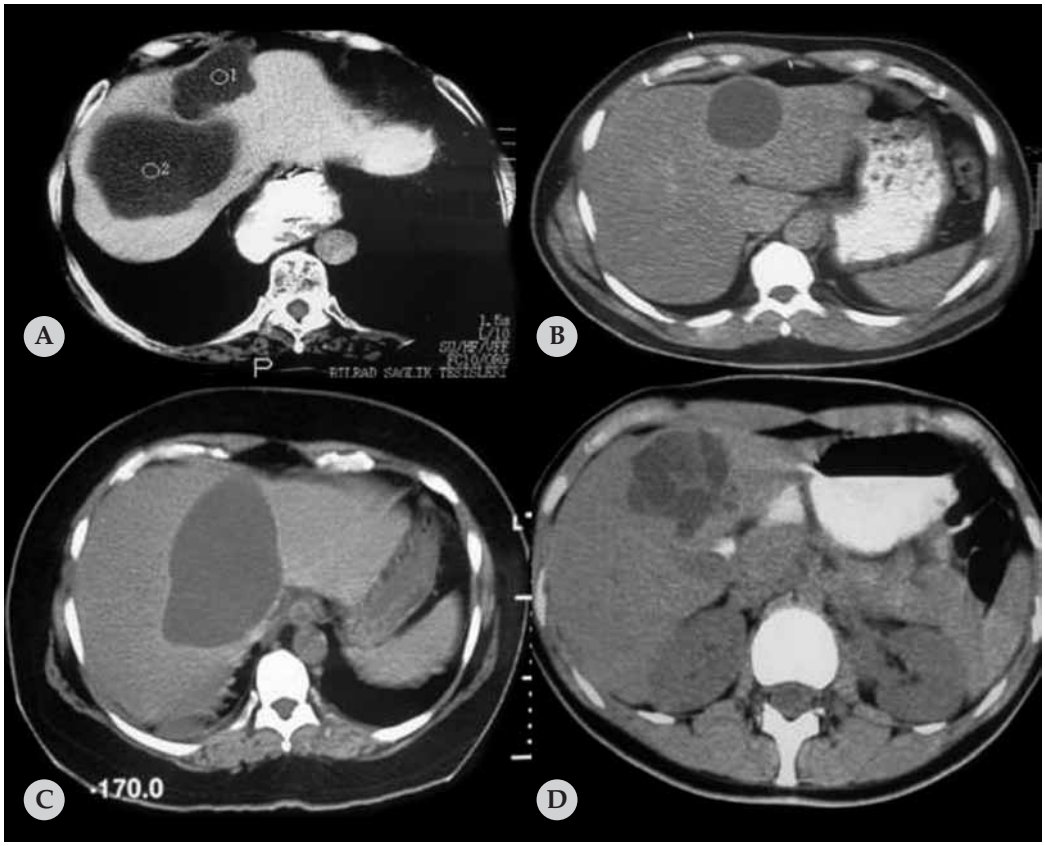

Figure 1. CT scan shows multiple (A) and uniloculer(B,C,D) RHC of the liver.

scolicidal solutions intra-operatively tends to kill the living daughter cysts, prevent the risk of spillage, and reduce the recurrence rate post-operatively. However, the recurrence rate of this disease is still disappointingly high, in the range of 9-20%.[3]

In our series of 146 patients with abdominal hydatid cysts that were managed surgically, a RHC arose in 14 (9.5%) of cases. Since the recurrence of an echinococcal cyst mainly follows a silent clinical course, unless its growth produces symptoms, its diagnosis is commonly based on the findings of ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI).[4]

The aim of this study was to appraise within an endemic country the diagnosis and management of surgically confirmed abdominal RHC caused by *E. granulosus* at various locations in the abdomen.

Patients and methods

We, retrospectively, reviewed the medical records of 14 adult patients operated on for RHC at the Department of 2nd Surgery at our Hospital (in Izmir, Turkey) during the period 1997- 2007. We defined a 'recurrent cyst' to be any growing cyst at the original operative site, in the neighboring liver tissue, or extrahepatic. Our diagnostic work-up for the study consisted of complete blood counts, liver function tests, hydatid serology with hemagglutination tests, and

clinical findings. Imaging studies comprised US, CT and MRI. All patients underwent a preoperative US examination with 3 MHz transabdominal probe. US findings were described according to *Gharbi* classification.[5] Type 1 includes the univesicular cyst- pure fluid collection, Type 2 covers the fluid collection with a split wall-detached laminated membrane 'water lily' sign. Type 3 involves the fluid collection with septa and daughter cysts. Type 4 has a heterogenous appearence that mimics a solid mass and Type 5 appears as reflecting thick walls and calcifications. CT examination was conducted for 11 patients with Toshiba spiral CT Asteion. MR studies were performed for two patients on a 1.5 T unit. The choice of the operative procedure was based on number, size, and location of cysts, and previous surgery. The pre- and post-operative one-month courses of anti-helmintic drugs (Albendazole) were administered to in all patients. The data were analyzed with a descriptive study.

Table 1. Time of previous surgery and location of the cysts

Patient	Age	Sex	Time of previous surgery	Location of the RHC
1	48	M	22 years	liver
2	39	F	5-8 years	liver
3	37	F	8 years	liver
4	57	M	5-7-8-9 years	Liver+mesentery
5	49	M	9-20-21 years	liver
6	40	M	7 years	liver
7	57	F	3 years	Liver+perivesical
8	30	M	6-7-9 years	liver
9	40	F	12 months	Liver+left subphrenic *fossa*
10	52	F	15 months	liver
11	53	M	4 months	liver
12	47	M	15 months	liver
13	43	M	16 months	liver
14	39	M	5 years	liver

M:male,F:female

Results

Fourteen of 146 of the patients in this study presented with RHC. The median age of 14 patients was 47.4 years (range, 30-64) at the time of diagnosis. Of the 14 patients, 6 (42.8%) were females and 8 (57.1%) were male.

Clinical symptoms varied and included abdominal pain (n = 14, 100%), nausea (n = 8, 57.1%), fever (n = 2, 14.2%), and jaundice (n = 1, 7.1%). Hepatomegaly was noticed in 8 (57.1%) patients and an abdominal mass was detected in 2 (14.2%). Cysts reoccurred in patients at irregular intervals between 4 months and 22 years. After their original operations, 5 patients experienced RHC less than 2 years later, 9 patients more than 2 years later (Table 1). Four patients had a recurrence of hydatid cyst between 5 and 21 years after one or more operations in their home hospital. The type of the initial operation performed was not known exactly. In one case, the same patient experienced recurrence twice, 5 and 8 years after the initial operation. Two patients had the surgical treatment for hydatid cyst three times. In one of those cases, cysts reoccurred 9, 20, and 21 years after the original surgery. In the other, a recurrence arose 6, 7, and 9 years after the first operation. One case was operated four times: 5, 7, 8 and 9 years after three times surgery.

Eosinophilia, leukocytosis, and an increased level of ALT/AST were found in 1, 4 and 5 patients. The hemagglutination test was applied in 10 (71.4%) patients and was positive in 4 of them. Abdominal

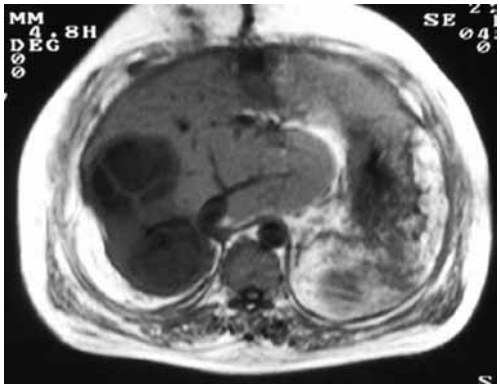

Figure 2. CT demonstrating the RHC of the liver and concomitant cyst of the splenic region. The patient was underwent splenectomy for splenic hydatid cyst in previous operation.

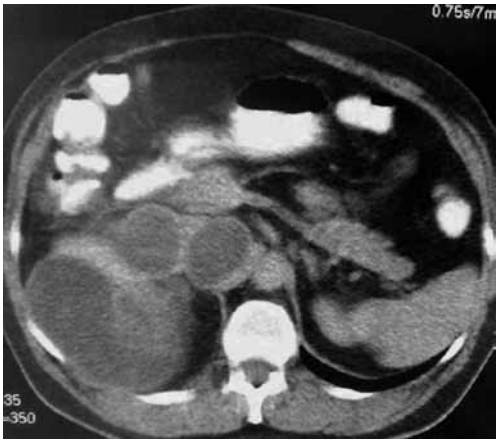

Figure 3. The patient was operated four times because of hydatid cyst. His CT scan shows RHC in the mesentery of the colon.

X-rays revealed an elevation of the right diaphragm in 3 (21.4%) cases. Abdominal US, CT (Figure 1) and MRI were utilized in 14 (100 %), 11 (78.5%), and 2 (14.2%) patients, demonstrating the RHC of the liver in all patients. According to *Gharbi* classification, the majority of the cases were Types 1, 3 and 2 (n = 9, 3 and 2 cases). Three (21.4%) patients from this group had associated hydatid cysts in other organs. The RHC was found in the left subphrenic space (Figure 2), the mesentery of the colon (Figure 3) and the perivesical region (Figure 4) in one patient. While one patient of the three had had a splenectomy as the treatment for a splenic hydatid cyst, the other two had been treated surgically for hydatid cyst of the liver, previously. Among 14 patients studied, the right lobe of the liver was affected in 11 (78.5%) cases, the left lobe in 3 (21.4%) cases. There were multiple liver cysts in 3 (21.4%) cases. The mean diameter of the cysts was 12 cm (range 3.5 to 15 cm). MRI was utilized successfully in 2 (14.4%) patients, respectively (Figure 5).

In thirteen (92.8%) of 14 patients studied, a subcostal incision was used. A midline incision was used for the remaining patient. At operation, we performed a complete removal of the contents of the hydatid cyst of the liver in all 14 patients. We carried out partial pericystectomy and introflexion including the closure of the remaining cyst cavity to prevent dead space. The closure of the remaining cavity were drained and performed with silicon tubes. Total cystectomy was performed to the cyst of the colonic mesentery, the cyst in the splenic region, and the perivesical cyst. Postoperative morbidity was found in two (14.2%) patients and consisted of wound infection. Only one patient was operated for *brid ileus*, 4 months later.

Discussion

In spite of modern therapeutic methods, RHC remains a significant problem for surgeons in endemic regions. A history of hydatid disease as well as the presence of its characteristic cystic lesions may well suggest the diagnosis of RHC, but it is often difficult to establish the unequivocal diagnosis before surgery. Although recurring cysts are commonly known to affect the liver and lung, studies also show that they can also affect other organs.[6,7] Pre-operative diagnosis of RHC may be difficult, because

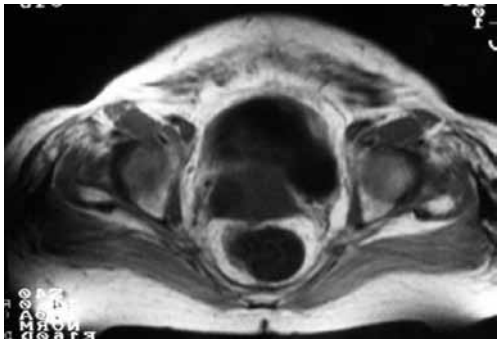

Figure 4. Perivesical location of the RHC in a 58-year-old woman.

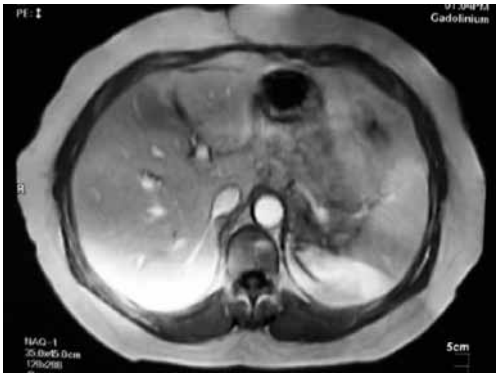

Figure 5. MRI appearence of the RHC on the left lobe of the liver.

it may be confused with primer or post-operative cysts (biloma,lymphocele). In our study, RHC was successfully diagnosed pre-operatively in all patients. The high success rate observed at our center could be explained by the referral of patients from endemic areas.

Unfortunately, a patient's prior history of hydatid cysts cannot in itself justify the diagnosis of the recurrent cyst. RHC develops most often as a new growth of an echinococcal cyst after the complete surgical removal of the primary one or due to a cyst developing postoperatively from the non-identifiable small cysts. Another clinical scenario involves a cyst resulting secondarily to the surgical technique via disseminated *vesicules*, intraoperatively. In our study, we encountered RHC most likely due to the dissemination from the previous surgery in four patients.

The clinical presentation of RHC depends on the size and site of the lesion and the accessibility of the organ involved for the clinical examination.[8] The cysts may become infected and present themselves as liver abscesses. This complication has been reported in the literature as occurring in 5% to 40% of patients.[9] In our experience, clinical symptomatology consists of abdominal pain, nausea, fever and jaundice. It appears that jaundice is related to the presence of a communication between a cyst and the biliary tree although MRI did not confirm this supposition in our patients.

Although eosinophilia is expected in patients with parasitic infestations at the rate of 30%[2], we only observed it in one (7.1%) case. A previous study showed that hydatid immunoelectrophoresis, enzyme-linked immunosorbent assay (ELISA), and indirect hemagglutination (IHA) tests were conducted for the diagnosis and post-operative follow up.[10] In our series of patients, serological tests identified cysts positively in 4 (28.5%) of cases. The number of our serological tests is low due to the dead parasite and the impaired immune reaction.

Without having a patient's clinical history, pre-operative diagnosis of RHC cannot be made with imaging studies in asymptomatic and mildly symptomatic patients. A pre-operative diagnosis of RHC may be difficult, because it may be confused with a primer hydatid cyst or true cysts. As documented in this study, as well as others[2], US and CT scans were the most helpful investigatory means for detecting abdominal cystic masses, successful in each of our 14 cases. US findings of the cysts may appear as purely cystic masses, completely detached membranes inside a cyst, multivesicular cysts, and cysts that are partially or totally calcified. CT findings of RHC include the round fluid collection in which membranes

are detected, septa and cyst walls that are calcified, and primer hydatid cysts that are similar in appearance. Further, MRI, MRI-angiography may be effective upon the visualization of suspected masses.[11,12] In our study, all of the cysts were typed according to *Gharbi* classification with US. However, the classification of the cysts did not affect our surgical procedures. The treatment of the recurrent hydatid disease is mainly surgical, as anti-helmintic chemotherapy alone has failed in many cases.[2] However, pre- and post-operative 1-month courses of anti-helmintic drugs should be considered in order to reduce the spillage of viable cysts during the surgery and to decrease the recurrence rate post-operatively. These drugs are recommended, as with our series of patients, for cases in which spillage of scoleces may have occurred during the surgery. A medical therapy may be used for patients with the inoperable disease, patients involved in the incomplete surgery, and for the prevention in patients of the secondary spread of echinococcal infection following the spontaneous rupture.

A surgical intervention seems to be a satisfactory approach to evacuate the contents of the cyst without spillage, and to prevent the cyst recurrence.[13] At present, despite the ease of application, the percutaneous drainage of the RHC should be avoided, because it may lead to an intraperitoneal dissemination of the daughter cysts. The number and location of RHC, and their connection to adjacent structures, determine the surgical approach. The surgical intervention can be performed using either a transperitoneal or an extraperitoneal approach with a wide exposure of the abdominal cavity, since it demonstrates the overlooked cysts at the previous surgery.[14] In our series, the subcostal incision was found to be effective, providing a good exposure for RHC within the liver.

Surgery may well be curative, but it carries risks including the secondary echinococcosis due to the spillage in 2% to 21% of cases.[2,15] Three key principles of the surgery are: aspiration of the cyst at its most superficial point, use of hypertonic saline solutions before opening the cavities (to kill the daughter cysts and prevent their further spread), and total cystectomy for extrahepatic locations intra-operatively.[16] Liver cysts must be punctured with a canulla for the decompression and to determine the nature of intracystic fluid. In most of our cases we performed a partial pericystectomy / introflexion for liver cysts, and a total cystectomy for cysts at the other sites. When we review previously published articles, we find various types of treatment models for RHC. That implies that a proper and effective treatment modality is still not described. Although the surgery is the gold standard of RHC treatment, the effectiveness of the procedure is still quite questionable.What should be the surgical strategy to prevent RHC? For example, has the surgery removed all recurrence focus? Is spillage prevented during the operation? Are morphological changes, which might be the irregularities of the endocyst, creating pockets and preventing the contact between scolicidal agent and parasites? Has the RHC been correctly detected intra-operatively? Previous studies show that the resective surgery alone has been ineffective in preventing the cyst reoccurrence – 20% of such surgeries result in recurrences. But, a combined treatment method, resective surgery for macro disease and anti-helmintic drugs for the residual infection, is demonstrably more effective decreasing the recurrence rate to 10%. Many authors recommend pericystectomy in the open surgery because it can be performed without opening the cyst, and without the spillage, and without the need for the cavity management.[17] The limitations of the procedure is that it can only

be performed on peripherally located small cysts and that it is associated with large amounts of blood loss.

RHC complications at recently reported rates of 10 - 37%, in multiple series of patients treated surgically, include infection, hemorrhage, rupture, and obstruction of other abdominal organs. Additionally, reoperation rates have been reported as 6%.[18] In our patients' series, laparotomy was performed in one patient, because of the *brid ileus*. Even though the mortality directly due to echinococcosis is rare, it can produce a very disabling morbidity. A mortality rate 1.5% has been reported.[19]

Conclusions

Surgical RHC failures may result in a new cyst(s) at a different location or in an undiscovered cyst(s) in a previous location. Since the prior history of the hydatid cyst cannot by itself justify the diagnosis of RHC, the rigorous evaluation of the patient is important for the improved diagnosis. An early diagnosis and the detection of small cysts are especially important – because if cysts can be detected and controlled at an early stage, they pose little or no threat pathologically or functionally to organs. Additionally, the proper perioperative evaluation and patients' support are efficacious in improving surgical results. We recommend a total or partial pericystectomy as the most appropriate procedure for the management of primary HC and also for RHC. Furthermore, we advocate RHC incidence may be decreased with the improvement of misdiagnoses, mistreatment, and appropriate follow-up and also the preventive immunologic research in the biology of the parasite.

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Radiol Oncol 2009; 43(3): 170-174. doi:10.2478/v10019-009-0020-1

case report

A case with myasthenia gravis, brain stem multiple infarcts, fracture of vertebrae Th6 and discal hernia to the Th7/Th8

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Background. *We report the case of a patient with myasthenia gravis accompanied with brain stem multiple infarcts, fracture of vertebrae Th6 and discal hernia of the Th7/TH8.*

Case report. *A 66-year-old male patient, one week prior to the hospitalization showed up complaints of dizziness, nausea, vomiting, numbness of the left side of the face, swallowing difficulty, left side body weakness, right side of the body numbness starting from the nipples and going down to the right leg as well as general fatigue. Six years ago the patient was diagnosed with myasthenia gravis based on electrophysiological investigations, pharmacologic tests and findings of acetylcholine (Ach) receptor antibodies in serum. He was then treated with the following medications: pyridostigmine of 60mg x 5/day, prednisolon of 20 mg (every other day), azathioprine 100mg tid. He was doing well under described therapy. Twenty years ago his left kidney was removed due to calculosis. He had also a sister that suffered of myasthenia gravis and diabetes mellitus.*

Conclusions. *Myasthenia gravis has a number of symptoms and signs which probaly are in common with stroke-including fatigue, muscle weakness, slurred speach and swallowing difficulty. The reported case supports the opinion that several medical conditions such as brain steam stroke may mimick myasthenia gravis.*

Key words: myasthenia gravis; brain stem multiple infarcts; fracture of vertebrae

Introduction

Myasthenia gravis (MG) is an autoimmune disorder of peripheral nerves in which antibodies are formed against acetylcholine nicotinic postsynaptic receptors (AChRs) at the myoneuronal junction. A reduction in the number of AChRs, results in a characteristic pattern of progressively reduction of muscle strength with repeated use of the muscle and recovery of muscle strength following a period of rest.[1-4] The bulbar muscles are affected most commonly and most severely, but most patients also develop some degree of intermittent generalized weakness.[3] Auto antibodies develop against AChRs nicotinic postsynaptic

Received 18 November 2008
Accepted 23 January 2009

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receptors for unknown reasons, although certain genotypes are more susceptible. The presynaptic terminal contains vesicles filled with acetylcholine (ACh). On arrival of a nerve action potential, the contents of these vesicles are released into the synaptic cleft in a calcium-dependent manner. The released ACh molecules diffuse across the synapse and bind to the AChRs on the postsynaptic membrane.[3,4]

Anti-AChR antibody is found in approximately 80-90% of patients with MG. Patients with anti-AChR antibodies are recognized as seropositive myasthenia gravis (SPMG). Patients become symptomatic once the number of AChRs is reduced to approximately 30% of normal. Patients without anti-AChR antibodies are recognized as seronegative myasthenia gravis (SNMG). Many of these patients with SNMG have antibodies against muscle-specific kinase (MuSK). MuSK plays a critical role in postsynaptic differentiation and clustering of AChRs.[2,4]

Immunogenic mechanisms play important roles in the pathophysiology of myasthenia gravis. Supporting clinical observations include the presence of associated autoimmune disorders in patients suffering from myasthenia gravis (*e.g.* autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis). The role of the thymus in the pathogenesis of myasthenia gravis is not entirely clear, but 75% of patients with myasthenia gravis have some degree of thymus abnormality (*e.g.* hyperplasia in 85% of cases, thymoma in 15% of cases). Given the immunologic function of the thymus and the improvement in the clinical condition of patients following thymectomy, the thymus is suspected to be the site of autoantibody generation. However, the stimulus that initiates the autoimmune process has not been identified.

The most common symptoms are: dropping of the eye lids, double vision, slurred speech, swallowing and chewing difficulty, muscle weakness of arms and legs, chronic fatigue and sometimes breath difficulty.[1-6]

To facilitate the clinical staging of therapy and prognosis, the following classification, introduced by Osserman, has been widely adopted:[1]

I	Ocular myasthenia (15-20%).
IIA	Mild generalized myasthenia with slow progression, no crises: drug responsive (30%).
IIB	Moderately severe generalized myasthenia; severe skeletal and bulbar involvement but no crisis, drug response less than satisfactory (25%).
III	Acute fulminating myasthenia; rapid progression of severe symptoms with respiratory crises and poor drug response; high incidence of thymoma; high mortality (15%).
IV	Late severe myasthenia; symptoms the same as III, but resulting from steady progression over 2 years from class I to class II (10%).

Female to male ratio in children and adults is 3:2. It can manifest at any age from the birth until the 80-ties. The peak age of onset is between 20 and 30 years in women and between 50-60 years in men. Under the age of 40, females are affected two to three times as often as males, whereas in later life, the incidence in males is higher 3:2.[1-4] The diagnosis is made by the following; pharmacologic investigations: edrophonium chloride (Tensilion) test, pyridostigmine (Prostigmin) test. electrophysiological investigations; repetitive nerve stimulation test, single fiber EMG studies (SFEMG) and serologic tests; serum AChR antibody test, muscular specific thyrosin kynase (anti-MuSk) antibodies.[4-8] The treatment consists of cholinesterase inhibitors, immunosuppressant, thymectomy, plasmapheresis and i.v. immunoglobulins.[9-13]

Case report

The patient was a 66-year old male. Six days prior to the hospitalization the patient showed up with complaints of dizziness, nausea, vomiting, numbness of the left side of the face and body, difficulty in swallowing, left side body weakness, right side of the body numbness starting from the nipples and down the right leg and general fatigue. Also six years ago the patient was diagnosed with myasthenia gravis (generalized form, Osserman II.B) with electrophysiological investigations, pharmacologic tests and findings of acetylcholine receptor antibodies in serum. For years his conditions were good with the following treatment: pyridostigmine (Mestinon) tablets of 60 mg 5x1, prednisolon tablets of 20 mg 1x1 (every second day), azathioprine (Imuran) tablets of 100 mg 2x1. He was doing well with the described therapy. Twenty years ago his left kidney was removed due to calculosis and he suffered from hypertension, too, which he treated with lisinopril and hydrochlorothiazide tablets of 10 mg 1x1. He had a sister also diagnosed with myasthenia gravis and diabetes.

Neurologic examination

He suffered from horizontal nystagmus on the right, diplopia, dysphagia, dysphonia, supranuclear paresis of the left facial nerve, the uvula deviated on the right, hemihypaesthesia on the left side of face, muscular weakness of jaw muscles and hemihypaesthesia on the left.

Upper extremities: muscle strength was weaker on the left side (grade 4), there was reflex asymetry presented (again weaker on the left). We found hypaesthesia for all qualities on the right side with the sensory level to the Th 5/6 vertebrae.

Lower extremities: muscular tone was weaker on the left side, muscle strength was also weaker on the left, there was hiperreflexia bill.

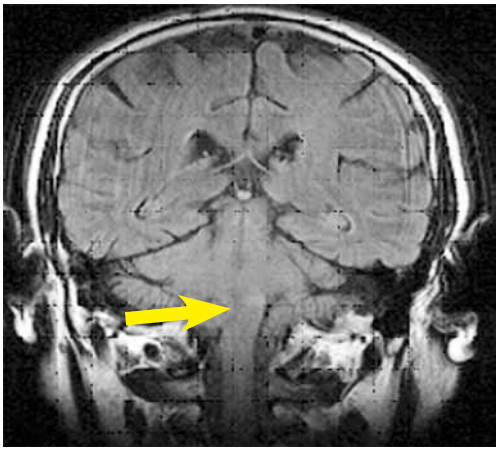

Figure 1. Brain MRI coronal FLAIR shows ischemic lesions in the brain stem (On the caudal part of the left side of brain stem, there is a hiperintense area with 5x6 mm dimensions and discrete hiperintense areas are present on the both sides of the pons).

Superficial abdominal reflexes were weaker on the left. Extensor plantar reflex (Babinski) was present left. Rombergs test was positiv. Gait was ataxic. Primitive reflexes: it was snout response presented.

Other investigations

On investigation the full blood count and routine biochemistry were normal. Screening with echocardiogram and X-ray chest were also normal. Without changes were TSH, T3 and T4 levels. Brucella tests and rheumatologic tests were negative. Prostate specific antigen (PSA) was negative. The abdominal ultrasound examination: the left kidney was missing (extirpated), the right one was with compensatory hypertrophy but without any urine present, ultrasound of carotid of blood vessels did no reveal stenosis or occlusion, CT of brain was normal. Brain MRI showed ischemic lesions in the brain stem (Figure 1). MRI of the spine cervical thoracic level revealed a fracture of the Th6 vertebrae, disc hernia to

the Th7/8 with narrowing the spinal canal and signs of spinal compression in this level with multiple protrusions of intervertebral discs in cervical and thoracic spine (Figure 2).

A cardiologic consultation established Hypertensio arterialis and physiatrist sugested physical therapy.

Discusion

Myasthenia gravis is one of the most challenging diseases when it comes to diagnosis and treatment.[1,3] Little is known about ishemic stroke in patients with myasthenia gravis. It is well known that several medical conditions may mimick stroke; however, myasthenia gravis mimicking stroke apears to be uncommon.[14,15] That is comprehensive, since myasthenia gravis has a number of symptoms in common with stroke-including fatigue, muscle weakness, slurred speach and swallowing difficulty. We presented here a patient with myasthenia gravis and brain stem stroke suffering a lot of symptoms as exacerbation of myasthenia gravis. Our patient with mysthenia gravis, developed ischemic lesions in the brain stem and also degenerative changes in the spinal cord with intervertebral right disc hernia to the Th7/8 and disc protrusions to the Th2/3 and Th6/7 level together with the fracture of Th6 vertebre. The vertebral and spinal cord patology was cleared up with MRI, which is still the best diagnostic modality providing to the clinician the best information.[16] We don't have data regarding eventual trauma. He has several risc factors for ischemic brain disease: hypertension, and he has been receving for six years now corticosteroids, immunossupresants and anticholinergic drugs.[15] Age of the patient, risc factors for cerebrovascular disease and the history of treatment for six years with corticosteroids and immunossupresive drugs indicate the possible linkage between ischemic changes in the brain stem and degenerative changes in the spinal colum with the therapy mentioned above for a long period of time.[12,15]

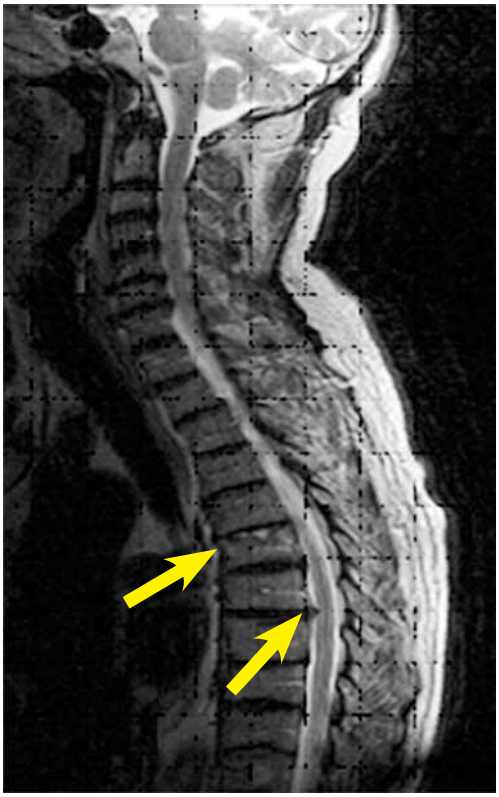

Figure 2. T2 MRI (sagittal image) of the spine cervical-thoracic level shows the fracture on the upper margin of the Th6. The intervertebral disc C3/C4 is presented with a dorsal median expansion. The intervertebral discs to the C5/C6 and C6/C7 are presented with a dorsal median expansion. The intervertebral discs to the Th2/Th3 and Th6/Th7 are presented with circular protrusions. Disc hernia to the Th7/Th8 with right dorsal paramedian expansion and narrowing of the spinal canal and signs of spinal compression.

Conclusions

Myasthenia gravis has a number of symptoms and signs which may be in common with stroke-including fatigue, muscle

weakness, slurred speach and swallowing difficulty. The reported case supports the opinion that several medical conditions as brain steam stroke may mimick myasthenia gravis, too.

The reason for presenting this case is to emphasize similarities and differences between these two disorders, especially when it comes to life threatening situations to which both can lead the particularly regarding treatment which usually is very different in different diseases. As for the described findings in the spinal cord without evidence of trauma in the past, we think that it is a case of casually comorbidity.

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Radiol Oncol 2009; 43(3): 175-179. doi:10.2478/v10019-009-0021-0

case report

Pineal gland metastasis of auricular squamous cell carcinoma: an unusual case and literature review

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Background. *The pineal gland is an unusual site for metastasis, and most metastatic pineal lesions are asymptomatic. Metastases to the pineal gland from skin cancer are extremely rare and reported mostly on autopsy series. Squamous cell carcinoma is the second most common type of skin cancer that occurs on the external ear. Auricular squamous cell carcinoma is an invasive and destructive tumour, and may cause hearing problems by local extension to the auditory canal. The vast majority of squamous cell carcinomas of the auricular region metastasize to the lung, bone, and brain.*

Case report. *We report the case of a patient with a giant squamous cell carcinoma of the auricula with extension deep into the temporal bone, metastasizing to the lung and pineal gland.*

Conclusions. *A metastasis should be considered as a possible cause, when encountering a mass in the pineal region, especially in elderly patients with a known primary cancer.*

Key words: pineal gland; metastasis; squamous cell carcinoma

Introduction

Metastases to the pineal gland region are rare, accounting for only 0.3% of all brain metastasis in a series from Japan[1] but ranges from 1.8% to 4% in other series. The most frequently reported sites of primary tumour involvement included breast and bronchogenic carcinomas, with melanotic, renal cell, pancreatic, ovarian, gastric, and frontal sinus malignancies being less common. To date there have been fewer than 100 reports of metastatic lesions in the pineal region.[1-6] In a large survey from Japan, metastases to the pineal region were found in 23 patients and the primary tumour sites were melanoma in five cases found at autopsy.[1] Cutaneous squamous cell carcinoma (SCC) is a common skin cancer. The most common sites of metastases are regional lymph nodes, lung, liver, brain, skin and bone. However, until now metastases to the pineal gland were not reported. Here

Received 26 January 2009
Accepted 4 May 2009

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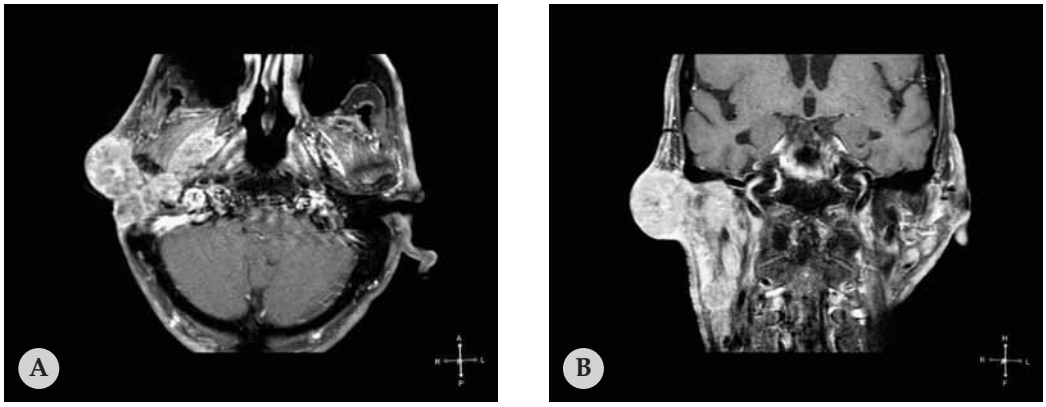

Figure 1. Cerebral MRI scans. (A) Axial spectral presaturation with inversion recovery (SPIR) image clearly demonstrates tumour invasion from the external auricular part deep into the temporal bone. (B) Coronal SPIR image delineate local aggressive extension of the squamous cell carcinoma to the cervical lymph nodes. Diffuse homogeneous contrast enhancement is seen after intravenous contrast injection in SPIR series.

we present, to the best of our knowledge, the first case of a skin squamous cell carcinoma that metastasized to the pineal gland.

Case report

A 75-year-old male farmer with progressive hearing loss and chewing problems was evaluated at the ear, nose, and throat outpatient clinic. The patient's history included the diagnosis of squamous cell carcinoma of the right auricula 15 years ago; the lesion was excised several times but recurred. Metastases to the right submandibular gland and right upper deep cervical chain lymph nodes were excised 6 years ago. Ten months previous, the patient was admitted to the hospital with haemoptysis and nonproductive cough, and multiple bilateral metastatic lung lesions were diagnosed on computerized tomography (CT) of the thorax. At that time, the patient underwent abdominal ultrasonography and cranial magnetic resonance imaging (MRI) to evaluate the possibility of metastases to other sites, and no other abnormality was found.

The patient had no other neurological signs or symptoms at the time of admission. On physical examination, he had an erythematous skin lesion on his right auricula and lesions of the lower lip and right hand. The auricular lesion had eroded the ear and tragus and obstructed the external acustic meatus. Cranial MRI was repeated, and its results showed that the auricular lesion invaded the temporal bone from the mastoid portion deep into the petrosal apex. Mastoid aeration was lost, and all parts of the temporal bone had an expansible character. Expansion in the petrosal part of the temporal bone exerted pressure on the muscles of mastication (Figure 1). In addition, an abnormal contrast-enhancing mass was observed in the pineal gland that was not seen on the previous cranial MRI (Figure 2 a,d). The well-defined mass was isointense on T1-weighted imaging and uniformly hypointense on T2-weighted imaging (Figure 2 b,c).

Discussion

Pineal metastases are generally considered unusual and incidental events that occur late in the course of widely metastatic systemic cancer. The first report of pineal

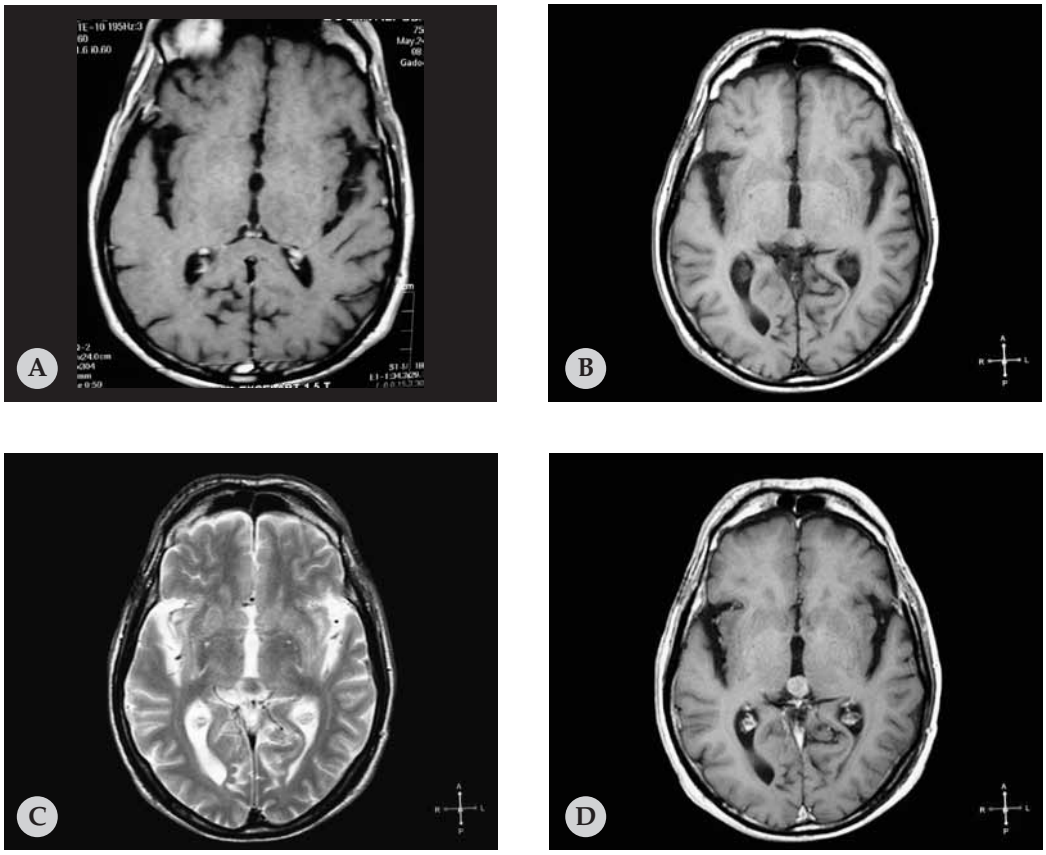

Figure 2. (A) Axial postcontrast T1-weighted image was normal when the patient was admitted to the hospital 10 months earlier. (B) Pineal mass is isointense on T1-weighted, (C) and uniformly hypointense on T2-weighted images. (D) Postcontrast T1-weighted axial images demonstrate uniform contrast enhancement.

gland metastasis was described in 1858 by Forster.[1] The most commonly reported primary tumours are carcinomas of the lung, breast, stomach, oesophagus, rectum, and kidney.[2] There also have been case reports of pineal region metastases from haematological malignancies and melanomas.[2] In a large number of older cases, metastases to the pineal gland likely metastases to the pituitary one were found at autopsy[3-7], but more recently, imaging, especially MRI, has markedly improved the earlier detection of such lesions.[2,8-12] Ortega *et al.*[4] found a 3.8% prevalence (5 cases) of pineal gland metastases in a cohort of 130 patients with the widespread neoplastic disease. Three of these cases had isolated pineal lesions, all of which had grossly replaced pineal tissue. The remaining 2 cases revealed other sites of intracranial involvement with only a minimal pineal gland replacement. Andrew *et al.*[12] observed a 5% prevalence in a series of patients referred for the surgical management of pineal gland tumours.

In a large survey of 7807 intracranial metastatic tumours in Japan,[1] metastases to the pineal region were found in 48 patients, for a frequency of 0.3%. Cases constituting a solitary mass, detectable by CT or MRI, were even less frequent. The primary tumour sites were lung (22 cases), breast (9 cases), malignancies of the gastrointestinal

tract (stomach, 3; oesophagus, 2; colorectal, 1), skin (melanoma, 5), hematologic system (multiple myeloma, 2; plasma cell leukaemia, 1; lymphoma, 1), kidney (clear cell carcinoma, which can also matastase to the pineal gland),[7] and frontal sinus.[1]

Squamous cell carcinoma is the second most common skin cancer, and it represents 20% of all cutaneous malignancies.[13] Certain cervicofacial regions, such as the ear and lower lip, are more prone to developing squamous cell carcinoma.[14] Squamous cell carcinoma of the external ear is a common diagnosis, and it occurs with greatest frequency on the superior or posterior portions of the helical rim. Several studies have demonstrated a higher recurrence rate as well as a poorer prognosis for squamous cell carcinoma of the external ear, compared to other cutaneous squamous cell carcinoma locations. Metastases from squamous cell carcinoma of the external ear occur in 5% to 18% of cases, compared to metastatic disease in only 0.5% to 2% of cutaneous squamous cell carcinoma occurring elsewhere.[15]

The lymphatic drainage of the auricula is plentiful, with at least 3 distinct lymphatic territories draining the skin of the auricula. It is useful to consider auricular squamous cell carcinoma separately from other high-risk squamous cell carcinoma when looking for potential markers of metastatic potential.[15] The parotid gland and the upper deep cervical chain are the most common sites of metastases.[15] The postauricular nodes are also frequently involved.[15] Auricular squamous cell carcinoma is associated with a significant mortality at 6.2%, which is usually due to the failure of control at the level of the local lymph node basins. Freedlander *et al.*[16] reported that tumours with a diameter over 3 cm have a metastatic potential of over 44%.

In the present patient, beside local recurrences of squamous cell carcinoma, submandibular gland and upper deep cervical chain lymph node metastases were found during the course of the disease, all of which caused local effects in the head and neck region. This patient also had widespread lung metastases that caused systemic complaints. Interestingly, the patient did not exhibit any neurological symptoms related to pineal metastases at the time of admission.

History of malignancy is the most important factor in differentiating metastatic intracranial disease from a primary lesion. In patients with a known history of malignant neoplasm, approximately 90% of supratentorial lesions represent metastases.[11] Young adults and children usually are those affected by primary pineal tumours. Our patient had a primary squamous cell carcinoma of auricular skin and was elderly, both of which are consistent with metastases to the pineal gland. The results of the patient's previous cranial MRI were normal when his lung lesions were diagnosed 10 months earlier. All of these factors led us to a diagnosis of metastatic disease, rather than a primary pineal tumour.

In conclusion, when encountering a mass in the pineal region, a metastasis should be considered as a possible cause, especially in elderly patients and those with a history of malignancy. Although such metastases are rare, the present patient provides information that might be useful for diagnosis.

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Radiol Oncol 2009; 43(3): 180-186. *doi:10.2478/v10019-009-0023-y*

research article

Segmenting CT images of bronchogenic carcinoma with bone metastases using PET intensity markers approach

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Background. *The evolution of medical imaging plays a vital role in the management of patients with cancer. In oncology, the impact of PET/CT imaging has been contributing widely to the patient treatment by its large advantages over anatomical imaging from screening to staging. PET images provide the functional activity inside the body while CT images demonstrate the anatomical information. Hence, the existence of cancer cells can be recognized in PET image but since the structural location and position cannot be defined on PET images, we need to retrieve the information from CT images.*

Methods. *In this study, we highlight the localization of bronchogenic carcinoma by using high activity points on PET image as references to extract regions of interest on CT image. Once PET and CT images have been registered using cross correlation, coordinates of the candidate points from PET are fed into seeded region growing algorithm to define the boundary of lesion on CT. The region growing process continues until a significant change in bilinear pixel values is reached.*

Results. *The method has been tested over eleven images of a patient having bronchogenic carcinoma with bone metastases. The results show that the mean standard error for over segmented pixels is 33% while for the under segmented pixels is 3.4%.*

Conclusions. *Although very simple in implementation, region growing can result in good precision ROIs. The region growing method highly depends on where the growing process starts. Here, by using the data acquired from other modality, we tried to guide the segmentation process to achieve better segmentation results.*

Key words: computed tomography segmentation; dual modality imaging; PET/CT

Introduction

Bronchogenic carcinoma normally known as cancer of the lung is the most frequently diagnosed "major" cancer in the world.[1] It is a common disease and a leading cause of death in many countries.[2,3] Lesions occur in breast, lung, prostate and kidney

Received 24 February 2009
Accepted 28 May 2009

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comprised 80% of all metastases to bone. In 1990, estimated 1.04 million new cases of lung cancer were diagnosed; representing 12.8% of total cancer incidence worldwide.[1] The prevention and early diagnosis of lung cancer thus assumes a major public health issue. Bone scan demonstrates the possible evidence of bone metastasis. The study by Kiho Kim *et al.*[4] suggests that bone scanning with 99m- monodiphosphate detected early bone metastases in patients with bronchogenic carcinoma before their lesions became evident clinically or radiographically. A group of researchers from Clinical Radiology of Kyushu University studied the comparison of Positron Emission Tomography (PET) using 18-F-Fludeoxyglucose (18-F-FDG PET) with 99mTc-HMDP scintigraphy for the detection of bone metastases in patients with breast cancer. Their results showed that 18-F-FDG PET tends to be superior to bone scintigraphy in detecting osteolytic lesions, but inferior in the detection of osteoblastic lesions.[5] The evolution of the imaging plays a vital role in managing the patients with lung cancer. The role of imaging ranges from screening lung cancer in high risk individuals to staging bronchogenic carcinoma in advanced stages of the disease.[6]

Tomography is a tool that provides information on what is actually happening inside the body. Positron Emission Tomography (PET) scans and Computerized Axial Tomography (CAT) scans or also known as Computed Tomography (CT) scans are all used to provide information about possible tumours and metastases of cancer. Tomographic imaging methods are important since proper staging of cancer is basic in planning the best treatment.[3,6]

PET images provide information about the functional and metabolic activity of a lesion while CT images demonstrate the anatomical location and the structural information. Integration of Positron Emission Tomography with Computed Tomography (PET/CT) imaging is becoming more popular and useful in the clinical application for an early tumour and cancer detection.[7-9] Superimposing the images of functional activity on structure gives the best of both imaging modalities – the anatomical detail of the CT and the ability to find small clumps of viable cancer cells of the PET. Initial studies by De Wever W *et al*.[2] demonstrate better results for PET/CT in the staging of lung cancer in comparison with PET alone, CT alone or visual correlation of PET and CT.

Although fusion techniques have helped visual perception of dual modality images, hundreds of images that are taken for each patient using this modality and analyzing all of them take time and expertise. The image segmentation procedure simplifies the image presentation and canalization. The importance of segmentation in medical images is to extract and characterize anatomical structures with respect to some input features or expert knowledge.[10] The medical image segmentation is a challenging task due to the various characteristics of the images which lead to the complexity of segmentation. In general, the autonomous segmentation is one of the most difficult tasks in digital image processing.[11] To address the problem, we introduced a new algorithm based on the supervised automatic segmentation which, we believe, can improve the diagnosis of bronchogenic carcinoma with bone metastases.

Conventionally, monitoring, treatment arrangement and assessment of response after the radiation therapy (RT) are mainly based on CT and MRI.[12,13] These methods, also called anatomical imaging, have the major advantage of viewing the anatomy with a high resolution and drive to the contribution on the highly sophisticated RT techniques such as the three-dimensional, conformal RT, stereotactic RT and radio surgery, intensity modulated RT (IMRT)

and RT with heavy particles.[13,14] All these techniques aim to concentrate the irradiation dose on the lesion area with high precision to spare the normal tissue. Generally, the higher the irradiation dose, the higher is the rate of local tumour control, whereas the lower irradiation dose in normal tissue leads to lower side effect risks.

High activity lesions in PET images always appear with higher intensity due to more absorbent of radio isotope tracer and higher rate of radio activity.[15] Cancer cells have higher activity compare to normal tissue, hence, they absorb more tracer material and the amount of radio activity increases in these cells. PET detectors detect photons propagated by this radio activity and produce an image, showing high activity pixels differently.

Methods

In this study, the patient was fasted overnight prior to the scanning day and injected with *18F-fluorodeoxyglucose (*18F-FDG) radionuclide 45 min before the scan. All imaging studies were performed on a dual-modality PET/CT device (Biograph 6, Siemens Medical Solutions Inc.). PET/CT images were acquired with the patient in the supine arms-up position and acquisition time was 3 min per bed position with seven bed positions covering from vertex to the mid thigh. CT imaging was performed prior to PET imaging with the patient in the same position. A bolus injection of 100 mL iodinated contrast media (Omnipaque 300, Amersham Health) was given intravenously. Acquisition parameters for 6 slices CT were 130 kV, 60 mAs, 0.8 s per CT rotation, 2.5 mm slice thickness, pitch 1.5.

Previously, one bed position of the oncological body investigation would take around 5 min to complete but scanners of the last generation need at least 1 – 3 min. The oncological whole body scan consisting of 6 to 8 bed positions still takes about 10 – 20 min.[13] Due to the limitations of PET imaging device on a relatively low spatial resolution, the restricted anatomic tumour location and limited possibilities to be co registered separately, new PET/CT scanners have been developed on a same platform and the patient will be imaged for both PET and CT at the same time and lying on the same bed with unchanged patient positioning.[16] Thus, little or no patient movement helps registration process not to be too complicated.[17]

Registration and segmentation are important steps in image post processing for radiotherapy. Here, images have been registered using the cross correlation.[18] The cross correlation coefficient matrix of both images has been calculated and the maximum value in that matrix which shows where images are best correlated has been selected. The location of this maximum value indicates where the images are best correlated. Images are then transformed and registered on each other to the position which they are best correlated.[11]

Our segmentation procedure starts by looking through PET image and selecting pixels with maximum value as candidate points that represent high activity and may lead to cancer tumours. Coordinates of these pixels will be used to segment the Region of Interest (ROI). Note that at each step the highest pixel value will be selected, so defining different brightness and contrast will not affect the pixel selection procedure. The overall segmentation procedure is shown in Figure 1.

Segmentation algorithms are mostly categorized in two approaches. One is the region based which relies on homogeneity of features and the other which is based on boundary finding and discontinuity measures.[19] Among these methods Region Growing has become very useful and prac-

tical due to simplicity of implementation.[20] Seeded Region Growing (SRG) has been chosen as segmentation algorithm of choice to segment CT image and candidate points found on PET have been used as seeds to a guide segmentation procedure.

Seeded Region Growing algorithm operates by using the coordinates given to it as starting points and expanding the Region of Interest (ROI) by checking their bilinear neighboring pixels. Each pixel value which is in a significant difference interval with the candidate point will be added to the ROI. This interval is set manually by the user so the sensitivity of region growing process can be defined depending on which part of body is going to be diagnosed. The growing process will continue until there is no other bilinear neighboring pixel that falls in the defined interval. Once all the relatively similar pixels have been added to the region, the growing process will stop.

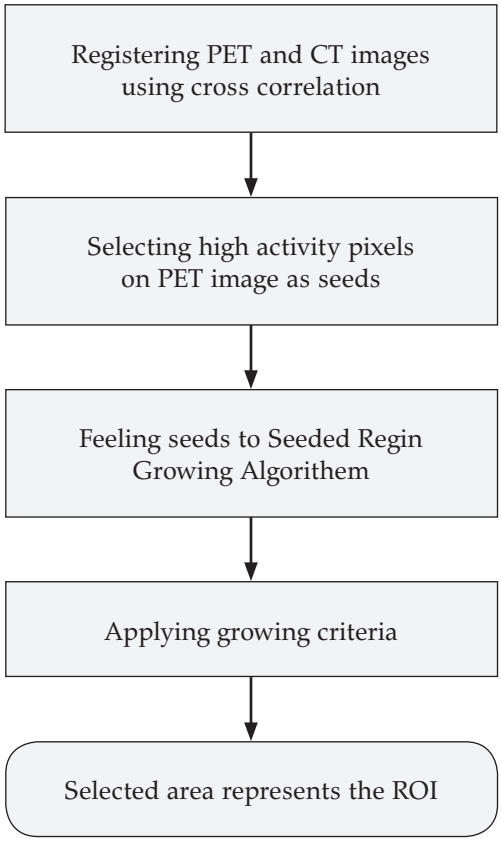

Figure 1. The overall segmentation procedure.

Results

In this experiment, 11 images from dual modality PET/CT imaging device (Biograph 6, Siemens Medical Solutions Inc.) have been used. Figure 2 shows a series of CT (first row), PET (second row) and PET/CT fused images (third row) of a patient having Bronchogenic Carcinoma with Bone Metastases. Areas of highest activity have been marked with arrows and can be easily seen in PET and PET/CT fused images.

In order to evaluate the segmentation process, areas of interest have been selected manually and surveyed by a professional radiologist as benchmarked images. Images shown on Figure 3 (second row) show the manually segmented region which we address as desired ROIs. The method has been applied on all images and the significant interval has been set for each image to make the segmented area as close to ideal segmentation as possible. Figure 3 (first row) shows the result of segmentation on image series shown in Figure 2. As can be seen in Figure 3, the first and last images show relatively same segmentation results with the desired ROI. The segmentation result on second image shows spots of under segmentation. In general, the method has been able to search and find the correct ROI, and visually, there is not much differ-

Table 1. Standard error of the segmentation process

	Over Segmented Pixels	Under Segmented Pixels
Mean Standard Error	33%	3.4%

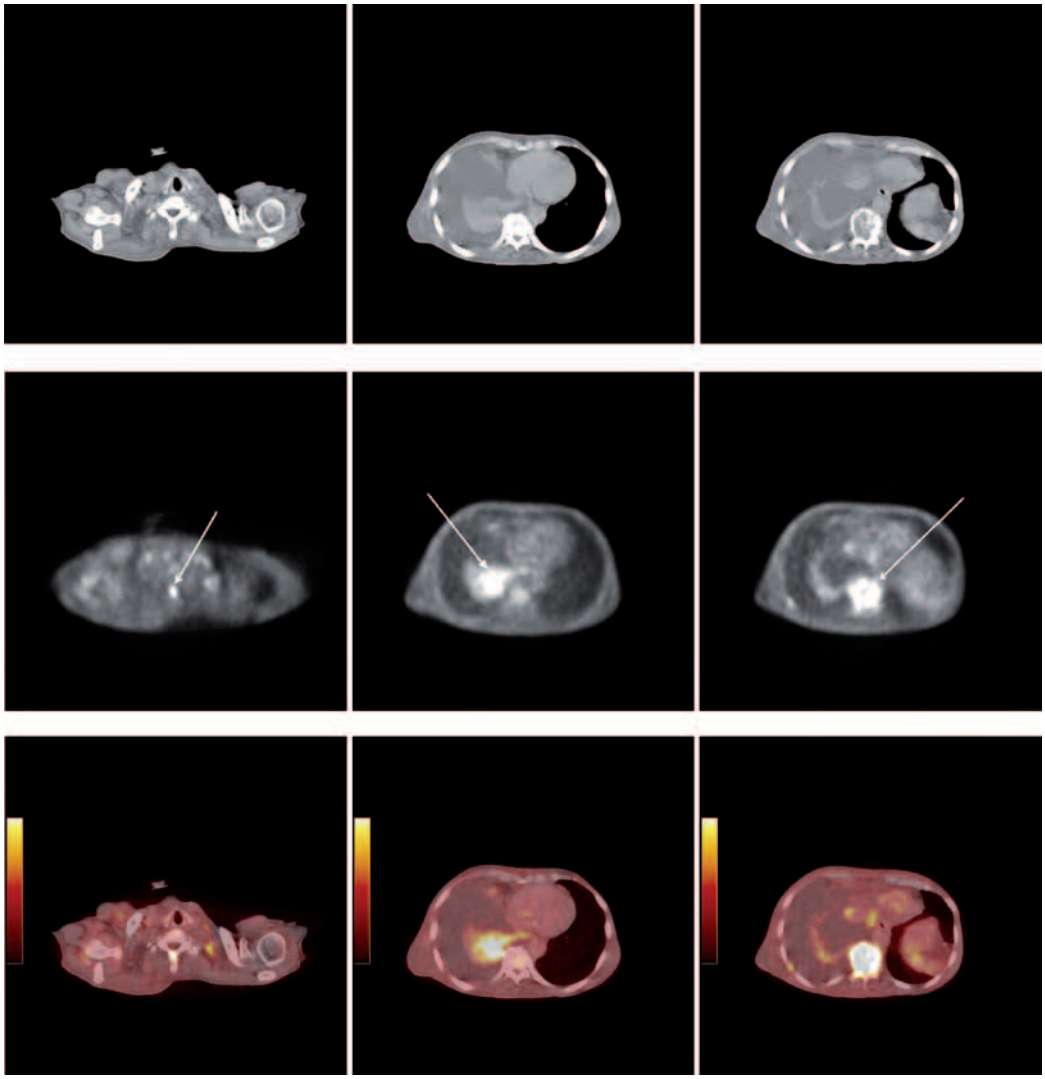

Figure 2. First row CT images, second row PET and the third row PET/CT fused image of a patient having Bronchogenic Carcinoma with Bone Metastases. The arrows indicate the highest activity areas.

ence between the proposed method and the benchmark data.

To look into the details, a standard error percentage has been calculated based on the number of pixels over and under segmented compare to desired segmentation for each image and their average has been calculated. Table 1 shows the percentage of over and under segmentation cause by SRG process.

As shown on Table 1, SRG suffers from over segmenting to homogenous neighboring areas. The small percentage of under segmentation is due to relatively bright or dark spots inside the segmented ROI which could not be prevented. An example of under segmentation can be seen in segmentation results on Figure 3 second image, which shows small dark spots in the segmented area. The individual segmentation

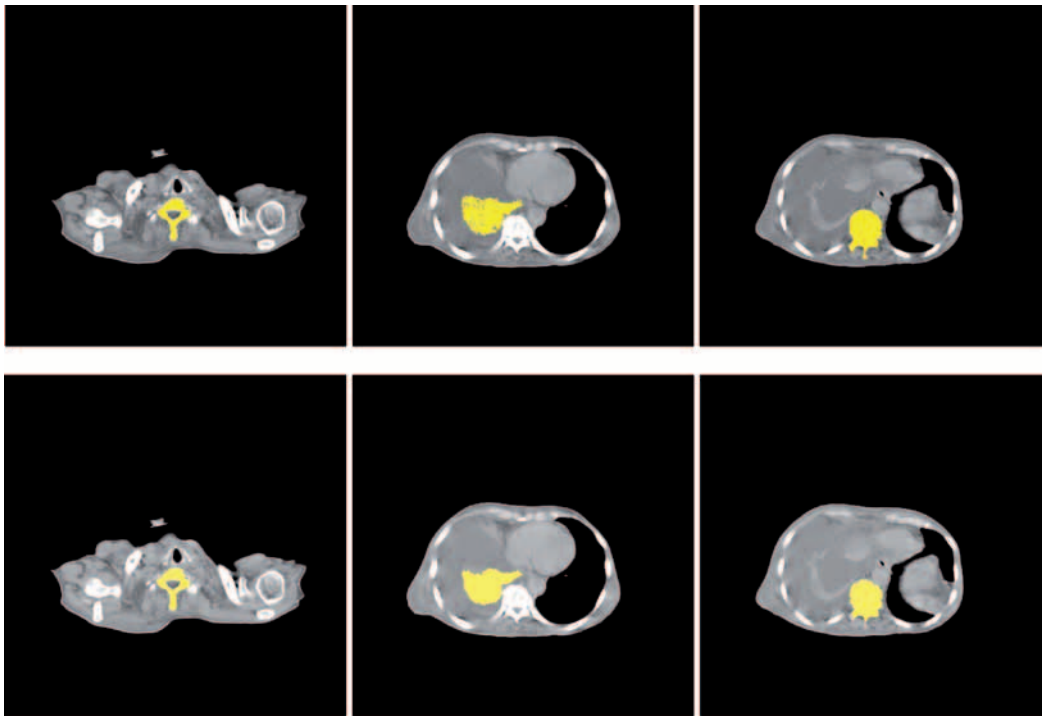

Figure 3. First row segmentation results and second row the desired ROI.

errors on each image have been shown as a chart on Figure 4.

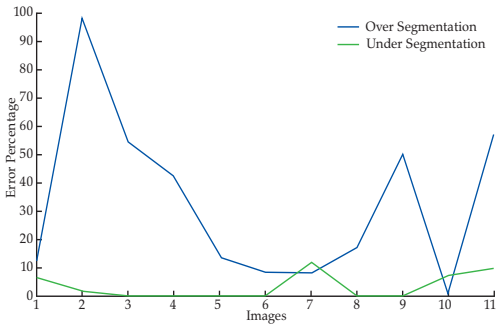

Figure 4. Over and under segmentation percentage of the SRG process.

Discussion

The image segmentation is a blind task and there have been lots of researches to guide segmentation in a way that results in the better precision ROI selection. Here, by acquiring dual modality imaging we have used PET image to guide segmentation on CT image.

Region growing algorithm highly depends on where the growing process starts and how to control it in order to avoid over growing to homogenous neighboring area.[21] The method described here uses predefined data to start segmentation, so from the starting point the area to be segmented is a part of the desired ROI but the whole segmentation process may be improved by using other aspects of region growing than manually selection of growing criteria.

This method is considered as a supervised automatic segmentation since at each step the growing interval needs to be defined by the user. Although the method has proven that it is possible to guide seeded region growing segmentation using hot spots from other modality, there still exist

a limitation on the selection of high activity points since it is not necessarily the highest active point that represents malignancy.

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Radiol Oncol 2009; 43(3): 187-194. *doi:10.2478/v10019-009-0019-7*

research article

Treatment of patients with "high grade" extremity localized chondrosarcoma. Preliminary results

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Background. *The treatment of high-grade chondrosarcoma consists of either amputation or radical surgical resection of the tumour. Introducing protocols with neo-adjuvant chemotherapy improves survival rates in patients with a high-grade chondrosarcoma.*

Patients and methods. *In 7 years period (2000-2006), 18 patients with chondrosarcoma were treated. Female were twice more than male (12/6). Patients age varied from 14 to 73 years (mean 51). Thirteen patients (72%) had extremities localised chondrosarcoma. Eight patients (8/13), or 62% with extremity localised high-grade chondrosarcoma were subjected to Scandinavian Sarcoma Group XVI chemotherapy protocol. Six of these patients (75%) complied with the criteria for limb salvage.*

Results. *The follow up was from 13 months to 8 years (mean 32 months). Two patients (2/8) or 25% had primarily amputated limb. After the hystopathological assessment of the resected high-grade chondrosarcoma, 6/8 patients (75%) had bad response to neoadjuvant chemotherapy. There was local recurrence in 3/8 (37%) and metastases developed in 6/8 (75%) of the operated patients with high-grade chondrosarcoma. Two of 6 patients (33%) with limb-salvage had amputations due to local recurrence. Two patients (2/8), or 25%, survived more than 5 years, and up to date they are disease-free.*

Conclusions. *Patients with extremities localised high-grade chondrosarcoma had higher survival rates and better functional outcome, compared to those with chondrosarcoma localised centrally.*

Key words: chondrosarcoma; limb-sparing; neo-adjuvant chemotherapy

Introduction

Chondrosarcomas are very rare tumours.[1] Their incidence varies from 2 to 3 cases on 1 000 000 inhabitants.[2,3] They usually appear in the 2nd or in the 4th decade of life, affecting active and most productive patients.[4,5] It is well known that they poorly react to chemotherapy, therefore, the radical surgical resection is essential in their

Received 23 January 2009
Accepted 8 April 2009

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treatment. There are very few published data on the survival, efficacy and role of chemotherapy of high-grade chondrosarcoma patients.[6,7] This facts were the motives for this study, and the aim was to analyse the chemotherapy protocol and various limb-salvage surgical techniques in correlation to survival of patients and function of spared limbs.

Patients and methods

In 7 years period (2000-2006), on the Clinic for Orthopaedic Surgery in Skopje, 18 patients with chondrosarcoma were treated. Female patients were twice more than male (12:6). Patients age varied from 14 to 73 years (mean 51).

Five of these patients, or 28%, had a central localised chondrosarcoma (3 on the pelvic ring, 1 on the rib and 1 on the scapula). The rest 13 patients had chondrosarcoma localised on extremities (Figure 1). Eight patients (8/13), or 44% with extremity localised high-grade chondrosarcoma were subjected to Scandinavian Sarcoma Group XVI chemotherapy protocol. Six of this patients (75%) complied with the criteria for limb salvage (Enneking stage IIA and IIB).[8]

Only 8 of 18 patients (44%), with high-grade chondrosarcoma were included in the further analysis. These patients must comply with following inclusion or exclusion criteria.

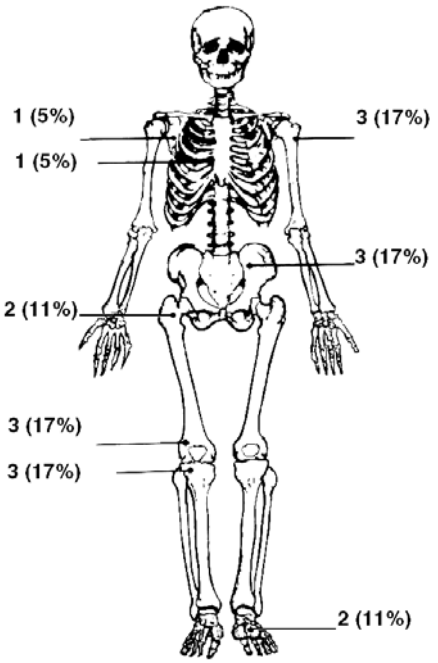


Figure 1. Anatomic distribution of chondrosarcoma in the patients.

Inclusion criteria

The selection of patients for the study inclusion was based on the following criteria:

Histopathologically proven high-grade osteosarcoma (grade III or IV); with no evidence of lung or other metastases; patient age between 8 and 65 years; normal hepatic and renal function; leukocyte count over $3.0x10^9$/L and platelet count over $100x10^9$/L; neo-adjuvant chemotherapy was introduced not longer than 1 month after the histological diagnosis of osteosarcoma.

Exclusion criteria

Exclusion criteria were: evidence of lymphatic or haematogenous metastases at the time of diagnosis; patients under 8 years or older than 65 years; pregnant or a nursing women.

Diagnostic procedures and treatment

The diagnosis was made by clinical examination, plain X-rays, CT, MRI and histopathologically with open biopsy. Staging was done with Tc 99m bone scan, chest X-rays and CT, and CT of the region with osteosarcoma. For the preoperative planning, MRI and standard or CT arteriography were carried out. After the completion

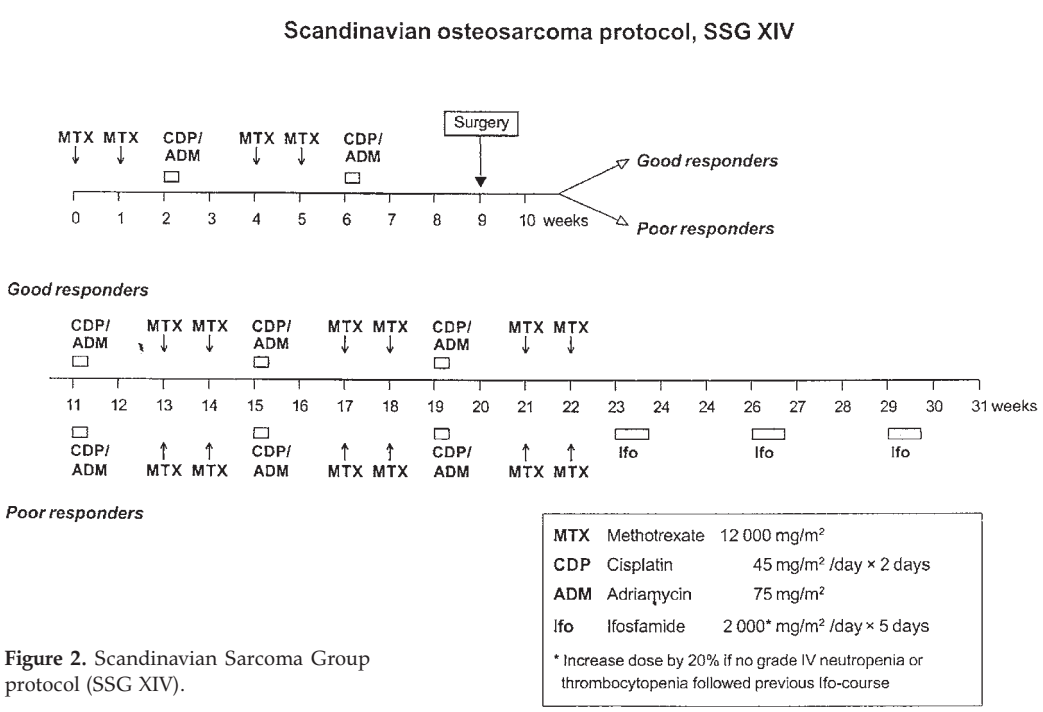


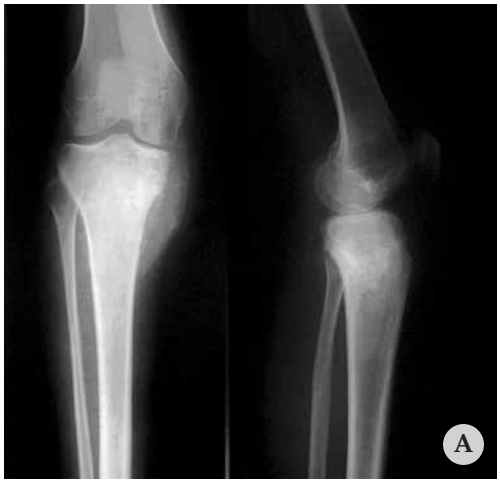
Figure 2. Scandinavian Sarcoma Group protocol (SSG XIV).

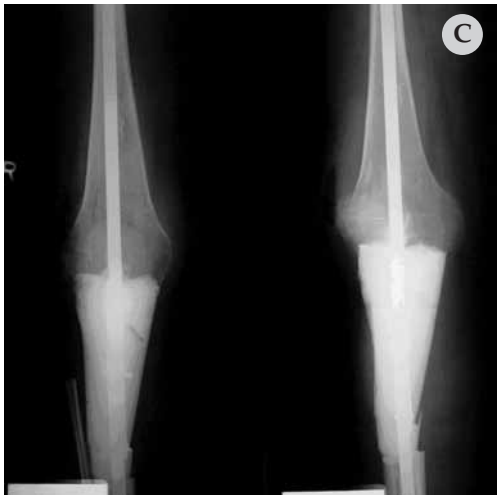
of the chemotherapy protocol, clinical and radiographic evaluation of the patients was done every 3 months in the first 3 years and twice a year thereafter.

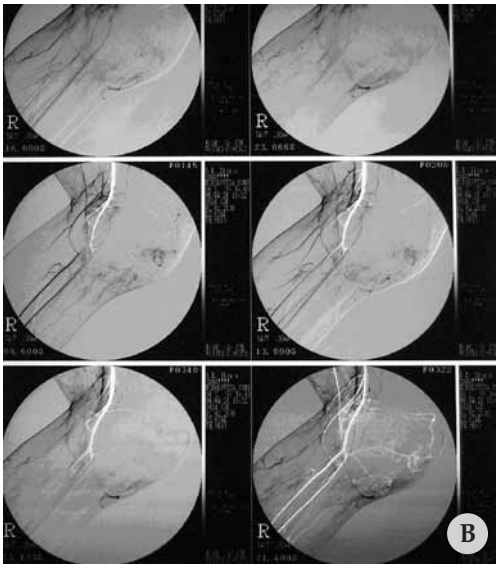
Eight of 18 patients (with high-grade chondrosarcoma) were administered to the Scandinavian Sarcoma Group XIV neoadjuvant chemotherapy protocol (SSG XIV). Patients received 2 cycles of preoperative chemotherapy (high dose methotrexate 1200 mg/m^2, cisplatin 45 mg/m^2/ x 2 days and doxorubicin 75 mg/m^2; (Figure 2). The surgical resection of the osteosarcoma was made 9 weeks after the beginning of neoadjuvant chemotherapy.

After the resection, a detailed histopathological assessment of the specimen was done to determine the extent of necrosis of the tumour tissue. Considering the percentage of necrotic tumour tissue, patients were classified into two groups. The first group was with good response to chemotherapy (>90% necrosis of the tumour). The second group was with a poor response to chemotherapy (>10% viable tumour). Regarding good or poor response of the tumour to chemotherapy, patients followed different branches of the protocol. All 8/18 patients received 3 courses of postoperative chemotherapy (the same as preoperative). After the hystopathological assessment of resected high-grade chondrosarcoma, 6/8 patients (75%) had bad response to neoadjuvant chemotherapy. Patients with a poor response received 3 more cycles of chemotherapy with a high dose Ifosfamide 2000 mg/m^2/day x 5 days plus uromitexan (Ifosfamide: uromitexan = 1:2). The course was repeated every 3 weeks (Figure 2).[7,9]

For the patients who could not satisfy the principles of limb preservation, the ablative surgery was taken into consideration. For those patients the disarticulation of the hip or shoulder griddle, femoral or below the knee, humeral or other amputations were more appropriate.[2-4,8,9] When tumour-







Figures 3 A,B,C. Preoperative X-ray, arteriography and postoperative X-ray of a patient with high-grade chondrosarcoma of proximal tibia, after resection reconstructed with modified Campanacci method.

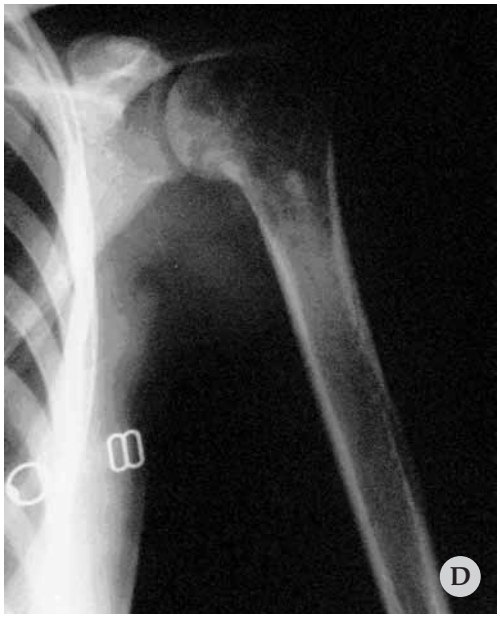
free margins were obtained, a large skeletal defect was often present, requiring the reconstruction of a bone, muscles, other soft tissues, and skin. Patients' age, tumour location and extent of resection narrowed the list of appropriate surgical alternatives.[10,11]

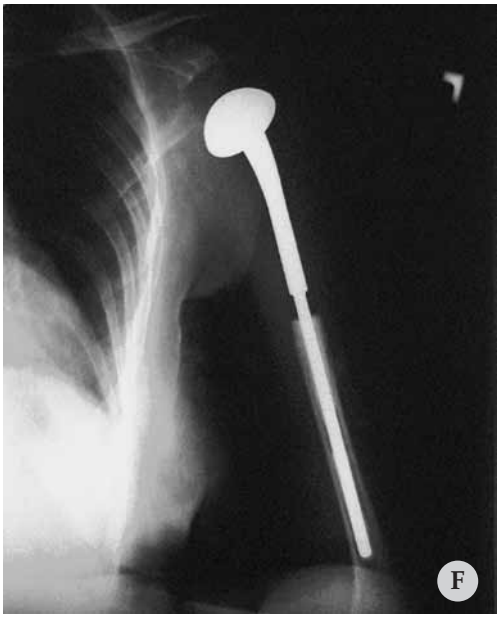
Several options for limb-sparing procedures were available:[12]

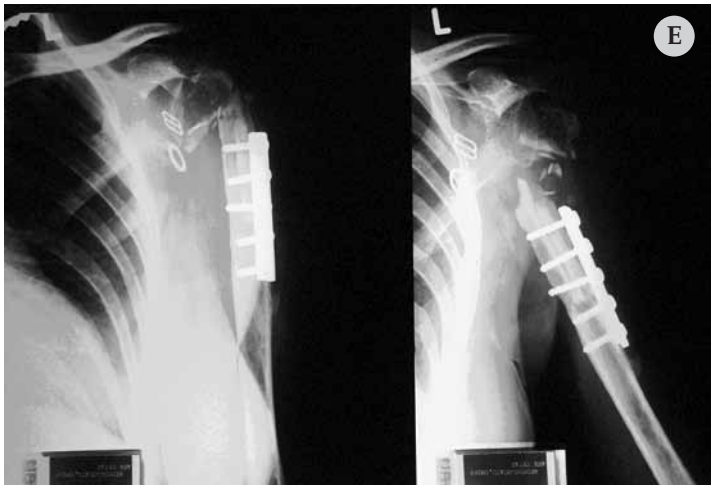
- resection arthrodesis and other special indication techniques (Figures 3a-c),[3,11]
- modular or special expanding endoprosthesis (Figures 3d, 3f),[13,14]
- cortico-spongious or bulk allograft (Figure 3e).[13,15]

Musculoskeletal Tumour Society score (MSTSS), based on the Enneking' system for the functional evaluation of reconstructive procedures, was used to determine the functional results. This scoring system evaluates pain, function, patient's emotional acceptance (pertinent to a patient as a whole) and specific factors for evaluating the upper limb (range of motion, manual dexterity and lifting ability) or the lower limb (need of support with orthopaedic accessories, ability to walk and gait). For each of 6 factors, values from 0 to 5 are assigned, with total of 30 (or 100% function of the limb). For each factor, values 1, 3 and 5 are equated with criteria levels of the achievement or performance. Intermediate values of 2 or 4 are assigned, based on the examiner's judgment, when the achievement or performance falls between the specified values. It is recommended results to be reported numerically in percentage of the normal function (last column in Table 1).[16]

Results were updated in December 2008.







Figures 3 D,E,F. X-ray of a patient with high-grade chondrosarcoma of proximal humerus; fracture of the reconstruction with fibular graft 16 months after the operation and x-ray after implantation of special tumour endoprsthesis in the same patient.

Results

The follow-up was 2-8 years (mean 36 ± 13 months). Eight of 18 patients (44%) were with a high-grade chondrosarcoma. Clinical data of patients with high-grade chondrosarcoma treated with chemotherapy and surgery are shown in Table 1. Two (2/8) patients (25%) had primarily amputated limb. Six (6/8) patients or 75% comply with criteria for limb-salvage. After the hystopathological assessment of a resected high-grade chondrosarcoma, 6/8 patients (75%) had a bad response to neoadjuvant chemotherapy. Six (6/8) patients, or 75% had minor or major postoperative complications. Complications developed in period of 1 to 6 months postoperatively (mean 4 ± 1). Most of the complications were seen after the 4th month.

Table 1. Clinical data of patients with a high-grade chondrosarcoma treated with chemo and surgery.

	Age	Gender (M/F)	Compli-cations	Recurrence (months)	Metastases (months)	Reoperat.	Died after (months)	Follow-up (months)	MSTSS (%)*
Patients with limb-salvage									
1	51	F	2	17	35	Yes	44	44	47%
2	14	F	0	0	0	No	0	67	93%
3	56	M	4	1	4	Yes	7	7	23%
4	65	M	1	0	0	Yes	0	99	53%
5	45	F	1+3	10	13	Yes	47	47	87%
6	64	M	3	0	16	Yes	31	31	50%
Patients with amputations									
7	65	F	0	0	9	No	20	20	/
8	14	F	3	11	15	No	21	21	/

Complications: 1- loosening or fracture of the reconstruction, 2- vein thrombosis, -skin necrosis 4- lung emboly.
***MSTSS**-Musculoskeletal Tumour Society Score.

There was local recurrence in 3/8 patients with a high-grade chondrosarcoma, or 37%. The recurrence developed in period of 1 to 19 postoperative months (mean 11±7). Most of the recurrences developed after the 10th month (Figure 4). Two of 6 patients (33%) with limb-salvage had amputations due to local recurrence.

Metastases developed in 6/8 of the patients (75%) with high-grade chondrosarcoma, in period of 1 to 35 months postoperatively (mean 17±10). Most of the metastases developed after the 16th month (Figure 4). Patients who developed metastases died in the period of 13 months to 4 years postoperatively (mean 28±14 moths).

Two patients (2/8), or 25%, survived more than 5 years, and up to date they are disease-free.

Musculoskeletal Tumour Society score was used for the evaluation of the function of the operated patients and results of the operated limbs were shown as percentage of the maximal function. In our study, the

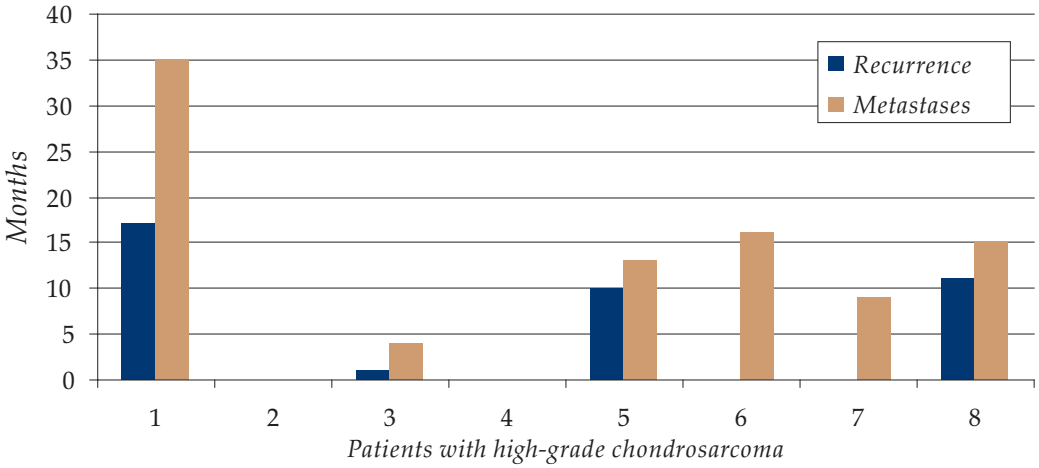


Figure 4. Local recurrence and distant metastases in patients with high-grade chondrosarcoma in our study.

function after limb-salvage procedures varied from 23% to 93% (median 59%).

Discussion

The incidence of local recurrence, metastases and prognosis of the chondrosarcoma treatment are highly variable and hard to predict.[3,6] Chemo and radiotherapy have low impact on the final outcome. The radical surgical resection of chondrosarcoma is primary treatment.[4,5] There are very few published data on the survival, efficacy and role of chemotherapy of high-grade chondrosarcoma patients.[6,7] Lately, some authors separate a high-grade chondrosarcoma as a special diagnostic and treatment problem.[10] Introducing protocols with a neo-adjuvant chemotherapy should improve survival rates in patients with high-grade chondrosarcoma.[2,7,15]

Our primary goal was to radically extract the tumour, and limb salvage was done only in carefully selected patients. We followed four basic principles of limb-sparing procedures: (1) local recurrence should be no greater and survival no worse than by amputation; (2) the procedure, or treatment of its complications, should not delay the adjuvant therapy; (3) reconstruction should be enduring and not associated with a large number of local complications requiring secondary procedures and frequent hospitalizations; (4) function of the limb should approach that obtained by amputation, although body image, patients preference and life style may influence the decision.[6,10,14,15] If multidisciplinary approach is accepted, and educated medical stuff in principles of tumour surgery is engaged, more than 50% 5-year survival is achievable. Similar or better results are reported in many studies.[9,10,13-15]

Eight of 18 patients (44%) in our study had a high-grade chondrosarcoma and were subjected to Scandinavian Sarcoma Group Protocol XVI. Two (2/8) patients (25%) had primarily amputated limb. Six (6/8) patients or 75% comply with criteria for limb-salvage, and 2 of them (33%) had amputations due to the local recurrence. After the hystopathological assessment of a resected a high-grade chondrosarcoma, 6/8 patients (75%) had bad response to neoadjuvant chemotherapy. High percentages of bad response to neoadjuvant chemotherapy are corresponding with results published in some other studies.[2,7] Two patients (2/8), or 25%, survived more than 5 years, and up to date they are disease-free. Function after limb-salvage procedures in our study varied from 23% to 93% (median 59%).

Conclusions

Patients with extremities localised high-grade chondrosarcoma had significantly higher survival rates and better functional outcome, compared to those with chondrosarcoma localised centrally. Introducing protocols with neo-adjuvant chemotherapy improves survival rates in patients with high-grade chondrosarcoma.

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Radiol Oncol 2009; 43(3): 195-202. *doi:10.2478/v10019-009-0029-5*

research article

Comparison between hypoxic markers pimonidazole and glucose transporter 1 (Glut-1) in murine fibrosarcoma tumours after electrochemotherapy

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Background. *Tumour hypoxia occurs as a result of an inadequate supply of blood-borne oxygen due to the disorganized and chaotic vascular network that develops in tumours. Because tumour hypoxia has been associated with a more aggressive phenotype and lower cure rate, there is a recognized need for a method of measuring tumour hypoxia that is suitable for widespread clinical use. The aim of the current study was to compare the expression of Glut-1 with the binding of the bioreductive hypoxia marker pimonidazole and to elucidate the characteristics and pitfalls when they are used as hypoxic markers.*

Materials and methods. *In the study, SA-1 solid subcutaneous tumours in A/J mice were treated by bleomycin given i.v. (1 mg/kg), or the application of electric pulses (8 pulses, 1400 V, 100 μs, 1Hz), or a combination of the two - electrochemotherapy. Pimonidazole was injected 16 hours before tumour excision. Tumours were excised at different time points (0.5, 1, 2, 8, 14 and 24 hours) after therapy. Immunohistochemistry for Glut-1 and pimonidazole adduct was carried out on two consecutive tumour sections and the percentages of positive staining areas were determined.*

Results. *Glut-1 staining was membranous and typically expressed peri-necrotically, whereas pimonidazole staining, although showing substantial co-localisation with Glut-1, was cytoplasmatic. More than 65% of the stained areas showed a high degree of colocalization when the two markers were compared. Our results show that Glut-1 expression significantly correlates with the level of pimonidazole binding ($r = 0.41$; $p = 0.028$).*

Conclusions. *Our study confirms that HIF-1 regulated genes, such as Glut-1, have potential for future use as predictors of a decreased sensitivity of tumours to radio- and chemotherapy mediated by hypoxia.*

Key words: hypoxia; pimonidazole; Glut-1; electrochemotherapy

Received 1 July 2009
Accepted 19 August 2009

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Introduction

Measurements of oxygen partial pressure in tumours performed with microelectrodes have yielded novel information concerning the contribution of the tumour

oxygenation status to the course of malignant growth and have shown that the presence of hypoxic areas to be a universal characteristic of solid malignant tumours.[1] Tumour hypoxia, mostly resulting from poor perfusion and anaemia, is one of the key factors for induction and development of tumour cell clones with an aggressive and treatment resistant phenotype, which leads to rapid tumour progression and poor prognosis.[2,3] Tumour hypoxia has an impact on such fundamental aspects of malignancy as a) cell survival and proliferation, b) angiogenesis, c) cancer cell invasiveness, d) metastasis, e) resistance to apoptosis, and f) genetic instability.[4] The expression of more than 70 genes is altered under hypoxic conditions, as a result of the change in stability of a critical transcription factor called hypoxia inducible factor-1 (HIF-1), which allows a tumour to survive the harsh tumour microenvironment.

Direct assessment with oxygen electrodes is often referred to as a gold standard, but is still considered to be an experimental tool. Since O_2 microelectrode measurements are invasive and applicable only to tumour entities accessible to needle electrodes, there is great interest in substitute methods for assessing of the oxygenation status. Bioreductive markers, such as pimonidazole, provide an alternative approach for assessing of the level and extent of tumour hypoxia. Pimonidazole, administered approximately 16 h prior to tumour excision, is reductively activated in an oxygen-dependent manner and is covalently bound to thiol-containing proteins in hypoxic cells, forming intracellular adducts that can be detected immunohistochemically.[5,6] A clinical comparative study has recently demonstrated a correlation between microelectrode measurements of pO_2 and the extent of pimonidazole adduct formation in carcinoma of the cervix.[7] However, studies on archived material are not possible because the drug must be administered prospectively.

There is an increasing need for endogenous markers to assess the presence of hypoxia. Endogenous markers would have additional advantages, since they do not require the application of a foreign substance and would allow studies of oxygenation status in archival paraffin material.[8] Glucose transporter- 1 (Glut-1) is one of the proteins upregulated in a hypoxic condition. In a tumour microenvironment, hypoxia results in an increased transcription of the Glut-1 gene, mediated by HIF-1. Tumours show increased uptake of glucose compared to normal tissue and Glut-1 is responsible for the passive transport of glucose across the cell membrane.[9] Glut-1 over-expression has been associated with enhanced tumour aggressiveness and an unfavourable clinical outcome in various tumour types.[4] It has been suggested that Glut-1 might represent an intrinsic marker of hypoxia.[10]

The goal of our study was to compare the expression of Glut-1 with the binding of the bioreductive hypoxia marker pimonidazole and to elucidate the characteristics and pitfalls when each of them is used as a hypoxic marker. For this purpose, solid subcutaneous murine SA-1 sarcomas were treated with hypoxia-inducible therapy (electrochemotherapy) and excised at different post-treatment times for the determination of selected markers of hypoxia.

Materials and methods

Murine fibrosarcoma SA-1 cells and A/J mice were used for this study. Solid subcutaneous tumours, located dorsolaterally in mice, were initiated by an injection of $5x10^5$ SA-1 cells in 0.1 ml 0.9% NaCl solution. Six to 8 days after implantation, when the tumours had reached approximately 40 mm^3 in volume, the mice were randomly divided

into experimental groups. In the first group, bleomycin (Heinrich Mack Nachf.,Illertisen, Germany) at a dose of 1 mg/kg was injected intravenously. In the second group, eight square electric pulses of 100 μs (at a voltage to distance ratio of 1400 V/cm) were delivered by two flat electrodes 8 mm apart. In the electrochemotherapy group, the mice were treated with electric pulses 3 minutes after bleomycin injection. Tumours without treatment were used as controls. The tumours were excised at different time points (0.5, 1, 2, 8, 14 and 24 h) after treatment with bleomycin, the application of electric pulses or electrochemotherapy. Pimonidazole HCl (Hypoxyprobe-1, Natural Pharmacia International Inc.) was administered intraperitoneally to mice at a single dose of 100 mg/kg 16 h before sacrifice and tumour excision. Treatment protocol was approved by the Ministry of Agriculture, Forestry and Food of the Republic Slovenia No. 3440-12/2009/6.

Tumour tissue specimens were formalin-fixed and paraffin-embedded. Two consecutive 5 μm thick sections were cut from each paraffin block for immunohistochemical analysis. Immunoperoxidase with diaminobenzidine tetrahydrochloride (DAB) substrate was performed to detect hypoxic regions indicated by the presence of pimonidazole or Glut-1. Sections were dewaxed and hydrated in graded alcohols, rinsed in distilled water and PBS and treated with 3% hydrogen peroxide in methanol for 10 min to eliminate endogenous peroxydase activity and thereby prevent non-specific reactions with DAB substrate. Sections for Glut-1 detection were pre-treated in a pressure cooker in citric buffer (pH 6.0) and allowed to cool at room temperature for 15 minutes. Fifty microlitres of mouse monoclonal antibody raised against intracellular pimonidazole adduct (Natural Pharmacia International Inc) at a dilution 1/100 for 2 h or anti-Glut-1 (Alpha Diagnostic International) at a dilution of 1/100 for 1 h was applied. An EnVision kit (Dako, UK) was used for primary antibody binding detection. Immunoreactivity was visualized with DAB, and hematoxylin was used as a counterstain. Erythrocytes in each section served as positive controls for Glut-1. As negative controls, adjacent sections were incubated in parallel with non-immune serum instead of the primary antibodies.

An Eclipse-80i (Nikon, Japan) light microscope with an attached CCD camera was used for acquisition of images of stained tumour sections. A semi-quantitative scoring system was applied to the Glut-1 and pimonidazole adduct stained sections, and a score of 0-4 was assigned for each microscopic field, representative of the approximate area of immunostaining: 0 negative, 1+ <5%, 2+ 5-15%, 3+ 15-40% and 4+ >40%. Areas of necrosis, stroma, normal skin over the tumour and distinct edge effects were ignored. The overall scores used in our study summarising pimonidazole binding or Glut-1 expression across the tumour was derived from the average score for all fields. Two-tailed, Spearman's rank correlations were used to assess the relationship between the hypoxia markers used in our study. A P value less than or equal to 0.05 was considered statistically significant.

Results

Electrochemotherapy with bleomycin has been very effective in the treatment of subcutaneous SA-1 tumours, resulting in substantial tumour growth delay and even a high percentage of tumour cures, compared to untreated tumours and tumours treated with bleomycin or application of electric pulses only, as also demonstrated in our previous study.[11]

In the present study we compared two hypoxia markers and two consecutive sec-

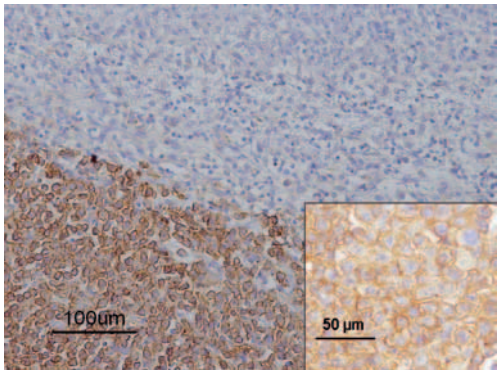

Figure 1. Immunohistochemical detection of Glut-1 in murine fibrosarcoma tumours after electrochemotherapy. Differences between Glut-1 positive and Glut-1 negative tumour areas are seen on large picture. Glut-1 expression is detected as membranous staining (small square).

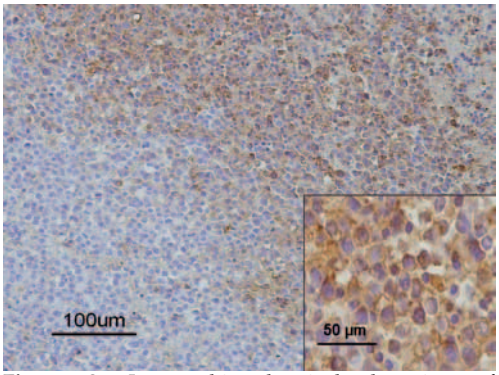

Figure 2. Immunohistochemical detection of pimonidazole bindig in murine fibrosarcoma tumours after electrochemotherapy. Differences between pimonidazole positive and pimonidazole negative tumour areas are seen on large picture. Pimonidazole bindig is detected as cytoplasmatic staining (small square).

tions from each tumour were therefore analysed. Glut-1 expression and pimonidazole binding were visualised by immunohistochemistry. The staining intensities for both markers generally increased in the vicinity of the necrotic area. Normal skin over the tumour failed to stain for both markers. However, strong immunoractivity exclusively to Glut-1 was found in red blood cells. A positive reaction for Glut-1 was seen in both cytoplasm and the tumour cell membrane. As the staining score increased, the cell membrane became more stained (Figure 1). Pimonidazole staining was found in the cytoplasm of tumour cells (Figure 2). Much of the staining was concentrated around necrotic tissue, and regions that were positive for pimonidazole were generally positive for Glut-1, although the Glut-1 expression areas were narrower in extent than the pimonidazole binding areas.

In the control and bleomycin groups the area of tumour hypoxia was approximately 10% at all time-points examined. After application of electric pulses alone, as well as after electrochemotherapy, the extent of tumour hypoxia detected by Glut-1 or pimonidazole reached its peak after 2 h (Figure 3) and lasted up to 8 h after the treatment. After the application of electric pulses, the recovery to pre-treatment level occurred at 14 h, whereas after electrochemotherapy the hypoxic area started to decrease after 14 h. However, recovery to pre-treatment level did not occur for at least 24 h (Figure 4).

The mean and range of the marker positive fraction varied between the two markers. However, there were significant correlations ($r = 0.41$) between Glut-1 and pimonidazole scores ($p = 0.028$). The degree of co-localisation between stained regions is also critical in their evaluation as hypoxia markers. More than 65% of the stained areas showed a high degree of co-localization when the two markers were compared.

Discussion

We used two hypoxic markers, pimonidazole and Glut-1, to detect hypoxic areas of SA-1 tumours treated with hypoxia-inducible therapy (electrochemotherapy). We found that there is a correlation between exogenous hypoxic marker pimonidazole binding and endogenous hypoxia marker

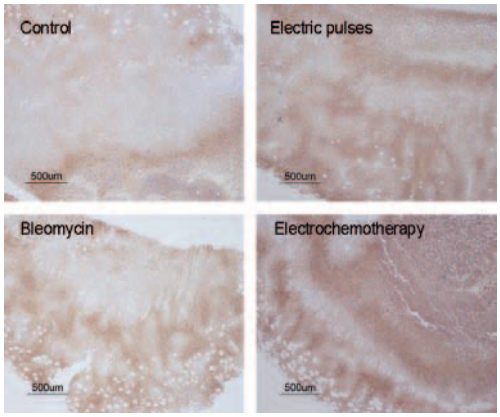

Figure 3. Glut-1 expression in representative sections of mourine fibrosarcoma tumours two hours after therapy with bleomycin, application of electric pulses or electrochemotherapy.

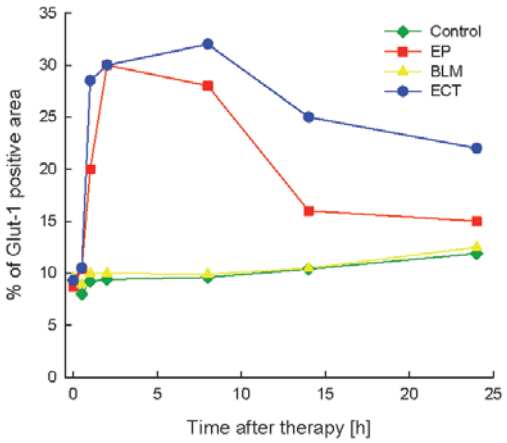

Figure 4. Time course of Glut-1 positive area in control tumours and after treatments with bleomycin (BLM), electric pulses (EP) and electrochemotherapy (ECT).

Glut-1 expression, so immunohistochemical staining of endogenous hypoxic marker can be used to track changes in tumour hypoxia. Our results resemble those of Russell *et al.*, who have previously shown that labelling hypoxic areas with the endogenous hypoxic marker carbonic anhydrase (CA) IX can be used to detect changes in tumour xenograft oxygenation.[5] Glut-1 and CAIX are two downstream genes regulated by hypoxia-inducible factor (HIF)-1α and both are considered to be endogenous hypoxia markers.

There is an intense effort to develop techniques that are able to visualize and quantify tumour hypoxia, because hypoxia can cause resistance to radiotherapies (hypoxic cells are 2-3 fold more radio-resistant than aerated cells)[12] and promote malignant progression. Hypoxic cells are also less accessible to nutrients and drugs, more likely to be non-cyclic, and therefore resistant to many forms of chemotherapy.[13,14] Currently, the two methods most widely used for direct measurement of tumour oxygenation are an Eppendorf polarographic oxygen electrode and the luminescence-based optical sensor OxyLite.[15] The drawback of those methods are their invasiveness and that they can not distinguish a hypoxic region in viable tumour tissue from a low oxygen level in necrotic tumour areas.

An alternative method is immunohistochemical assessment of pimonidazole binding, injected prior to the biopsy being taken.[16] The advantage of the immunohistochemical marker approach is that the same or contiguous formalin-fixed tissue sections may be examined for relationships between hypoxia and other physiological parameters for which immunohistochemical assays exist. In addition, histological sections permit the study of the geographical distribution of hypoxia, and micro-environmental factors such as blood vessels, areas of cell proliferation and angiogenesis.[17] Pimonidazole has been used for hypoxia assessment with various xenograft tumour treatment protocols[12,18], but pimonidazole must be administered 16 to 24 h before tumour biopsy and it is likely to reflect the presence of more long term or chronic hypoxia or, put in another way, pimonidazole may not indicate the level of acute hypoxia.[19]

The discovery that tumours metabolise sugars at an increased rate to normal tissue was made over 70 years ago. Cancer cell energy metabolism has received inter-

est recently, with some common oncogenic mutations having been directly linked to the glycolytic phenotype.[18] Glut-1 is one of the glucose transporters located in the cell membrane. It is known that increased expression of Glut-1 is not only found in a wide variety of tumour types, but invariably indicates a poor prognosis.[20,21] It has also been suggested that Glut-1 might represent an intrinsic marker of hypoxia.[14,17] There is a fundamental drawback, in that Glut-1 expression does not exclusively correspond to the tumour oxygenation status. Rather, the expression in tumour cells might reflect the activation of other oncogenic pathways, independent of hypoxia. In fact, two recent reports comparing oxygen tension in cervical cancers to HIF-1α and Glut-1 expression provided strong evidence for a regulation of these pathways independently of hypoxia.[9,22] However, Kunkel *et al*. recently confirmed the value of Glut-1 expression as a predictive marker for radio-resistant squamous cell carcinoma of the oral cavity. In addition to providing prognostic information, data suggest that modulation of radiation resistance by inhibition of glucose transport in the tumour may be a novel strategy for improving the effectiveness of radiotherapy in tumours.[23] The advantage of using intrinsic markers of hypoxia, such as Glut-1, is that the approach is simple and quick, and could potentially be applied to a wide variety of solid tumour types.

Our results indicate that pimonidazole and Glut-1 show a similar ability for detecting hypoxic cells. The mean tumour area of marker positivity varied between the two markers; however, there was a correlation between them. A small number of studies have compared endogenous marker expression with either oxygen microelectrode measurements or exogenous hypoxia marker binding. There are some reports of a lack of correlation between oxygen electrode measurements and Glut-1 expression[24] or pimonidazole binding.[25] In contrast, two recent studies have shown that levels of Glut-1 expression in carcinoma of the cervix correlated with the level of tumour hypoxia, measured using either polarographic needle electrodes[21] or pimonidazole staining.[14] A strong correlation was also observed between pimonidazole and Glut-1 in human bladder cancer and Glut-1 was an independent prognostic factor for overall survival of these patients.[22] The relationship between marker expression and oxygen electrode measurement is a complex one, since these methods do not sample the same tumour micro-environment or provide directly comparable measures of hypoxia. A general conclusion has been that endogenous markers offer promise for the routine measurement of tumour hypoxia but they may not provide the same information as O_2 measurements using microelectrodes or binding of chemical hypoxia markers.[26]

The induction of tumour hypoxia has often been intuitively linked to an inability of the tumour vascular network to provide a nutritive blood supply to the rapidly proliferating tissue. Highly angiogenic tumours should thus be well oxygenated. However, several studies have indicated that, paradoxically, tumour hypoxia correlates with high vascular density *in vivo*.[27,28] It is likely that several factors contribute to tumour hypoxia. During the rapid growth of a tumour, an aberrant microvasculature develops. The abnormal structure and function of the tumour microvasculature will reduce perfusion, increase the amount of fluid leaking into the extravascular space of the tumour, and thus increase the viscous resistance to flow. There is currently great interest in the relationship between tumour hypoxia and tumour vasculature because tumour blood vessels are an attractive target for tumour therapy.

In our study, we analysed tumours treated with electric pulses and/or bleomycin. After electrochemotherapy the hypoxic tumour area (determined with pimonidazole or Glut-1) increased to 35% within 1 h after treatment, reaching a peak 2 h after treatment. The antitumour efficiency of electrochemotherapy is not only due to increased cytotoxicity but also due to an anti-vascular effect, which results in reduced tumour blood flow and increased tumour cell hypoxia.[29] It has been proposed that electrochemotherapy, in addition to the direct cytotoxic effect, also has a vascular disrupting action.[11]

Conclusions

The correlations between the endogenous hypoxia marker Glut-1 and pimonidazole binding established in this study confirm that intrinsic markers of hypoxia, such as Glut-1, are a reliable means of evaluating tumour hypoxia, which will continue to be useful in future investigations involving archival material from a range of sources. However, application of these markers requires careful validation against established methods, especially when many other factors could complicate the use of hypoxia responsive gene expression as an indication of tumour hypoxia.

Acknowledgement

The authors acknowledge the financial support of the state budget by Slovenian Research Agency (Program No. P3-0003). All the authors declare that they have no conflict of interest.

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Radiol Oncol 2009; 43(3): 203-212. *doi:10.2478/v10019-009-0030-z*

research article

Dosimetric implications of two registration based patient positioning methods in prostate image guided radiation therapy (IGRT)

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Background. *We compare the dosimetry of daily patient positioning based on prostate matching versus bone matching for patients treated with helical tomotherapy.*
Methods. *Ninety-nine pre-treatment 3D megavoltage (MV) CT images of four high risk prostate patients were registered to their respective planning images using two automatic registration algorithms, one achieving bone matching and the other prostate matching. Dose distributions that would have been delivered had patient positioning been based on each matching method were evaluated. Contours were delineated on each MVCT image and prostate, bladder, and rectum dose volume histograms were compared for each image guidance strategy using endpoints adapted from inverse planning constraints.*
Results. *The standard deviation of per fraction prostate ΔD95 values, defined as prostate matching D95 minus bone matching D95, was 0.01 Gy (Range: -0.02 to 0.02 Gy). Defined analogously, bladder ΔD45 and rectum ΔD30 values were 0.12 Gy (Range: -0.22 to 0.52 Gy) and 0.14 Gy (Range: -0.40 to 0.34 Gy), respectively.*
Conclusions. *Bladder ΔD45 and rectum ΔD30 standard deviation values corresponding to 6.1% and 7.5% of their respective planning constraints suggesting critical structure doses are dependent on positioning method. A relationship between critical structure dosimetry and the direction of daily prostate motion was also observed.*

Key words: prostate radiotherapy; helical tomotherapy; patient positioning; image registration

Received 4 June 2009
Accepted 7 July 2009

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Background

The field of image-guided radiation therapy (IGRT) rose from the need to account for daily anatomical variations in the delivery of fractionated radiation therapy. This is particularly relevant to the treatment of prostate cancer as it has been repeatedly

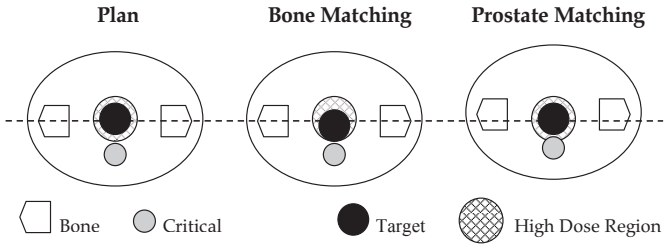

Figure 1. Simplified schematic demonstrating the potential increased dose to a critical structure as a result of prostate (*i.e.* target) matching. A gap is present between the target and critical structure in the planning CT, but the target has moved towards the critical structure when the patient is treated. With appropriate margins, bone matching results in complete coverage of the target without having any of the critical structure situated in the high dose region. On the other hand, part of the critical structure receives the target dose if prostate matching is used for patient positioning.

demonstrated that the position of the prostate gland varies as a result of bladder and rectal filling.[1,2] A number of correctional strategies including implanted fiducials[3-5] and on-line three-dimensional (3D) computed tomography (CT) imaging[6-9] have been developed and clinically implemented. Although both methods provide daily image guidance, the latter is advantageous in that it allows for the evaluation of daily delivered doses.[10]

The principle modality for prostate IGRT at our clinic is the Hi*Art II helical tomotherapy unit (TomoTherapy, Inc. Madison, WI). Prior to each fraction, clinicians acquire a 3D megavoltage CT (MVCT) of the patient in treatment position which is subsequently registered to the patient's planning CT and based on the registration; the patient is repositioned and treated. To ensure the target is situated in the same geometric location on a daily basis, registration should result in the overlap of the prostate volumes in the MVCT and planning CT images. This varies from traditional prostate treatment protocols where the lack of soft tissue contrast in portal images made prostate matching impossible and patient re-positioning was based on the matching of bony anatomy.[11-16] This change in patient positioning methodology has potential detrimental consequences to the dosimetry of critical structures. For example, consider the scenario where the prostate has moved slightly in the direction of a critical structure. Bone matching, in combination with sufficient margins, will ensure the entire target receives the prescription dose, however, prostate matching would certainly lead to an increased dose to the critical structure (Figure 1).

Unfortunately, the dosimetric implications of using prostate matching instead of bone matching for daily image guidance have not been sufficiently investigated. The objective of this work is to quantify and compare the doses that would be delivered to the prostate, bladder, and rectum if image guidance on the Hi*Art II system was based on prostate matching or on bone matching. The dependence of dosimetric variations on the direction of daily prostate motion will also be investigated.

Methods

Treatment data from four research patients treated for high risk prostate cancer on the Hi*Art II unit were available for this local research ethics board approved retrospective study. The primary planning target volume (PTV), treated to 68.0 Gy over 25 fractions (2.72 Gy/fraction), was defined by margins of 7-mm posteriorly and 10-mm in all other directions around the prostate gland and seminal vesicles. Constraints for the rectum and bladder during inverse planning were that no more than 30% of the rectum volume receive 45.0 Gy (1.80 Gy/fraction) and no more than 45% of the bladder volume receive 50.0 Gy (2.00

Gy/per fraction). Patients were instructed to have a full bladder and empty rectum during simulation and each daily treatment fraction. Prior to each fraction, a pelvic MVCT was acquired and used for patient re-positioning. For our purposes, one MVCT was removed from the data set because the entire prostate was not imaged, leaving ninety-nine fractions available for this study.

As a result of daily prostate motion with respect to rigid pelvic bony anatomy, prostate matching and bone matching of daily MVCT and planning images produces two different image alignments.[17] In this work, prostate matching and bone matching was performed using in-house developed automatic rigid registration software. For prostate matching, daily MVCT images were registered to planning CT images by optimizing the correlation coefficient metric. To ensure the overlap of the MVCT and planning CT prostate volumes, only the planning CT voxels corresponding to prostate plus a small 6.0-mm border were used in cost function calculation.[18-20] Voxels in the border region corresponding to bone and intestinal gas were filtered via thresholding to eliminate their influence on registration. In addition, a noise reducing median filter[21] was applied to MVCT images prior to registration. For bone matching, we used the mutual information algorithm proposed by Mattes *et al.*[22], however, only the automatically segmented planning CT voxels corresponding to bony anatomy were used to evaluate the cost function. Both the prostate and bone matching procedures rely on the Nelder-Mead simplex algorithm for cost function optimization.[23]

Following completion of bone matching and prostate matching procedures, dose distributions that would have been delivered using both image guidance strategies were evaluated with the High*Art II system's inherent Planned Adaptive software. The software evaluates delivered dose distributions by applying the treatment delivery sinogram to daily MVCT images, and has been demonstrated to have dosimetric accuracy comparable to that of planning CT dose calculations.[10] A number of studies have been published in which the tool was used to compare planned and delivered doses[24,25], however, to the best of our knowledge, the software has not been used to calculate theoretical dose distributions that would have been delivered had patient positioning been performed differently.

Retrospectively, prostate, rectum, and bladder volumes were contoured by a radiation oncologist on all pre-treatment MVCT images using the Planned Adaptive software and dose volume histograms (DVH) were evaluated for each dose distribution. Structures on each MVCT image were delineated only once and external software was used to account for the translational shifts in the contour co-ordinates between the two matching methods. Dosimetric endpoints for DVH analysis were adopted from the tumour and sensitive structure constraints implemented during inverse planning. As such, values for D95, D45, and D30 were extracted from each prostate, bladder, and rectum DVH, respectively. In addition to absolute evaluation, the differences between endpoints for each method were also evaluated.[26] As such, for comparison of prostate matching and bone matching image guidance strategies, ΔD95, defined as prostate D95 for prostate matching minus prostate D95 for bone matching, was determined for each fraction. Defined analogously, bladder ΔD45 and rectum ΔD30 values were also evaluated. In addition, five MVCT images were selected at random and re-contoured upon which dosimetric analysis was repeated to determine the effect of uncertainties in structure delineation on the evaluated endpoints.

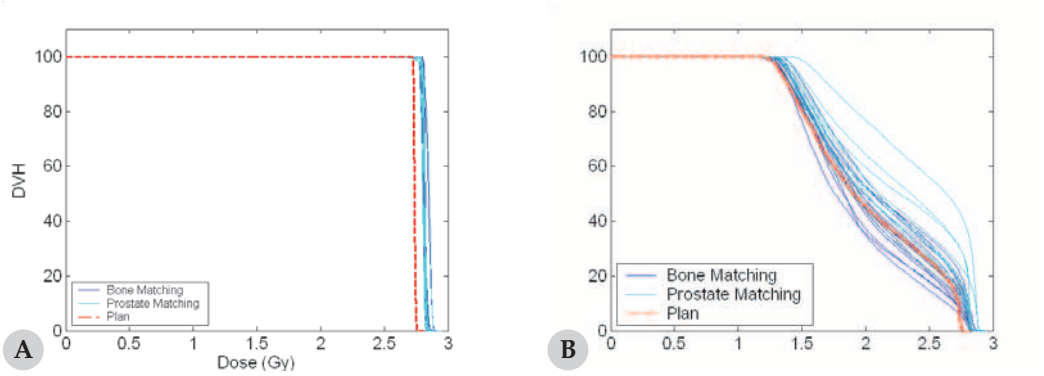

Figure 2. DVH comparison of prostate matching (PM) and bone matching (BM) for patient 1 odd numbered fractions (*i.e.* fraction 1, 3, ..., 23, 25). (a) Prostate, (b) bladder, (c) rectum.

The relationship between bladder[27,28] and rectal[27-29] filling and prostate motion in the superior/inferior (SI) and anterior/posterior (AP) directions has been repeatedly documented in the literature. Bladder D45 and rectum D30 values are clearly dependent on organ volumes, and as such, endpoints were also evaluated with respect to the measured daily prostate motion. Daily prostate motion (*i.e.* for each fraction) was calculated from the differences between the bone matching and prostate matching alignments.

Results

Daily prostate motion

The mean (± standard deviation) of the prostate motion for the ninety-nine fraction cohort was 2.4 ± 1.9 mm superiorly, 0.7 ± 2.5 mm anteriorly, and 0.3 ± 0.5 mm to the left. Although motion was skewed superiorly, standard deviations are comparable with values previously reported in the literature,[1] albeit on the lower end. Statistics for each individual patient are reported in Table 1.

Dose volume histogram analysis

The mean (± standard deviation) prostate D95, bladder D45 and rectum D30 values for each matching method are given in Table 2. Although mean prostate D95 values are identical for prostate matching and bone matching, evaluated critical structure endpoints are dependent on the matching method. Worth mentioning is the fact that all reported values exceed the aforementioned inverse planning constraints. In light of these observations, the percentage of fractionated bladder D45 and rectum D30 values that exceeded the constraints by differing dosimetric amounts were evaluated and appear in Table 3. Observed bladder and rectum endpoints correlate with the observed trends of anterior and superior prostate motion reported in the previous section. Presumably, if the prostate has moved superiorly towards the bladder, prostate matching would increase the volume of bladder that receives the prescription dose. Similarly, anterior prostate motion away from the rectum would result

Table 1. Prostate motion statistics for each individual patient. Negative values correspond to motion superiorly, anteriorly and to the left

Patient	Direction	Mean ± SD (mm)	Range (mm)
1	LR	0.0 ± 0.4	-0.8 to 0.8
	AP	-2.3 ± 3.2	-8.3 to 8.4
	SI	-4.1 ± 1.6	-8.0 to -1.6
2	LR	-0.1 ± 0.4	-1.0 to 0.7
	AP	0.0 ± 1.5	-3.3 to 3.0
	SI	-2.1 ± 1.2	-6.7 to -0.2
3	LR	-0.8 ± 0.4	-1.7 to -0.3
	AP	-1.7 ± 1.9	-5.3 to 1.9
	SI	-1.1 ± 2.0	-4.7 to 2.8
4	LR	-0.3 ± 0.6	-2.1 to 0.4
	AP	0.9 ± 1.8	-2.3 to 6.5
	SI	-2.2 ± 1.6	-5.0 to 2.4
Combined	LR	-0.3 ± 0.5	-2.1 to 0.8
	AP	-0.7 ± 2.5	-8.3 to 8.4
	SI	-2.4 ± 1.9	-8.0 to 2.8

in the prescription dose being delivered to less rectal volume. The thirteen odd numbered fraction dose volume histograms for patient 1 are plotted in Figure 2 to demonstrate the daily variations in prostate, bladder and rectum dosimetry for each matching method.

Image guidance comparison

Histograms of the theoretical prostate ΔD95, bladder ΔD45, and rectum ΔD30 values for all ninety-nine fractions are displayed in Figure 3. The mean (± standard deviation) prostate ΔD95 for the cohort was 0.00 ± 0.01 Gy, with values ranging from -0.02 to 0.02 Gy. Observed bladder ΔD45 values ranged from -0.22 to 0.52 Gy, having a mean value of 0.07 ± 0.12 Gy. Finally, the mean rectum ΔD30 value was -0.06 ± 0.14 Gy, with values ranging from -0.40 to 0.34 Gy. Statistics for each individual patient are reported in Table 4. Measured bladder ΔD45 and rectum ΔD30 values are plotted as a function of prostate motion in the AP and SI directions in Figure 4. A dependence on the direction of prostate motion is clearly evident.

Contour dependence

The absolute difference between endpoints evaluated using original and repeat contours were calculated for each of the five re-contoured MVCT images. The mean (± standard deviation) absolute difference of the ten (five for each matching method) bladder D45 values was 0.03 ± 0.02 Gy. This represents 1.2 ± 0.7% of the prescription dose. Corresponding values for rectum D30 absolute differences were slightly higher at 0.07 ± 0.07 Gy or, 2.5 ± 2.6% of the prescription dose. The mean (± standard deviation) of the five bladder ΔD45 absolute differences was 0.01 ± 0.02 Gy or 0.3 ± 0.6% of the prescription dose. Rectum ΔD30 values were 0.04 ± 0.04 Gy or 1.4 ± 1.2%. Mean and standard deviations of the absolute differences in both prostate D95 and prostate ΔD95 values were less than 0.1% of the prescription dose. Based on these observations, the reported magnitudes of prostate ΔD95, bladder ΔD45 and rectum ΔD30 values exceed their uncertainties relating to errors in contour delineation.

Table 2. Per fraction mean ± standard deviation prostate D95, bladder D45 and rectum D30 values for all ninety-nine fractions for each matching method. Inverse planning constraints are given in brackets

	Bone Matching (Gy)	Prostate Matching (Gy)
Prostate D95 (≥ 2.72 Gy)	2.81 ± 0.02	2.81 ± 0.02
Bladder D45 (≤ 2.00 Gy)	2.06 ± 0.17	2.13 ± 0.21
Rectum D30 (≤ 1.80 Gy)	2.29 ± 0.22	2.23 ± 0.17

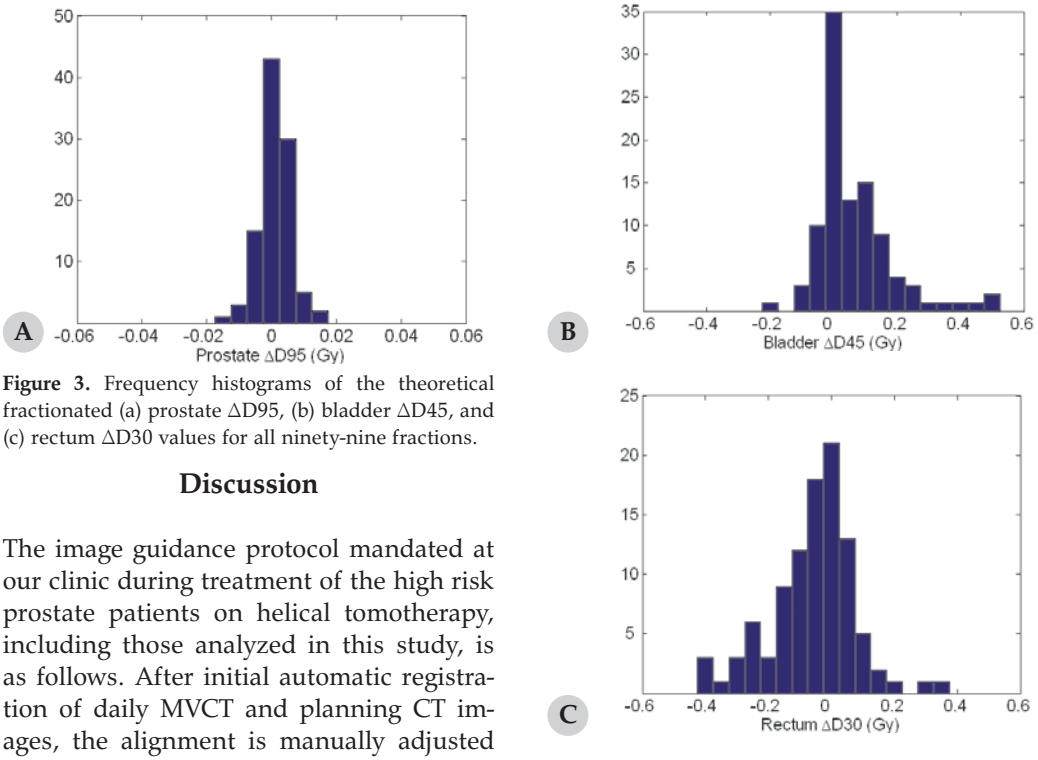

Figure 3. Frequency histograms of the theoretical fractionated (a) prostate ΔD95, (b) bladder ΔD45, and (c) rectum ΔD30 values for all ninety-nine fractions.

Discussion

The image guidance protocol mandated at our clinic during treatment of the high risk prostate patients on helical tomotherapy, including those analyzed in this study, is as follows. After initial automatic registration of daily MVCT and planning CT images, the alignment is manually adjusted by a radiation therapist with the goal of overlapping the prostate gland in the two images using the prostate/rectum interface at the mid-plane of the prostate as a reference. Recently, Langen *et al*.[30] investigated the accuracy of a manual method similar to ours and found that over 224 manual registrations performed by two radiation therapists, prostate misalignment exceeded 3-mm 24%, 33%, and 3% of the time in the AP, SI, and LR directions, respectively. Misalignment never exceeded 5-mm in any single direction. Although our work compares image matching strategies specifically, the observed alignment differences between prostate and bone matching are representative of the range of possible prostate misalignments during treatment. As such, the prostate ΔD95 values observed in this study suggest that for the margins used clinically and the errors associated with the manual patient positioning method employed at our centre, delivered prostate D95 values are unaffected by observed prostate positioning errors. This suggests that daily image guidance based on prostate matching of treatment and planning CT images allows for a reduction of the 10 mm margins used for

Table 3. Percent of fractions in which the bladder and rectum inverse planning constraints were dosimetrically exceeded, exceeded by 10% and exceeded by 25% for each matching method

	Bone matching (%)	Prostate matching (%)
Bladder D45 exceeded (≥ 2.00 Gy)	59	67
Bladder D45 exceeded by 10% (≥ 2.20 Gy)	12	32
Bladder D45 exceeded by 25% (≥ 2.50 Gy)	4	7
Rectum D30 exceeded (≥ 1.80 Gy)	100	100
Rectum D30 exceeded by 10% (>1.98 Gy)	97	96
Rectum D30 exceeded by 25% (>2.25 Gy)	51	42

Table 4. Individual patient statistics for prostate ΔD95, bladder ΔD45 and rectum ΔD30. Δ denotes prostate matching minus bone matching. The combined patient values are also normalized to the inverse planning constraints (*i.e.* prostate: 2.72 Gy, bladder: 2.00 Gy and rectum: 1.80 Gy)

Patient		Standard Deviation (Gy)	Range (Gy)
1	Prostate ΔD95	< 0.01	-0.01 to 0.00
	Bladder ΔD45	0.16	-0.22 to 0.52
	Rectum ΔD30	0.15	-0.40 to 0.32
2	Prostate ΔD95	< 0.01	-0.02 to 0.01
	Bladder ΔD45	0.05	-0.09 to 0.17
	Rectum ΔD30	0.09	-0.26 to 0.22
3	Prostate ΔD95	< 0.01	0.00 to 0.01
	Bladder ΔD45	0.08	-0.08 to 0.20
	Rectum ΔD30	0.10	-0.34 to 0.06
4	Prostate ΔD95	< 0.01	0.00 to 0.02
	Bladder ΔD45	0.04	-0.08 to 0.08
	Rectum ΔD30	0.09	-0.10 to 0.34
Combined	Prostate ΔD95	< 0.01 (0.2%)	-0.02 to 0.02 (-0.6 to 0.6%)
	Bladder ΔD45	0.12 (6.1%)	-0.22 to 0.52 (-11.2 to 26.0%)
	Rectum ΔD30	0.14 (7.5%)	-0.40 to 0.34 (-22.0 to 19.1%)

the patients included in this study. Recent work by Meijer *et al.*[31] demonstrated that a prostate margin of 6 mm is clinically acceptable when daily image guidance is based on the alignment of implanted fiducials. Without fiducials, as is the case for the helical tomotherapy patients at our centre, daily prostate positioning errors will increase [30] meaning a 6 mm margin is insufficient. Further investigation is required to determining where in the 6 to 10 mm range that the acceptable margin for prostate matching without fiducials is situated.

In relation to the two critical structures, the observed ranges of bladder ΔD45 and rectum ΔD30 values in combination with the fact that reported mean bladder D45 and rectum D30 values exceed inverse planning constraints, suggests that the selection of matching procedure has clinically significant repercussions on the dosimetry of the critical structures. However, over the entire ninety-nine fraction cohort analyzed in this study, positive and negative bladder ΔD45 and rectum ΔD30 values offset each other, giving rise to mean values of 2.6% and -2.2% of the prescription dose, respectively. How this fractionated trend translates when comparing matching methods based on the cumulative critical structure dosimetry over entire treatments remains unanswered.

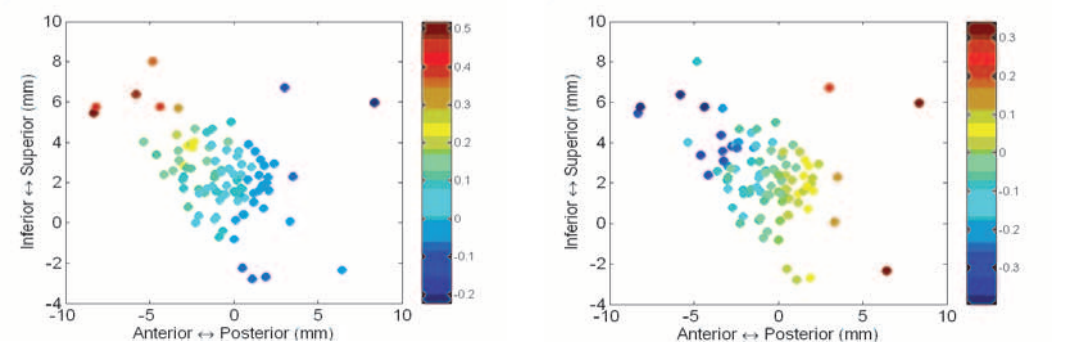

Figure 4. Scatter plot of per fraction (a) bladder ΔD45 and (b) rectum ΔD30 values for all ninety-nine fractions as a function of prostate motion in the superior/inferior and anterior/posterior directions.

Investigating this requires accurate deformable registration to track daily anatomical variations[32,33] and will be the focus of future work. However, whether or not fractionated dosimetrical differences between matching methods cancel out over prolonged treatment regiments, the fractionated analysis reported in this paper is beneficial for a number of reasons. First, the easiest way to ensure treatment protocols are satisfied over protracted treatment regiments is to ensure those same protocols are satisfied each fraction. Furthermore, the radiobiological effects of varying daily doses differ from those associated with static daily dosimetry, regardless of whether the cumulative dosimetry is equivalent. Finally, results demonstrate that systematic trends in daily prostate motion for individual patients can lead to large discrepancies in the dosimetry of prostate and bone matching. Patient 1 for example, had consistently and often significantly less bladder volume in daily treatment images as compared to planning CT acquisition, which contributed to a mean superior 4.1 mm prostate shift over all twenty-five fractions.[28] This systematic prostate motion resulted in a mean bladder ΔD45 of 0.20 Gy, which represents 10.0% of the inverse planning D45 constraint, suggesting that the selection of daily matching strategies can potentially have a clinically significant effect on cumulative critical structure dosimetry as well.

Conclusions

We have used the Planned Adaptive software on the Hi*Art II system to compare the doses that would have been delivered to high risk prostate patients if daily patient re-positioning was based on bone matching versus prostate matching. DVH analysis demonstrates that the difference in prostate dose for each matching technique is insignificant, allowing for potential margin reduction. However, observed ranges in the differences between critical structure dosimetry for bone and prostate matching suggest that the selection of matching method employed during patient re-positioning has clinical repercussions. In fact, the doses delivered to the bladder and the rectum were found to be highly dependent not only on the image guidance strategy, but also the direction of daily prostate motion. In particular, for prostate motion anteriorly and superiorly, bone matching decreases bladder dose whereas prostate matching decreased the rectal dose. Potentially, the matching method can be selected each day based on the observed prostate motion in order to minimize dose and subsequent complications to the bladder and rectum.

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Radiol Oncol 2009; 43(3): 144-151.

Zdravljenje recidivnega raka danke

Velenik V

Izhodišča. Čeprav se je s predoperativno radiokemoterapijo in izpopolnjeno kirurško tehniko preživetje bolnikov z rakom danke izboljšalo, je lokalna ponovitev bolezni še vedno terapevtski problem. Pri do 50% bolnikov se rak danke ponovi le lokalno, brez sistemskih zasevkov. V prispevku je podan pregled izsledkov s področja multimodalnega zdravljenja recidivnega raka danke.

Zaključki. Izbira najprimernejšega zdravljenja pri teh bolnikih še ni dorečena. Osrednjo vlogo v zdravljenju z namenom ozdravitve ima radikalna resekcija. Obsežno operacijo pa lahko spremljajo hudi zapleti in zmanjšana kakovost življenja bolnikov. Predoperativna radiokemoterapija omogoča zmanjšanje velikosti tumorja v obdobju pred operacijo in s tem večjo verjetnost njegove popolne odstranitve. V kombinaciji z intraoperativnim obsevanjem pa sta lahko lokalna kontrola in preživetje še boljša. Možno je tudi ponovno obsevanje bolnikov, ki so že bili obsevani v sklopu zdravljenja primarnega raka danke.

Radiol Oncol 2009; 43(3): 152-161.

Zdravljenje hemoptiz s katetersko embolizacijo bronhialnih arterij

Vidjak V, Novačić K, Hebrang A, Mažuranić I, Samaržija M, Ljubić S, Breitenfeld T, Klasić B

Izhodišča. Za masivno hemoptizo je značilno, da bolnik izkašlja 300-600 ml krvi v 24 urah in lahko privede do ogrožajoče asfiksije. Namen naše raziskave je bil oceniti učinkovitost kateterske embolizacije bronhialnih arterij (BAE) pri zdravljenju masivne hemoptize.
Bolniki in metode. V 33 mesecih je bilo 11 bolnikov z masivno hemoptizo napotenih v našo bolnišnico, da bi jim naredili digitalno subtrakcijsko angiografijo in BAE. Obravnavali smo 8 moških (starih 43-69 let, srednja starost 56 let) in 3 ženske (stare 63-65 let, srednja starost 64 let). Pri vseh bolnikih smo najprej naredili aortografijo prsne aorte; nato pa selektivno angiografijo bronhialnih in interkostalnih arterij ter interkostobronchialnega vejevja, kot je bilo indicirano. Selektivno arterialno embolizacijo smo naredili pri 9 bolnikih (9 primarnih in 3 sekundarne embolizacije). Poseg smo kontrolirali s fluoroskopijo, uporabili smo injekcijo mešanice kontrastne raztopine (1 ccm) in embolizacijske snovi imenovane Embosphere (BioSphere Medical Inc., MA, USA), kjer so bili delci veliki 350-500 μm.
Rezultati. Bronhiektazije so bile najpogostejši vzrok krvavitve (45,4%), hipervaskularizacija in intenzivno parenhimalno obarvanje pa sta bila najpogostejša angiografska znaka krvavitve (100%). Druga zelo pogosta znaka sta bila zavitost in hipertrofičnost arterij (72,7%). Primarna BAE je bila učinkovita v 81,9%. V 24 mesecih smo izvedli sekundarno BAE pri 33,3% bolnikih, tercialni (operativni) poseg pa je bil potreben pri 22,2% bolnikih. Lažji težavi, kot sta bolečina in kašelj, sta se ob BAE pojavil pri 44,4% bolnikih.
Zaključki. BAE je zanesljiva in minimalno invazivna metoda pri zdravljenju bolnikov z masivno hemoptizo. Zato menimo, da je primerna kot primarna metoda zdravljenja ali pa kot metoda priprave bolnika pred operacijo.

Radiol Oncol 2009; 43(3): 162-169

Diagnostika in kirurško zdravljenje ponavljajočih hidatidnih cist v endemskem področju

Yildirim M, Engin O, Oztekin O, Akdamar F, Adibelli ZH

Izhodišča. Ehinokokoza je zoonoza, ki se pojavlja predvsem na endemskih področjih. Ugotavljanje in zdravljenje ponavljajoče hidatidne ciste (RHC) predstavlja za kirurga resen izziv. Namen pričujoče raziskave je bil oceniti diagnostiko in kirurško zdravljenje RHC v delu Turčije, kjer je bolezen endemična.

Metode. Analizirali smo 146 bolnikov z abdominalno hidatidno cisto, ki so bili kirurško zdravljeni od leta 1997 do 2007. Pri 14 (9,5%) od njih se je pojavila RHC.

Rezultati. Zdravili smo 6 žensk in 8 moških z RHC. Srednja starost je bila 47,4 leta. Najpogostejši simptomi bolezni so bili: trebušne bolečine, slabost, vročina in zlatenica. Ciste so se ponovno pojavljale sporadično od 4 mesecev do 22 let po prvem zdravljenju. Ultrazvok trebuha smo naredili pri 14 (100%) bolnikih, CT pri 11 (78,5%) in MR pri 2 (14,2%) bolnikih. Tako smo pri vseh bolnikih slikovno prikazali RHC v jetrih in tudi ciste drugod (v vranici, mezenteriju kolona in perivezikalno). Ponavljajoče ciste (s srednjim premerom 12 cm) smo kirurško odstranili z delno pericistektomijo, introfleksijo in popolno cistektomijo. Pooperativni zapleti so se pojavili pri 14% bolnikov.

Zaključki. Zlasti v endemskih deželah, kot je Turčija, moramo v diferencialni diagnozi cističnih mas v trebuhu upoštevati RHC. Pomembno je, če je bil bolnik že operiran zaradi hidatidnih cist. Kirurško zdravljenje je še vedno najustreznejše. Zgodnje operacije in perioperativna obravnava omogočajo visoko stopnjo ozdravitve.

Radiol Oncol 2009; 43(3): 170-174.

Primer bolnika z miastenijo gravis, multiplimi infarkti v možganskem deblu, zlomom prsnega vretenca in hernijo medvretenčne ploščice v prsni hrbtenici

Kukaj V, Beqiri S, Pushka M, Kabashi M, Komoni E

Izhodišča. Prikazujemo primer bolnika z miastenijo gravis, multiplimi infarkti v možganskem deblu, zlomom 6. prsnega vretenca in hernijo medvretenčne ploščice med 7. in 8. prsnim vretencem.

Prikaz primera. Pri 66-letnem bolniku se je teden dni pred sprejemom v bolnišnico pojavila vrtoglavost, slabost, bruhanje, odrevenelost leve strani obraza, težko požiranje, levostranska hemipareza, desnostransko mravljinčenje, ki se je pričelo v prsni bradavici in se nadaljevalo v desno nogo ter splošna utrujenost. Pred 6 leti je zbolel za miastenijo gravis, ki smo jo potrdili z elektrofiziološkimi preiskavami, farmakološkimi testi in z odkritjem protiteles proti acetilholinskim receptorjem v serumu. Zdravljen je bil s piridostigminom, 60 mg petkrat dnevno; prednisolonom 20 mg vsak drugi dan; azatioprinom, 100 mg dvakrat dnevno. Omenjena zdravila so mu znatno pomagala in se je takrat počutil dobro. Zaradi kalkuloze so mu že pred 20 leti odstranili levo ledvico Njegova sestra se je zdravila zaradi miastenije gravis in sladkorne bolezni.

Zaključki. Miastenija gravis lahko povzroča številne simptome in znake bolezni, ki so pogoste pri možganski kapi, vključno z utrujenostjo, slabostjo mišic, motnjami govora in požiranja. Prikazan primer kaže, da lahko simptome različnih drugih bolezni – kot n.pr. možganske kapi – pripisujemo miasteniji gravis.

Radiol Oncol 2009; 43(3): 175-179.

Zasevek ploščatoceličnega raka uhlja v pinealno žlezo. Nenavaden primer in pregled literature

Oztekin O, Savas R, Apaydin M, Ozan E, Yasar O

Izhodišča. Pinealna žleza je nenavadno področje za širjenje zasevkov. Največkrat ti ne povzročajo simptomov. Tudi kožni rak izredno redko zaseva v pinealno žlezo. O tovrstnih zasevkih poročajo predvsem na podlagi obdukcijskih najdb. Ploščatocelični rak je druga najpogostejša vrsta kožnega raka v področju uhlja. Je invaziven in destruktiven tumor in lahko povzroča težave s sluhom zaradi preraščanja v zunanji sluhovod. Velika večina ploščatoceličnih karcinomov uhlja zaseva v pljuča, kosti in možgane.
Prikaz primera. Opisujemo primer bolnika z obsežnim ploščatoceličnim rakom uhlja in s širjenjem v globino temporalne kosti ter zasevanjem v pljuča in pinealno žlezo.
Zaključki. Zasevek je lahko vzrok za tumorsko spremembo v pinealnem področju, zlasti pri starejših bolnikih z znanim primarnim rakom.

Radiol Oncol 2009; 43(3): 180-186.

Segmentirana CT preiskava pljučnega raka s kostnimi zasevki ob upoštevanju intenzivnosti kopičenja izotopa pri PET preiskavi

Avazpour I, Roslan RE, Bayat P, Saripan MI, Nordin AJ, Raja Abdullah RSA

Izhodišča. Slikovna diagnostika je postala izjemnega pomena pri obravnavi bolnikov z rakom. PET/CT preiskava je omogočila hitrejšo diagnozo, natančnejšo anatomsko opredelitev bolezni in njenega stadija. PET nam posreduje podatke o metabolni aktivnosti določenega področja v telesu, CT pa to področje anatomsko opredeli. Tako lahko s PET preiskavo prepoznamo rakaste celice, s CT preiskavo pa določimo, kje ležijo, oziroma kateri anatomski strukturi pripadajo.

Metode. V raziskavi osvetljujemo lokalizacijo raka v bronhijih s pomočjo slikovnih točk z visoko intenzivnostjo v PET sliki kot osnovi za določitev interesnih področij v CT sliki. Najprej geometrijsko uskladimo PET in CT slike z uporabo križne korelacije, nato predizbrane točke PET slike vstavimo v algoritem, s katerim postopno povečujemo rob lezije v CT. To nadaljujemo do trenutka, ko dosežemo signifikatno lokalno spremembo.

Rezultati. Metoda je bila preverjena na enajstih slikah bolnika, ki je imel pljučni rak s kostnimi zasevki. Rezultati kažejo, da je srednja standardna napaka za prekomerno segmentirane točke 33%, za premalo segmentirane pa je 3,4 %.

Zaključki. Čeprav je algoritem »naraščajočega interesnega področja« zelo enostaven za uporabo, lahko z njim natančno določimo ta interesna področja. Algoritem je močno odvisen od tega, kje opredelimo začetek procesa naraščanja. Da bi izboljšali rezultate, smo v raziskavi pri izvajanju segmentacijskega procesa uporabili podatke z druge slikovne naprave.

Radiol Oncol 2009; 43(3): 187-194.

Zdravljenje bolnikov s hondrosarkomom visokega gradusa na udih. Preliminarni rezultati

Samardziski M, Zafiroski G, Tolevska C, Kalicanin-Markovska M, Doncovska D, Anevska V, Runceva M

Izhodišča. Bolnike s hondrosarkomov visokega gradusa na udih zdravimo z amputacijo uda ali radikalno kirurško resekcijo tumorja. Če bolniki predhodno prejmejo še neoadjuvantno kemoterapijo, lahko njihovo preživetje izboljšamo.
Bolniki in metode. V obdobju od leta 2000 do 2006 smo od 18 bolnikov s hondrosarkomom visokega gradusa 8 zdravili z adjuvantno in neoadjuvantno kemoterapijo. Teh 8 bolnikov smo analizirali v naši raziskavi. kemoterapija je bila skladna s protokolom skandinavske sarkomske skupine XVI. Pri 6 (75%) bolnikih smo ud lahko ohranili.
Rezultati. 8 bolnikov, ki so bili zdravljeni s kombinirano kemoterapijo, smo spremljali od 13 mesecev do 8 let (povprečje 32 mesecev). Pri 2 od 8 (25%) bolnikov smo naredili primarno amputacijo uda. Po histopatološki diagnozi hondrosarkom visokega gradusa je 6 od 8 (75%) bolnikov slabo odgovorilo na neoadjuvantno kemoterapijo. Pri 3 od 8 (37%) operiranih bolnikih s hondrosarkomom visokega gradusa je prišlo do lokalne ponovitve in pri 6 (75%) bolnikih do oddaljenih zasevkov. Pri 2 (25%) od 6 bolnikih, pri katerih je bil ud ohranjen, je bila potrebna naknadna amputacija zaradi lokalne ponovitve bolezni. 2 od 8 (25%) bolnikov pa sta preživela več kot 5 let, ne da bi se bolezen ponovila.
Zaključki. Bolniki s hondrosarkomov visokega gradusa na udih imajo daljše preživetje kot bolniki, kjer je tumor nastal v centralnem delu skeleta. Kombinirano zdravljenje omogoča ohranitvene operacije.

Radiol Oncol 2009; 43(3): 195-202.

Primerjava hipoksičnih označevalcev pimonidazola in transporterja glukoze 1 (Glut-1) pri mišjih fibrosarkomih po elektrokemoterapiji

Cör A, Čemažar M, Plazar N, Serša G

Izhodišča. Hipoksija tumorjev je rezultat nezadostne preskrbe tumorskih celic s kisikom zaradi neorganiziranega in kaotičnega tumorskega žilnega mrežja. Ker je hipoksija tumorja povezana z večjo agresivnostjo novotvorbe in slabšo možnostjo ozdravitve, bi bilo pomembno poiskati klinično uporabno metodo za ugotavljanje hipoksičnih tumorjev. Namen naše raziskave je bil primerjati vezanje bioreduktivnega hipoksičnega označevalca pimonidazola in izražanje transporterja glukoze 1 (Glut 1) v različno zdravljenih mišjih fibrosarkomih ter ugotoviti značilnosti in pomanjkljivosti obeh označevalcev za ugotavljanje hipoksije tumorjev.

Material in metode. Solidne SA-1 podkožne tumorje pri A/J miših smo zdravili z bleomicinom i.v. (1mg/kg) ali z električnimi pulzi (8 pulzov, 1400V, 100 μs, 1Hz) ali s kombinacijo obeh – elektrokemoterapija. Pimonidazol smo injicirali 16 ur preden smo odstranili tumor. Tumorje pa smo odstranili 0,5; 1; 2; 8; 14 in 24 ur po zdravljenju. Pri vsakem tumorju smo na dveh zaporednih rezinah tumorja imunohistokemično analizirali izražanje Glut-1 in vezanje pimonidazola ter določili odstotek imunohistokemično označenega področja tumorja.

Rezultati. Glut-1 je obarval predvsem membrane tumorskih celic in se je izražal zlasti peri-nekrotično, medtem ko se je pimonidazol na podobnih mestih v tumorjih kot Glut-1 prikazal citoplazmatsko. Primerjava obeh imunohistokemičnih barvanj je v 65% pokazala visoko stopnjo kolokalizacije. Rezultati so pokazali, da je izražanje Glut-1 statistično značilno povezano z nivojem vezave pimonidazola (r=0,41; p=0,028).

Zaključki. Raziskava potrjuje, da so geni kot n. pr. Glut-1, ki jih regulira HIF-1, uporabni za odkrivanje s hipoksijo povzročene zmanjšane občutljivosti tumorjev za radioterapijo in kemoterapijo.

Radiol Oncol 2009; 43(3): 203-212.

Dozimetrične posledice namestitve bolnika pri slikovno vodeni radioterapiji prostate (IGRT) z dvema poravnalnima metodama

Rivest DTC, Riauka TA, Murtha AD, Fallone BG

Izhodišča. Primerjali smo dozimetriji ob dnevni namestitvi bolnika z metodama ujemanja prostate in ujemanja kosti pri spiralni tomoterapiji.
Metode. Pred posameznimi obsevanji štirih visoko rizičnih bolnikov z rakom prostate smo naredili 99 3D megavoltnih (MV) CT slik in jih poravnali (registrirali). Uporabili smo dva avtomatična poravnalna algoritma: prvega, ki doseže ujemanje kosti in drugega, ki doseže ujemanje prostate. Ovrednotili smo dozne porazdelitve, ki bi izhajale iz namestitve bolnika po obeh metodah. Na vsako MVCT sliko smo vrisali obrise prostate, sečnega mehurja in danke in za obe strategiji slikovnega vodenja primerjali njihove dozno-volumske histograme. Primerjavo smo naredili v točkah, kjer smo v predhodnem postopku inverznega načrtovanja postavili dozne omejitve.
Rezultati. Standardni odklon vrednosti ΔD95 prostate, ki jo definiramo kot razliko vrednosti D95 pri metodah ujemanja prostate in ujemanja kosti ter se nanaša na eno frakcijo, je bil 0,01 Gy (Razpon: –0,02 do 0,02 Gy). Podobno opredeljena standardna odklona vrednosti ΔD45 sečnega mehurja in ΔD30 danke sta bila 0,12 Gy (Razpon: –0,22 do 0,52 Gy) in 0,14 Gy (Razpon: –0.40 do 0,34 Gy).
Zaključki. Standardna odklona ΔD45 sečnega mehurja in ΔD30 danke, ki ustrezata 6,1% in 7,5% njunih načrtovalnih mejnih doz, nakazujeta, da je doza na kritične organe odvisna od metode namestitve. Opazili smo tudi odnos med dozimetrijo kritičnih struktur in smerjo dnevnega gibanja prostate.

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.*

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

Dr. J. Cholewa Foundation for Cancer Research and Education continues to support the activities and advancement of oncology related sciences and cancer education associated with recent advances in oncology. The Foundation is of opinion that new and unorthodox ideas must not be hindered in their development, their publication and application for the lack of financial resources. It supports cancer research and education activities in Slovenia and continues to assess carefully requests for research and education grants submitted by experts in oncology and other associated scientific activities in Slovenia. The goal of the Foundation is to form a viable link between the latest advancements in cancer diagnostics and therapy worldwide to everyday research and clinical environment in Slovenia. It is hoped that this activity will directly benefit the ever increasing number of patients with various types of cancer in Slovenia, since the incidence rates of many cancer types as lung, breast, prostate and others have kept rising in the recent years.

The "Dr. J. Cholera Foundation for Cancer Research and Education« continues to support the regular publication of "Radiology and Oncology" international medical scientific journal presenting scientific articles in English, that is edited, published and printed in Ljubljana, Slovenia. This support emphasizes the need for the spread of information of advances in experimental and clinical cancer research to professionals and public in Slovenia and elsewhere. "Radiology and Oncology" is an open access journal, available free of charge on its own website, thus allowing its users and readers to access it freely. The Foundation is in this way active in promoting cancer research and education not only in Slovenia but in a wider area and with a wider scope, with the intention to gradually increase its impact in the international scientific community and consequently also in general population.

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

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

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

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

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

AstraZeneca
ONKOLOGIJA

ARI 03/07 P

*adjuvant [ae´džuv*nt]*

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

*advanced [*dva:nst]*

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

switch [swič]

1. *transitive verb* udariti, bičati s šibo (z repom); šibati z, hitro mahati z; naglo pograbiti; railway ranžirati, zapeljati (usmeriti) (vlak) na drug tir; electrical vključiti, vklopiti; spremeniti (pogovor), obrniti drugam (tok misli); to ~ back to figuratively (v mislih) vrniti se na;
~ to Arimidex: Adjuvantno zdravljenje zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji pri ženskah po menopavzi, ki so se dve do tri leta adjuvantno zdravile s tamoksifenom.

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ZASTOPA PODJETJA:

MENTOR

Prsni vsadki napolnjeni s silikonskim gelom, ekspanderji in drugi pripomočki pri rekonstrukciji dojk

Köttermann (Nemčija):
laboratorijsko pohištvo, varnostne omare za kisline, luge, topila, pline in strupe, ventilacijska tehnika in digestorji

Ehret (Nemčija):
Laminar flow tehnika, inkubatorji, sušilniki, suhi sterilizatorji in oprema za laboratorijsko vzrejo živali - kletke

Angelantoni scientifica (Italija):
hladilna tehnika in aparati za laboratorije, transfuzijo, patologijo in sodno medicino

Dako (Danska):
testi za aplikacijo v imunohistokemiji, patologiji, mikrobiologiji, virologiji, mono- in poliklonalna protitelesa

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

Sakura finetek (Evropa):
aparati za pripravo histoloških preparatov: mikro-inkriotomi, zalivalci, tkivni procesorji, barvalci, pokrivalci

Micronic (Nizozemska):
sistemi za shranjevanje vzorcev, pipete, nastavki za pipete

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

Implantech (Amerika):
obrazni in glutealni vsadki

SpectrumDesigns MEDICAL (Amerika):
moški pektoralni vsadki

Biomerica (Amerika):
hitri testi za diagnostiko, EIA /RIA testi

Byron (Amerika):
liposuktorji in kanile za liposukcijo

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

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

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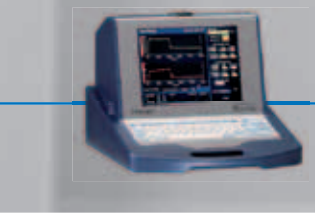
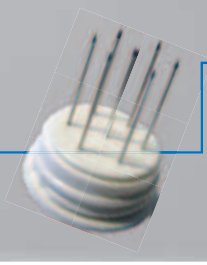
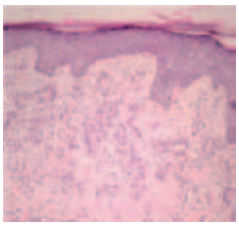
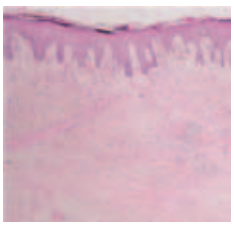




Before electrochemotherapy

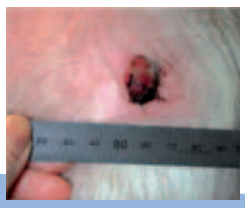


60 days after electrochemotherapy

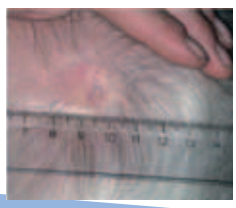


Quaglino P, Annals Of Surgical Oncology. 15 (8): 2215-2222. 2008

Before electrochemotherapy



10 weeks after electrochemotherapy



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

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

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

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

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

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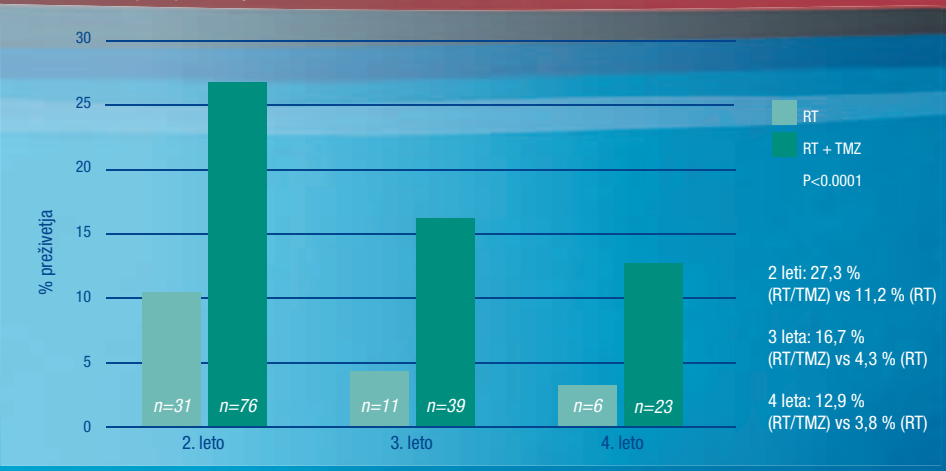

2 leti: 27,3 %
(RT/TMZ) vs 11,2 % (RT)

3 leta: 16,7 %
(RT/TMZ) vs 4,3 % (RT)

4 leta: 12,9 %
(RT/TMZ) vs 3,8 % (RT)

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

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

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

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

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

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

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

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

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

Režim izdaje zdravila: H/Rp.

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

Verzija: 1.0/09.

Informacija pripravljena: marec 2009.

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

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

Chapman S, Nakielny R. *A guide to radiological procedures.* London: Bailliere Tindall; 1986.

Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

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