RADIOLOGY AND ONCOLOGY

September 2007
Vol. 41 No. 3
Ljubljana

ISSN 1318-2099

GEMZAR je indiciran za zdravljenje:

- nedrobnoceličnega karcinoma pljuč
- adenokarcinoma trebušne slinavke
- karcinoma sečnega mehurja
- karcinoma dojke in
- karcinoma ovarijev

GEMZAR®
(gemcitabin)

ikrajšan povzetek glavnih značilnosti zdravila

emzar 200 mg prašek za raztopino za infundiranje, Gemzar 1 g prašek za raztopino za infundiranje
estava zdravila: 200 oz. 1 g gemcitabina, manitol, natrijev acetat, klorovodikova kislina in/ali natrijev hidroksid (za uravnavanje pH).
rapevtske indikacije: Lokalno napredovali ali metastatski karcinom sečnega mehurja, v kombinaciji z drugimi citostatiki imi zdra-
li. Lokalno napredovali ali metastatski nedrobnocelični karcinom pljuč, v kombinaciji z drugimi citostatičnimi zdravili. Lokalno na-
redovali ali metastatski adenokarcinom trebušne slinavke, pri bolnikih v dobrem splošnem stanju z zadostnimi rezervami kostne-
a mozga. Lokalno napredovali ali metastatski karcinom dojke v kombinaciji s paklitakselom pri bolnicah, pri katerih je prišlo do re-
psa bolezni po predhodnem predoperativnem in/ali dopolnilnim zdravljenju s citostatiki. Predhodno zdravljenje mora vključevati
ntracikline, razen če so kontraindicirani. Lokalno napredovali ali metastatski epitelijski karcinom ovarijev, v kombinaciji s karboplа-
nom, pri bolnikih z relapsombolezni po vsaj 6-mesečnem obdobju brez relapsa po zdravljenju prvega izbora na osnovi platine.
dmerjanje in način uporabe: *Karcinom sečnega mehurja (v kombinaciji s cisplatinom 70 mg/m²), odrasli in starejši:* Priporočeni od-
erek gemcitabina je 1000 mg/m², dan kot infuzija v 30 minutah. Odmerek dajemo 1., 8. in 15. dan vsakega 28-dnevnega ciklusa.
isplatin dajemo v odmerku 70 mg/m² 2. dan vsakega 28-dnevnega ciklusa. Ta štiritedenski ciklus nato ponavljamo. *Karcinom dojke
poraba v kombinaciji), odrasli:* Priporočamo uporabo gemcitabina v kombinaciji s paklitakselom, paklitaksel (175 mg/m²) damo 1.
an preko približno 3 ur kot intravensko infuzijo, temu sledi gemcitabin (1250 mg/m²) kot 30-minutna intravenska infuzija 1. in 8. dan
akega 21-dnevnega ciklusa. Bolniki naj imajo pred uvedbo kombiniranega zdravljenja z gemcitabinom in paklitakselom absolutno
oncentracijo granulocitov vsaj 1.500 (x 10⁹/l). *Nedrobnocelični karcinom pljuč (v kombinaciji s cisplatinom), odrasli in starejši:* Pri
ravljenju po tritedenski shemi je priporočeni odmerek gemcitabina 1250 mg/m² površine telesa, dan kot 30-minutna intravenska
fuzija 1. in 8. dan ciklusa zdravljenja (21 dni). Odmerek lahko med tekočim ciklusom zdravljenja ali ob naslednjem ciklusu zdravlje-
a znižamo glede na individualno opazovano toksičnost. Pri zdravljenju po štiritedenski shemi je priporočeni odmerek gemcitabina
000 mg/m² površine telesa, dan kot 30-minutna intravenska infuzija 1., 8. in 15. dan ciklusa zdravljenja (28 dni). *Karcinom jajčnika
poraba v kombinaciji), odrasli:* Priporočamo gemcitabin v kombinaciji s karboplatinom, z uporabo 1000 mg/m² gemcitabina 1. in 8.
an vsakega 21-dnevnega ciklusa, v obliki 30-minutne intravenske infuzije. Po gemcitabinu 1. dan damo karboplatin, da dosežemo
ljno AUC 4,0 mg/ml x minuto. *Karcinom trebušne slinavke, odrasli in starejši:* Priporočeni odmerek gemcitabina je 1000 mg/m² po-
šine telesa, ki ga dajemo kot intravensko infuzijo v 30 minutah. To ponavljamo enkrat tedensko v obdobju do 7 tednov, ki mu sle-
enotedenska prekinitev. V naslednjih ciklusih Gemzar dajemo enkrat tedensko v obdobju treh tednov, ki mu sledi enotedenska
rekinitev. Odmerek lahko med tekočim ciklusom zdravljenja ali ob naslednjem ciklusu zdravljenja znižamo glede na individualno opa-
vano toksičnost. Odmerek lahko z vsakim ciklusom ali med tekočim ciklusom znižamo glede na toksičnost, izraženo pri bolniku.

Kontraindikacije: Preobčutljivost za gemcitabin ali katero od pomožnih snovi. Bolnikom z zmerno do hudo okvarjenim jetrnim delovanjem ali hudo okvarjenim ledvičnim delovanjem Gemzarja ne smemo dajati.
Posebna opozorila in previdnostni ukrepi: Podaljšanje časa infuzije in skrajšanje priporočenega intervala med odmerki povečuje toksičnost. Gemcitabin moramo pri bolnikih z blago do zmerno okvarjenim ledvičnim delovanjem in pri bolnikih z blago okvarjenim jetrnim delovanjem uporabljati previdno. Če se pojavijo kakršnikoli znaki mikroangiopatske hemolitične anemije je treba zdravljenje z Gemzarjem prekiniti. Dajanje gemcitabina bolnikom s sočasnimi jetrnimi zasevki ali hepatitisom, alkoholizmom ali jetrno cirozo v preteklosti lahko povzroči poslabšanje osnovnega popuščanja delovanja jeter. Pri bolnikih z okvarjenim delovanjem kostnega mozga je treba zdravljenje začeti previdno. Moškim, zdravljenim z Gemzarjem, odsvetujemo spočetje otroka med zdravljenjem in do 6 mesecev po njem. Pred vsakim odmerkom je treba preveriti koncentracije trombocitov, levkocitov in granulocitov. Tveganje za neželene učinke, povezane z dihali, je višje pri bolnikih s karcinomom pljuč in pljučnimi zasevki, kot pri drugih tipih tumorjev. V primeru intersticijskega pnevmonitisa skupaj s pljučnimi infiltrati ter hudih, redko smrtnih pljučnih neželenih učinkih, denimo pljučnem edemu, intersticijskem pnevmonitisu in sindromu akutne dihalne stiske je treba zdravljenje z Gemzarjem prekiniti. Gemcitabin so prio trocih preučevali v omejenih preskusanjih faze 1 in 2 pri različnih tipih tumorjev. Te študije niso podale zadosti podatkov za zagotovitev učinkovitosti in varnosti gemcitabina prio trocih.
Interakcije: Ob sočasni radioterapiji (obsevanja istočasno ali v roku ≤ 7 dni pred kemoterapijo ali po njej) gemcitabin deluje radiosenzitizirajoče, poročali pa so tudi o obsevalnih poškodbah na ciljnih tkivih.
Neželeni učinki: Obsevalna toksičnost in odpoki c obsevanja: *Zelo pogosti:* levkopenija, trombocitopenija, anemija, dispneja, slabost, bruhanje, povišane vrednosti AST, ALT in alkalne fosfataze, alergijski izpuščaj, pogosto s srbenjem, blaga proteinurija in hematurija, edem in periferni edem, gripi podobni simptomi, kašelj, rinitis, znojenje, motnje spanja, povišana temperatura in astenija; *Pogosti:* febrilna nevtropenija, anoreksija, glavobol, zaspanost, nespečnost, diareja, zaprtje, stomatitis, povišane vrednosti bilirubina, znojenje, srbenje, alopecija, mialgija, bolečine v hrbtu, mrzlica, edem obraza; *Manj pogosti:* pljučni edem, bronhospazem, intersticijski pnevmonitis; *Redki:* miokardni infarkt, popuščanje srca, aritmija, hipotenzija, sindrom dihalne stiske pri odraslem, povišane vrednosti gama-GT, luščenje, tvorba mehurjev in razjed, odpoved ledvic, hemolitično-uremični sindrom; *Zelo redki:* trombocitoza, anafilaktoidna reakcija, klinični znaki perifernega vaskulitisa in gangrene, hude kožne reakcije, vključno z luščenjem in bulozними izbrstmi.
Imetnik dovoljenja za promet: Eli Lilly Holdings Limited, Kingsclere Road, Basingstoke, Hampshire, RG21 6XA Velika Britanija
Način in režim izdaje zdravila: H – Zdravilo se izdaja le na recept, uporablja pa se samo v bolnišnicah.
Datum revizije besedila: 14.10.2006

:li Lilly farmacevtska družba, d.o.o.
Dunajska 156, 1000 Ljubljana, Slovenija
'el.: (01) 5800 010, faks: (01) 5691 705

Lilly

RADIOLOGY AND ONCOLOGY

Editorial office
Radiology and Oncology
Institute of Oncology
Zaloška 2
SI-1000 Ljubljana
Slovenia
Phone: +386 1 5879 369
Phone/Fax: +386 1 5879 434
E-mail: gsersa@onko-i.si

September 2007
Vol. 41 No. 3
Pages 99-160
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: SI560201000900067 51
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:
BIOMEDICINA SLOVENICA
CHEMICAL ABSTRACTS
EMBASE / Excerpta Medica
Sci Base
Scopus

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 2007
Vol. 41 No. 3

ISSN 1318-2099
UDC 616-006
CODEN: RONCEM

CONTENTS

Radiology and Oncology is covered in *Biomedicina Slovenica, Chemical Abstracts, EMBASE / Excerpta Medica, Sci Base and Scopus*

Radiol Oncol 2007; 41(3): 99-106. *doi:10.2478/v10019-007-0017-6*

CT-guided percutaneous transthoracic needle biopsy of lung lesions – 2-year experience at the Institute of Radiology in Ljubljana

Igor Kocijančič and Ksenija Kocijančič

Institute of Radiology, University Clinical Centre Ljubljana, Ljubljana, Slovenia

Background. *In 1883, Leyden described percutaneous lung biopsy, but it was not until 1970s that image guided fine needle chest biopsy gained widespread acceptance. Haaga and Alfidi reported CT-guided thoracic biopsy in 1976. Currently, tissue sampling of a thoracic lesion is indicated when the diagnosis is not obtained by the endobronchial technique and when the cytological diagnosis will modify the stage of the disease or influence the therapeutic strategy. Cytology obtained by small-gauge needle aspiration biopsy confirms the nature of the lesion in 80 – 95% of cases and carry a low incidence of major complications according to the literature. The purpose of this retrospective analysis was to provide basic data about diagnostic accuracy and incidence of pneumothorax and chest tube insertion with respect to percutaneous transthoracic CT-guided needle biopsy of lung lesions.*

Methods. *After positioning of the patient we performed a spiral CT of the thorax with the accordingly placed metal mark, which helped us to set the optimal cutaneous entry point. After that we re-checked the localisation of the lesion and marked the entry point with a pen and clean the surface to keep it sterile. After we applied local anaesthetic subcutaneously, we used coaxial 18G Gallini aspiration biopsy needles with cutting tip for CT- guided aspiration cytologic examination. The length of the needle was chosen according to the distance of the targeted lesion.*

Results. *From January 2005 to January 2007 forty-three patients – 24 men and 19 women who were 26-79 years old (mean +/- SD, 59.8 +/- 10 years) were referred to the Institute of Radiology to undergo the PTNB. One patient was referred twice. Consequently, the hospital records and images of 44 consecutive cases of percutaneous transthoracic fine needle aspiration biopsy procedure were retrospectively analysed.*

The overall diagnostic accuracy was 93.2%, the pneumothorax rate was 27.2% and the chest tube insertion rate with percutaneous transthoracic CT-guided needle biopsy was 4.5%.

Conclusions. *Based on these cases, our 2-year experience is indicating that percutaneous transthoracic CT-guided needle biopsy is an effective and safe procedure for evaluation of undetermined lung lesions.*

Key words: lung neoplasms – pathology, biopsy needle; pneumothorax

Received 22 September 2007

Accepted 29 September 2007

Correspondence to: Assist. Prof. Igor Kocijančič, MD, PhD, Institute of Radiology, Clinical Center Ljubljana, Zaloška 2, SI - 1000 Ljubljana, Slovenia; Phone: + 386 1 520 85 31; Fax: + 386 1 520 24 97; E-mail: igor.koc@kclj.si

Introduction

In 1883, Leyden first described percutaneous lung biopsy, but it was not until the 1970s that image guided fine needle lung

biopsy gained widespread acceptance. In this early years percutaneous lung biopsies and advances in cytopathology were reported as well in our institution[1,2]. Haaga and Alfidi[3] first reported the CT-guided biopsy in 1976. Since that many authors confirmed the technique as safe and accurate in diagnosing benign and malignant lesion of the chest.[4-8] Nowadays, tissue sampling of a thoracic lesion is indicated when the diagnosis is not obtained by endobronchial technique and when cytological diagnosis will modify the stage of the disease or influence the therapeutic strategy.

With the advent of lung cancer screening using low-dose helical CT an increased incidence of smaller lung lesion and also small lung cancer has been reported in some countries.[9,10] It is well known that the detection of lung cancer in early stage may improve the prognosis of such patients.[11-13] In management of solitary pulmonary nodule we use a repeated CT examination with the evaluation of volume change of the small pulmonary nodule but when an increase in size is recognized on follow-up CT examination a verification of the lesion becomes mandatory. Beside this, main indications for percutaneous transthoracic needl e biopsy (PTNB) are: pulmonary nodule or nodules without specific diagnostic criteria on computed tomography (CT) ascertaining benignity; pulmonary nodule(s) or mass(es) suggestive of malignancy, pulmonary nodule in a patient with a history of extrapulmonary primary malignancy, a residual nonregressive lesion following radiotherapy and chemotherapy, a residual nonregressive infiltrate following specific antibiotic therapy, chronic diffuse pulmonary infiltrate in selected cases.

The need for the preoperative diagnosis of a solitary pulmonary nodule depends on the pretest probability of diagnosing a lesion that would obviate an unnecessary thoracoscopy or thoracotomy.[16]

Concerning CT characteristics of pulmonary nodules, it is known that 43% of nodules smaller than 1 cm are benign as well as that 97% of nodules bigger than 3 cm are malignant. Thirty-three % of primary malignant nodules have regular contours and 46% of benign nodules are spiculated. Twenty-six % of benign nodules and 5% of malignant nodules are more or less calcified while 21% of benign and 40% of malignant nodules show air bronchogram.

Overall, a correct diagnosis can be established by CT in 66-98% cases.[17]

The aim of this analysis was to provide basic data about the diagnostic accuracy and frequency of complications of lung biopsy procedures with CT guidance of needle insertion over the last two years.

Methods

When the transthoracic needle biopsy was performed, the procedure itself, possible complications and its accuracy had been carefully explained to the patient. Upon this conversation the patient was requested to sign the Informed consent form.

The clinicians obtained routine partial thromboplastine time (PTT), prothrombine time (PT) and platelets level in all patients.

We performed CT guided PTNB, which enabled a precise localisation of the lesion. All procedures were conducted on a multislice CT scanner (Somatom 16, Siemens, Erlangen, Germany) by two radiologists experienced in thoracic radiology and image-guided biopsy techniques. The scanning parameters of the Somatom 16 were 120 kVp, 120-200 mA, 1.5 mm collimation; 3- to 5-mm slice thickness and a table speed of 30 mm/sec (pitch up-to 1.5). Biopsies were performed without injection of i.v. contrast media. Necrotic tissue and cystic lesions were identified during prior diagnostic contrast enhanced CT. Unenhanced CT scans

were reviewed with a lung window setting (window width 1600 HU, window level -600 HU) and with a mediastinal window setting (window width 350 HU, window level 35 HU).

The position of the patient was then selected according to the desired needle path. It should be remembered that the position of the lesion can vary considerably when changing position from supine to prone or to oblique. The needle path should avoid transversing intercostals vessels so the needle entry was optimally defined at mid intercostals space whenever possible. In addition, it was necessary to try avoiding transgression of a pleural fissure, bullae or puncture of large vessel, bronchi and the oesophagus. We tried to insert the needle through the normal lung and to keep the length of the needle path to a minimum. We believed this reduced the risk for complication to a minimum.

The patient was instructed to stop breathing after normal inspiration at functional residual capacity. The technique of breath-holding was explained to each patient and was practiced shortly before the procedure.

To evaluate the procedure we could use adjusted (narrow) spiral scans or thick collimation (1 cm) sequence scans. The real time CT control should be avoided due to high doses for the patient and the staff.

After positioning of the patient we performed a spiral CT of the thorax with the accordingly placed metal mark, which helped to set the optimal cutaneous entry point. After that we re-checked the localisation of the lesion with regard to its anatomical environment. Once having the patient positioned at the desired table position, we marked the entry point with a pen and cleaned the surface to keep it sterile. We applied the local anaesthetic subcutaneously (2-5 ml 2% lidocain) and waited a few minutes. We do not apply any sedo-analgesia on routine basis.

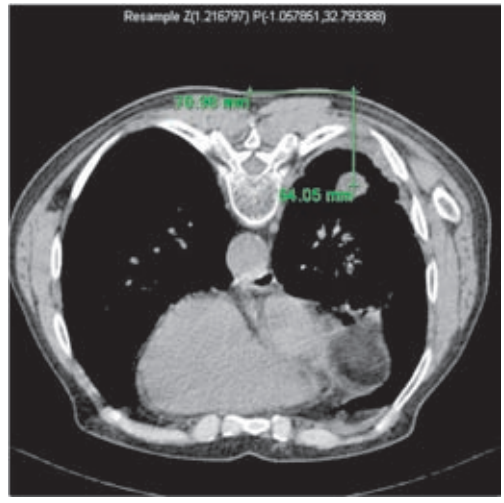


Figure 1. CT scan showing the puncture plan to diagnose the solitary pulmonary nodule in right lower lobe of 68-year-old man. Note the distance between the metal mark along the thoracic spine and the entry site and between the entry site and the centre of the nodule.

For CT- guided aspiration cytologic examination coaxial 18G Gallini aspiration biopsy needles with cutting tip were used. The length of the needle was chosen according to the distance of the targeted lesion.

The cytologist was always present to check the quality of the material. If needed, additional percutaneous passes were performed to get the satisfactory tissue sample.

Finally, the patient underwent post-procedural CT scan to check for possible complications (pneumothorax, haemorrhage, pleural effusion...). In case of large pneumothorax or moderately to severe dyspnoeic patient the placement of chest catheter or tube was considered. Others had the size of pneumothorax re-evaluated 7 days after the last follow-up examination if the patient was asymptomatic. In case of the increased pneumothorax (on follow-up chest radiographs) or the patient becoming sympto-

matic or large pneumothorax was found, a chest tube was placed.

Following the biopsy the patient was turned around to lie on the side which had been punctured for 15 to 30 minutes to prevent the possibility of pneumothorax evolution or progress.

Patients were generally observed, advised to stay in a recumbent position and under the medical staff supervision for at least for 4 to 5 hours after biopsy, then an erect expiratory chest X-ray was obtained. If normal, the compliant patients were discharged home. In the event a patient became symptomatic, an immediate follow up erect expiratory posteroanterior chest radiograph was obtained and in case of large pneumothorax (>30%) a chest catheter or tube was considered.

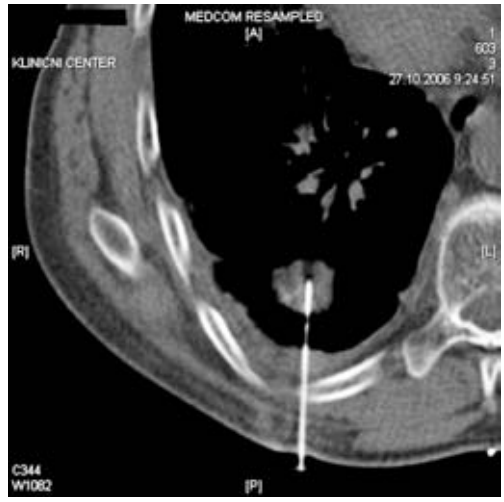


Figure 2. The same patient as at Figure 1. The lesion was penetrated, the tip of the needle was checked and aspiration specimen was obtained. The on-site cytologist confirmed the adequacy of the sample which was typical for adenocarcinoma.

Results

From January 2005 to January 2007 43 patients – 24 men and 19 women who were 26-79 years old (mean +/- SD, 59.8 +/- 10 years) were referred to the Institute of Radiology to undergo the PTNB. One patient was referred twice.

Consequently, the hospital records and images of 44 consecutive cases of percutaneous transthoracic fine needle aspiration biopsy procedure were retrospectively analysed. Diameter of pulmonary nodules/masses was measured on lung window settings. They measured from 0.8 cm to 6 cm in diameter (mean 2.3 cm, SD+/- 1.3 cm).

Cytological results were compared to the histological diagnosis after the surgery or to clinic and/or imaging follow up findings. To ascertain the benign nature of a lung nodule we used the following criteria: a technically successful biopsy, fair aspiration that is not normal lung, no signs of malignancy among aspirated cells and normal finding on bronchoscopy.

In our study, aspiration specimens were cytologically diagnosed into three groups by an experienced cytologist and/or by a cytology counsel as follows: negative for malignant cells 14/44 (32%) specimens, insufficient component 2/44 (4.5%) specimens and malignant lesion 28/44 (63.5%) specimens. All malignant lesions were nodules: 8 adenocarcinoma, 8 non-small cell lung cancer, 1 small-cell lung cancer, 2 carcinoids, 1 bronchiolo alveolar carcinoma, 1 lymphoma and 7 metastases. Unspecific/inflammatory lesions (n=7) were most frequently benign lesions.

The overall diagnostic accuracy, pneumothorax rate and chest tube insertion rate were determined.

Positive results at PTNB were considered to be true-positive when surgically confirmed, in case of biopsy of another site confirmed cancer with the same cytological characteristics, when the lesion increased in size or other proven metastases were found. According to the medical information all 28

cytologically positive cases turned out to be true positive.

Negative results at PTNB were considered to be true-negative when surgically confirmed, when the lesion disappeared or decreased in size on subsequent follow-up examinations or when it remains stable on the follow-up CT for 24 months. Thirteen of 14 cytologically negative cases turned out to be true negative.

There was one false-negative case. This was a solitary mass in an elderly, smoking women, located in the apex of the left lung, surrounded by a few non-specific parenchymal changes. Cytology revealed no malignant cells but the lesion was surgically removed since it was asymptomatic and not seen on radiographs a few months ago. The histology examination of removed tissue showed adenocarcinoma.

We considered true-positive and true-negative findings to be diagnosed cases while false-positive cases, false-negative cases and insufficient samples were considered non-diagnosed cases.

The overall diagnostic accuracy of PTNB (number of accurately diagnosed cases/total number of PTNB) turned out to be 93.2% in our series.

There were no major peri or post-procedural complications observed. During or after the biopsy we diagnosed pneumothorax in 12/44 patients. In two of them the chest catheter or tube was inserted. That makes the pneumothorax rate to be 27.2% and the chest tube insertion rate to be 4.5%. In 5 patients minor, asymptomatic intraparenchymal bleeding was observed. There was also one case of major parenchymal bleeding immediately after the needle position (prior to the first sample taking), accompanied by moderate hemoptysis. After a while symptoms decreased, the procedure was resumed and also successfully completed. In the post-procedural course the patient experienced a few minor events of haemoptysis which spontaneously resolved within a week.

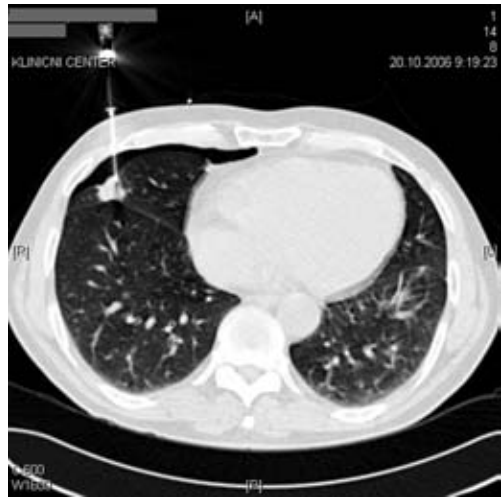


Figure 3. CT section through the level of small pulmonary nodule in 66-year-old man. The tip of the aspiration needle is clearly seen in the peripheral part of the lesion. Small pneumothorax already developed although this was the first attempt to target the lesion.

In 36/44 (82%) cases of PTNB, the co-operating on-site cytologist evaluated the cytological sample from an initial puncture as being sufficient for the diagnosis. However, in the remaining 8 cases patients we had to repeat the puncture and sample taking up to maximum four times. Even then the final cytology report in two cases indicated the tissue sample as inadequate. Both lesions were small (less than 1.5 cm) and deep (needle path more than 10 cm long) – the so called "difficult thoracic lesions". The retrospective analysis of the procedures evaluated both to be inaccurately targeted.

Discussion

Haaga and Alfidi reported the first case of aspiration biopsy guided by CT in 1976.[3] Ever since the technique have expanded and many papers confirmed it as safe and

accurate in diagnosing benign and malignant lesions of the chest.[4-8]

According to the published data so far, the percutaneous needle aspiration biopsy is a safe and accurate technique to diagnose benignant and malignant pulmonary lesions.[4-8,14-28]

Only the puncture of vascular structure such as an aneurysm or pulmonary arteriovenous malformation represent is absolutely contraindicated. The correct diagnosis should be obtained with contrast enhanced cross section imaging modalities such as CT and magnetic resonance imaging (MRI). Relative contraindications are: puncture of both lungs within the same session, puncture of only one functional lung, chronic respiratory insufficiency, pulmonary arterial hypertension, cardiac insufficiency, recent acute coronary event, severe emphysema and uncorrected coagulation defect. Cough, dyspnoea and reduced patient cooperation are further limiting factors. Mechanical ventilation is also a relative contraindication of PTNB.

The overall diagnostic accuracy (93.2%) was very high in our series and exceeds most of the ranges of results of CT-guided biopsy, reported in the literature, which include the data on pulmonary nodules of any size[2-6,12-26] as well as that of fiberoptic bronchoscopy.[29]

The pneumothorax rate (27.2%) as well as the chest tube insertion rate (4.5%) in our series were within the ranges of results of CT-guided biopsy reported in the literature.[16,24-28] Two important factors that affect the diagnostic accuracy are lesion size and needle path length. Many investigators report that diagnostic accuracies of CT-guided needle aspiration biopsies were influenced mainly by the lesion size[4-7,17-20,25-28] but only one suggesting needle path length is a more important factor in the diagnostic accuracy of CT-guided transthoracic needle aspiration biopsy.[16] It is also indicated that solitary pulmonary nodules of 10 mm or less should be followed up by repeated CT rather than biopsies because the diagnostic accuracy for these nodules is significantly lower than for larger solitary pulmonary nodules.[16] The percentage of predicted FEV1 is a well known measure of the degree of chronic obstructive pulmonary disease in patients[22] while decreased FEV1 is suggested to be a factor influencing pneumothorax rate.[5,21]

Beside the percentage of predicted FEV1 of the patient also the needle path length and the number of needle passes were often considered to be related to the pneumothorax rate as well as to the chest tube insertion one. Other factors like lesion size, needle-pleural angle, needle size, location of the nodule and needle approach sometimes did but sometimes did not improve pneumothorax and chest tube insertion rates.[5,6,16,18-21,27,26]

Unfortunately, the number of our cases is too low to allow the reliable stepwise regression analysis to test the importance of these factors that may affect the diagnostic accuracy, pneumothorax rate and chest tube insertion rate.

Knowing that the number of punctures can significantly affect pneumothorax and chest tube insertion rate, some investigators recently applied a coaxial technique for CT-guided thoracic interventions[19,20,30,31] in order to reduce both of them. In case of such technique the leading needle only once passes through the pleural space regardless to the numbers of tissue sampling and, consequently, the risk for pneumothorax has been reduced. In our study we did not adapt a coaxial technique since the great majority of our procedures ended up with a sufficient sample of tissue after only a single puncture. For such workflow it is necessary to cooperate with the on-site cytologist in order to repuncture and obtain another specimen in cases of insufficient

material for the diagnosis from the initial attempt.

We always considered the needle path length because a longer needle path tends to damage a larger part of lung parenchyma in between the pleura and the target lesion and may, consequently, increase the risk of pneumothorax. Hence, it is preferably to try an accurate single puncture of target lesion and to plan the needle trajectory to be as short as possible.

Other possible complications (e.g. intraparenchymal bleeding, pleural effusion, infection) are not common. Air embolism, a rare but potentially fatal complication can happen during CT-guided PTNB of the lung.[23]

In conclusion, our results confirmed CT-guided transthoracic needle biopsy as a useful and safe diagnostic tool for the determination of different lung lesions. The overall diagnostic accuracy, pneumothorax rate and chest tube insertion rate are within ranges, reported by other authors. From our experience and according to the data in the literature an accurate single puncture with the shortest needle path should be applied in order to minimize the risk of complication. If there is no on-site cytologist present, one should consider the coaxial technique of CT-guided biopsy, which probably has the potential to further reduce the chest tube insertion rate which is significantly increased if the operator risks an additional puncture.

References

1. Jereb M, Us Krasovec M. Transthoracic needle biopsy of mediastinal and hilar lesions. *Cancer* 1977; **40**: 1354-7.

2. Jereb M. The usefulness of needle biopsy in chest lesions of different sizes and locations. *Radiology* 1980; 134: 13-5.

3. Haaga JR, Alfidi RJ. Precise biopsy localisation by computer tomography. *Radiology* 1976; **118:** 603-7.

4. Westcott JL. Direct percutaneous needle aspiration of localized lesions: results in 422 patients. *Radiology* 1980; **137:** 31-5.

5. Kazerooni EA, Lim FT, Mikhail A, Martinez FJ. Risk of pneumothorax in CT-guided transthoracic aspiration needle biopsy of the lung. *Radiology* 1996; **198:** 371-5.

6. Li H, Boiselle PM, Shepard JO, Trotman-Dickenson B, McLoud TC. Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: comparison of small and large pulmonary nodules. *AJR Am J Roentgenol* 1996; **167:** 105-9.

7. Khouri NF, Stitik FP, Erozan YS. Transthoracic needle aspiration biopsy of benign and malignant lung lesion. *AJR Am J Roentgenol* 1985; **144:** 281-8.

8. Stanley JH, Fish GD, Andriole JG. Lung lesions: cytologic diagnosis by fine-needle biopsy. *Radiology* 1987; **162:** 389-91.

9. Barsky SH, Cameron R, Osann KE, Tomita D, Holmes EC. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. *Cancer* 1994; **73:** 1163-70.

10. Travis WD, Travis LB, Devesa SS. Lung cancer. *Cancer* 1995; **75(S1):** 191-202.

11. Sone S, Takashima S, Li F, Honda T, Maruyama Y, Hasegawa M, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; **351:** 1242-5.

12. Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high-risk cohort. Lung *Cancer* 2001; **32:** 227-36.

13. Henschke Cl, Naidich DP, Yankelevitz DF, McGuinness G, McCauley DI, Smith, et al. Early Lung Cancer Action Project: initial findings on repeat screenings. *Cancer* 2001; **92:** 153-9.

14. Klein JS, Zarka MA. Transthoracic needle biopsy: An Overview. *J Thorac Imaging* 1997; **12:** 232-49.

15. Minami M, Kawauchi N, Oka H, Itai Y, Sasaki Y: High resolution CT of small lung nodules: Malignancy versus Benignancy. *Radiology* 1992; **185:** 357-60.

16. Ohno Y, Hatabu H, Taneka D, Higashino T, Watanabe H, Ohbayashi C, et al. CT-guided transthoracic needle aspiration biopsy of small solitary pulmonary nodules. *AJR Am J Roentgenol* 2003; **180**: 1665-9.

17. Laurent F, Latrabe V, Vergier B, Michel P. Percutaneous CT-guided biopsy of the lung: comparison between aspiration and automated cutting needles using a coaxial technique. *Cardiovascular Intervent Radiol* 2000; **23:** 266-72.

18. Garcia-Rio F, Pino JM, Casadevall J, Gómez L, Atienza JM, Díaz-Lobato S, et al. Use of spirometry to predict risk of pneumothorax in CT-guided transthoracic needle aspiration biopsy of the lung. *J Comput Assist Tomogr* 1996; **20:** 20-3.

19. Laurent F, Michel P, Latrabe V, Tunon de Lara M, Marthan R. Pneumothoraces and chest tube insertion after CT-guided transthoracic lung biopsy using a coaxial technique: incidence and risk factors. *AJR Am J Roentgenol* 1999; **172:** 1049-53.

20. vanSonnenberg E, Casola G, Ho M, Neff CC, Varney RR, Wittich GR, et al. Difficult thoracic lesions: CT-guided biopsy experience in 150 cases. *Radiology* 1988; **167:** 457-61.

21. Ko JP, Shepard JO, Drucker EA, Aquino SL, Sharma A, Sabloff B, et al. Factors influencing pneumothorax rate at lung biopsy: are dwell time and angle of pleural puncture contributing factors? *Radiology* 2001; **218:** 491-6.

22. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respire Dis* 1991; **144:** 1202-18.

23. Hirasawa S, Hirasawa H, Taketomi-Takahashi A, Morita H, Tsushima Y, Amanuma M, et al. Air embolism detected during computed tomography fluoroscopically guided transthoracic needle biopsy. *Cardiovasc Intervet Radiol* 2007 (in press).

24. Kinoshita F, Kato T, Sugiura K, Nishimura M, Kinshita T, Hashimoto M, et al. CT-guided transthoracic needle biopsy using a puncture site-down positioning technique. *AJR Am J Roentgenol* 2006; **187:** 926-32.

25. Heck SL, Blom P, Berstad A. Accuracy and complications in computed tomography fluoroscopy-guided needle biopsies of lung masses. *Eur Radiol* 2006; **16:** 1387-92.

26. Lourenco R, Camacho R, Barata MJ, Canario D, Gaspar A, Cyrne C. CT-guided percutaneous transthoracic biopsy in the evaluation of undetermined pulmonary lesions. *Rev Port Pneumol* 2006; **12:** 503-24.

27. Andreson JM, Murchison J, Patel D. CT-guided lung biopsy; factors influencing diagnostic yield and complication rate. *Clin Radiol* 2003; **58:** 791-7.

28. Gupta S, Krishnamurthy S, Broemeling LD, Morello FA, Wallace MJ, Ahrar K, et al. Small subpleural pulmonary lesions: short- versus long-needle path CT-guided biopsy. Comparison of diagnostic yields and complications. *Radiology* 2005; **234:** 631-7.

29. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. *Chest* 2000; **117:** 1049-54.

30. Charig MJ, Phillips AJ. CT-guided cutting-needle biopsy of lung lesion-safety and efficacy of an outpatient service. *Clin Radiol* 2000; **55:** 964-9.

31. Geraghty PR, Kee ST, McFarlane G, Razavi MK, Sze DY, Dake MD. CT-guided needle aspiration biopsy of pulmonary nodules: needle size and pneumothorax rate. *Radiology* 2003; **229:** 475-81.

case report

Adult obstructing ileocolic intussusception

Ivan Žokalj[1], Zvonimir Magaš[2], Zlatko Pavčec[1], Hussein Saghir[1], Andrej Pal[1], Zvonimir Kolarić[3] , Miljenko Marotti[4]

[1]Department of Radiology and Ultrasound, County Hospital Čakovec, Croatia; [2]Department of Surgery, County Hospital Čakovec, Croatia; [3]Department of Internal Medicine, County Hospital Čakovec, Croatia; [4]Department of Diagnostic and Interventional Radiology, University Hospital "Sisters of Mercy", Zagreb, Croatia

Background. *We report a case of the adult obstructing ileocecal intussusception caused by carcinoma of the coecum.*

Case report. *A 44-year-old male patient has been admitted to the hospital with strong pain in the upper abdomen, vomiting and high amylase level in the blood serum 154 U/L (norm. 23-91 U/L at 37ºC) and in the urine 792 U/L (0-400 U/L at 37ºC). Sudden worsening of the patient's general condition on the 9th day after the admission associated with clinical and radiological signs of bowel obstruction were the reasons to perform emergency computerized tomography (CT) after days of clinical observation and follow-up with abdominal X-rays and ultrasound (US). CT revealed multiple concentric rings with centrally placed soft-tissue structure with higher attenuation on post-contrast scans, "target mass". Right haemicolectomy with terminolateral ileotransversoanastomosis without preoperative reduction was performed. Intraoperatively aboral loops of the ileum were found prolapsed into the coecum and ascendant colon with carcinoma of the coecum (Dukes B, Astler-Coller B2) acting as a neoplastic lead point for intussusception.*

Conclusions. *The adult intussusception may be a rare cause of abdominal pain but it must be on the differential diagnosis list in the case of intermittent abdominal pain, especially with clinical and radiological signs of the bowel obstruction. The reported case supports the opinion that CT is the imaging method of choice for the adult intussusception.*

Key words: intestinal obstruction; intussusception; adult; ileocecal valve

Introduction

Intussusception is a prolapse of a bowel loop with its mesenteric fold (intussusceptum) into the lumen of a contiguous segment (intussuscipiens).[1] Intussusception in adults is rare, it counts for 5-16% of all cases of all intussusceptions This condition is often at the end of the differential diagnosis list.[2,3] The clinical presentation of intussusception in adults is variable in appearance. The signs and symptoms of the bowel obstruction predominate in

Received 18 September 2007

Accepted 30 September 2007

Correspondence to: Ivan Žokalj, MD, Department of Radiology and Ultrasound, County Hospital Čakovec, Croatia; E-mail: ivan.zokalj@ck.htnet.hr

82% of cases.[4] Patients usually complain on chronic intermittent abdominal pain or prolonged abdominal pain, nausea, vomiting and constipation.[3,4] The most common reason for the operative intervention is the acute bowel obstruction. Unfortunately, the preoperative diagnosis of intussusception in adults is relatively rarely established.[4] In most of the adult intussusception cases, in over 90%, there is a pathological lead point.[5] Malignant tumour is the lead point in approximately two thirds of colonic intussusceptions, but only in one quarter of enteric intussusceptions in adults.[4]

Abdominal computerized tomography (CT) is the most useful imaging diagnostic method for the diagnosis of intussusception. Ultrasound (US) is the second most effective imaging tool.[6,7] Adult intussusceptions are usually treated surgically, especially colonic variants. Resection without reduction was suggested as the best method. Opinions differ among surgeons what is the best modality of the treatment of adult intussusceptions today. The role of preoperative reduction of adult intussusception is in the focus of the debate.[7,8]

Case report

A 44-year-old male patient had medical history of uretherolithiasis and chronic gastritis which has been treated with H2 antagonists. Two days before the admission he complained on upper abdominal pain and vomiting, which relieved spontaneously. On the day of admission, he complained again on upper abdominal pain. During the physical examination painless palpable mass which extended from epigastrum to the umbilicus with dimensions of 10 x 5 cm, has been found. First laboratory tests showed higher amylase level in the blood serum 154U/L (norm. 23-91 U/L at 37°C) and the urine 792 U/L (0-400 U/L at 37 C) and normal results of WBC 9.1 x 10^9, erythrocytes 4.8 x 10^{12}, erythrocyte sedimentation rate 4/10, C-reactive protein (CRP) 1.1 mg/L.

Abdominal X-rays depicted bowel meteorism without distension in the ileocecal region and lienal flexure. The endoscopic evaluation of the upper gastrointestinal tract performed on the 4th day after the admission revealed small oesophageal varices placed in the aboral third of the oesophagus just beneath cardia and a mild form of antral gastritis. The first abdominal US performed on the 5th day after the admission did not show any abnormalities. The control abdominal US on the 7th day after the admission depicted expansive formation in the epigastrium with concentrically placed hypoechoic and hyperechoic layers with a maximal diameter of 10 cm ("target mass"). The working diagnosis was acute pancreatitis with suspected pseudocyst of the pancreas.

In the following days the patient developed clinical signs of bowel obstruction. On the 9th day after the admission the patient had severe and much stronger pain in the upper abdomen in comparison with the first day of this episode. Control abdominal X-rays showed the distension of enteric loops without earlier depicted colonic meteorism. The follow-up abdominal US, performed on the same day, revealed earlier depicted "target mass" in the upper abdomen with bigger maximal diameter of 12 cm and more clearly delineated contours from the surrounding structures. The patient underwent abdominal CT which revealed multiple concentric rings on the place of sonographically depicted "target mass" with centrally placed soft-tissue structure which had higher attenuation on post-contrast scans. Control laboratory tests revealed again normal levels of WBC, erythrocytes, CRP and decreased amylase blood serum (111 U/L) and urine level (1041 U/L).

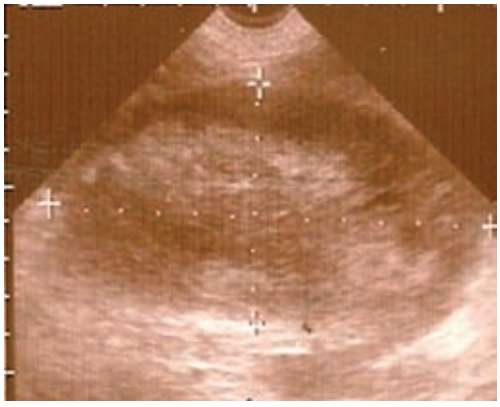


Figure 1. Abdominal ultrasound – axial plane. Expansive formation in the epigastrium with concentrically placed hyper and hypoechoic layers – "target mass".

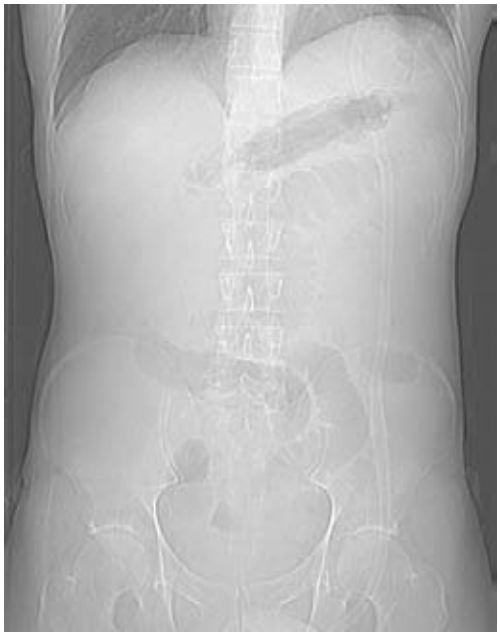


Figure 2. AP scout view of abdominal CT – coronal plane. Distension of the small bowel loops – bowel obstruction.

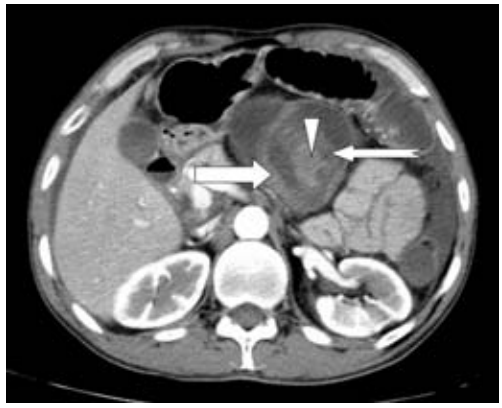


Figure 3. CT of the abdomen – post-contrast axial scan - horizontal plane**.** Mass consisted of multiple concentric rings placed in the middle upper abdomen with external hyperdensity ring (returning intussusceptum and intussuscipiens – white right arrow), hypodensity ring , internal hiperdensity ring (canal and wall of intussusception – white notched right arrow) and soft tissue density structure in a central position – a malignant lead point (white arrowhead). Dilatation of small bowel loops.

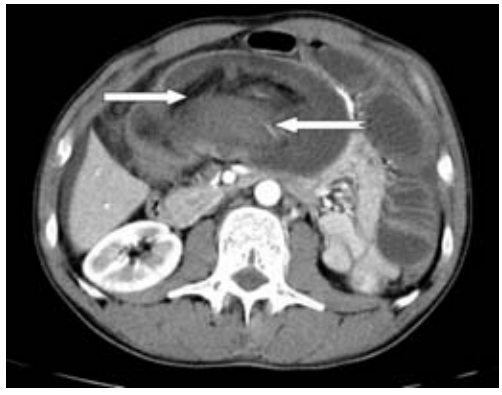


Figure 4. Abdominal CT post-contrast axial scan – horizontal plane. Crescent-shaped fat density due to the eccentrically placed mesentery (white right arrow). Mesenterial vascular structures (white notched right arrow).

Due to a worsen clinical condition of the patient the emergency right haemicolectomy with terminolateral ileotransversoanastomosis was performed. Ileocolic invagination with terminal ileum invaginated in transverse colon was found. The polypoid form of coecal carcinoma served as a lead point in this case of the adult intussusception. The result of the patohystologic analysis was adenocarcinoma of the coecum, classified as Dukes B stage, Astler-Coller B2 and T3NOMX. The patient was discharged

from the intensive care unit on the second day after the surgical intervention. The patient's general condition was improved and he was discharged from the hospital after the total stay of 21 days.

Discussion

The case presented in this article represents difficulties in establishing the aetiology of the prolonged upper abdominal pain connected with non-specific clinical signs and laboratory test results. The diagnosis of the intussusception in adults is rarely established preoperatively. The diagnosis is usually established during the surgery performed because of the bowel obstruction. The adult intussusception is the cause of bowel obstruction in only 1% of patients.[7] Cross-sectional imaging tools like US and CT, especially modern fast scanners with possibilities of volumetric scanning, make the preoperative diagnosis of the adult intussusception more possible.

Intussusceptions are usually divided according to the location. Dean, Ellis and Sauer have classified intusussceptions into four groups:

1 *Enteric*-small bowel invagination into small bowel
2 *Ileocecal*-the ileocecal valve being the leading point of the intususception
3 *Ileocolic*-ileum protruding through the ileocecal valve with the coecum remaining stationary
4 *Colocolic*-colon invaginating into colon.[4]

Organic lesions are the underlying pathologic cause in 10-20% of the patients. Aetiology of intussusception in adults is demonstrated in 70% to 90%. Large bowel intussusceptions are usually caused by malignant tumours. In small bowel intussusceptions a lead points are predominantly non-malignant tumours, like lipomas and polyps. Enteroenteric intussusceptions, in the transient non-obstructing form, can be found in patients with coeliac disease and Crohn's disease where a pathologically changed bowel wall with altered peristalsis can form a leading edge for the intususceptum.[1,3,4,9,10]

In the study published in 1999, conducted by Warshauer and Lee, less than 1/3 of adult intussusceptions depicted with CT or MR had a neoplastic lead point. Non-neoplastic intussusceptions were mostly enteroenteric, significantly shorter and smaller in diameter.[3]

The bowel obstruction is uncommon in adult non-neoplastic intussusceptions.[3] Non-neoplastic adult intussusceptions can be transient and may not demand aggressive work-up.[1,3]

Diagnostic studies in evaluation of the suspected intusussception are plain abdominal film (*abdominal X-rays*), US, barium enema (*irigography*), CT, magnetic resonance (MR) and colonoscopy.[3,4,6]

CT is the diagnostic method of choice because of its non-invasiveness and short scanning time on modern scanners. CT can also depict changes which are responsible in development of intussusception (the leading edge).

CT appearance of intussusception has a few different forms:

1 *Target pattern* - multiple concentric rings
2 *Reniform pattern* – renal like or bilobed mass with peripheral high attenuation values
3 *Sausage-shaped pattern* – sausage-shaped mass with alternating areas of low and high attenuation.[1,11]

On axial CT scans a target lesion is often depicted (multiple concentric rings) with alternating circumferential areas of high and low attenuation. The external ring on axial scans (or outer cylinder) usually consists of returning intussusceptum and intussuscipiens. The crescent of the mesenteric fat forms the middle ring (middle cylinder) and

the internal ring (central cylinder) contains the wall of intussusception and canal.[1]

Using the alternative cross-sectional methods, like US and MR, the intussusception will also be depicted as a lesion with the target appearance (multiple concentric rings). In the early phase the intussuception is usually a "target mass" associated with the bowel obstruction. The progression of the disease causes the bowel wall thickening and layering on the images. Finally, if the patient is not treated, the bowel wall necrosis appears as an amorphous mass on the images.[1,11] In this case we had a target pattern of an ileocolic intussusception on US and CT images.

Non-specific clinical signs and symptoms were the main reasons why CT was not used earlier for the evaluation of this patient. Abdominal CT has been originally planned because the treating physician assumed that the main cause of the upper abdominal pain in this case is the acute pancreatitis complicated with pseudocyst of the pancreas. Sudden worsening of the patient's general condition connected with clinical and radiological signs of the bowel obstruction were the reasons to perform emergency CT which depicted the ileocecal intussusception with a characteristic target pattern. In this case, CT results gave the key reason to surgeons for their decision to perform an emergency surgical treatment.

The form of the surgical treatment depends on the patient's medical history and intraoperative findings. Opinions about the treatment of different variants of adult intussusception differ today, especially colonic intussception should be reduced before the resection.[6,7,8] The treatment in the adults for colonic variants of intussception is always operative and the resection without reduction is recommended according to Azar and Berger.[7] Sarr in his invited commentary to article of Omori *et al.* published in 2003 proposed the preoperative reduction in selective cases of intussusceptions to allow an elective procedure.[8] The preoperative reduction of the colonic intussusception may help to reduce the extent of the surgical procedure, for example, to treat the ileocolonic intussusception with a small bowel resection instead of a right hemicolectomy, according to Sarr.[8] Benign enteric lesions without adhesions and benign colonic lesions are usually treated with the resection to prevent a recurrent intussusception.[7]

Conclusions

In this case we report about a patient with non-specific clinical symptoms characterized with the intermittent abdominal pain and with the slowly progressive bowel obstruction. After nine days of clinical observations and a follow-up with abdominal X-rays and US the upper abdomen lesion with target appearance was detected. Because of the worsened general condition the patient underwent the CT examination which demonstrated typical findings of the intussusception. CT findings and a worsened clinical picture were the reasons for an urgent surgical intervention. The right haemicolectomy without a preoperative reduction of the intussusception has been done. The adult intussusception may be a rare cause of the abdominal pain but it must be on the differential diagnosis list in the case of the intermittent abdominal pain, especially with clinical signs of the bowel obstruction. The reported case also supports the opinion that CT is the imaging method of choice for the adult intussusception.

References

1. Catalano O. Transient small bowel intussception: CT findings in adults. *Br J Radiol* 1997; **70:** 805-8.

2. Agha FP. Intussusception in adults. *AJR Am J Roentgenol* 1986; **146:** 527-31.

3. Warshauer DM, Lee JKT. Adult intussusception detected at CT or MR imaging:Clinical-imaging correlation. *Radiology* 1999; **212:** 853-60.

4. Stubenbord WT, Thorbjarnarson B. Intussusception in adults. *Ann Surg* 1970; **172:** 306-10.

5. Garner JP, Haldipur, Ravi K, Amarnath TS, Gupta R. Colonic intussusceptions in adults: three cases and review of the literature. *Indian J Surg* 2006; **68:** 322-4.

6. Omori H, Asahi H, Inoue Y, Irinoda T, Takahashi M, Saito K. Intussusception in adults: a 21-year experience in the University-affiliated Emergency Center and indication for nonoperative reduction. *Dig Surg* 2003; **20:** 433-9.

7. Azar T, Berger DL. Adult intussusception. *Ann Surg* 1997; **226**: 134-8.

8. Sarr M. Commentary on Intussusception in adults: a 21-year experience in the University-affiliated Emergency Center and indication for nonoperative reduction. *Dig Surg* 2003; **20:** 438-9.

9. Merine DS, Fishman EK, Jones B, Siegelman SS. Enteroenteric intussusception: CT findings in nine patients. *AJR Am J Roentgenol* 1987; **148:** 1129-32.

10. Knowles MC, Fishman EK, Kuhlman JE, Bayless TM. Transient intussusception in Crohn disease: CT evaluation. *Radiology* 1989; **170:** 814.

11. Eisen LK, Cunningham JD, Aufses AH Jr. Intussusception in adults: institutional review. *J Am Coll Surg* 1999; **188:** 390-5.

images in clinical medicine

Basal cell carcinoma in the inner canthus

Boris Jančar

Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia

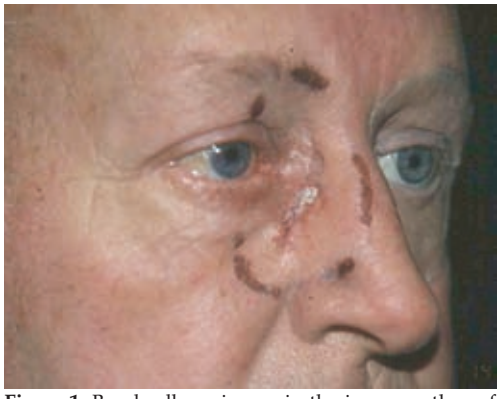


Figure 1. Basal cell carcinoma in the inner canthus of the right orbit; irradiation field is marked.

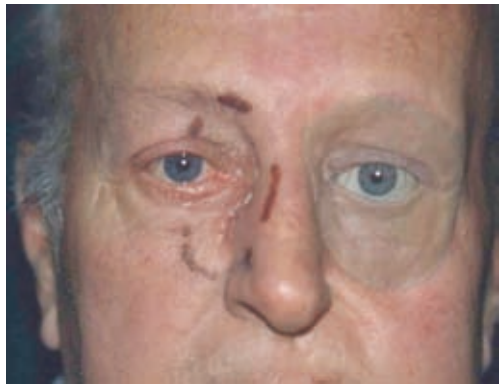


Figure 2. Tumour in the inner canthus of the right eye and epithesis of the left orbit and ethmoid.

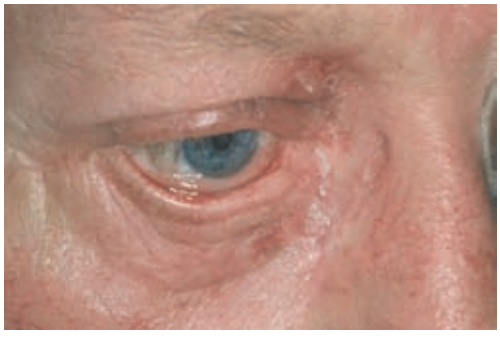


Figure 3. One year after irradiation.

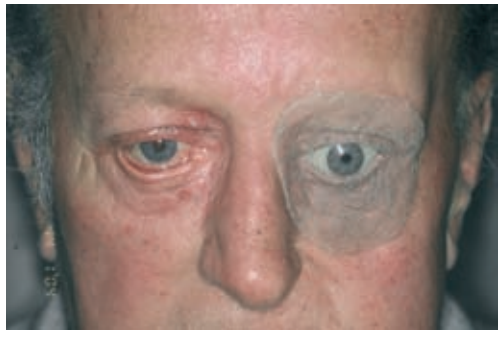


Figure 4. One year after irradiation.

Received 12 April 2007
Accepted 19 April 2007

Correspondence to: Prim. Boris Jančar, MD, MSc, Department of Radiation Oncology, Institute of Oncology Ljubljana, Zaloška 2, Ljubljana, Slovenia; Phone; + 386 1 5879 295; Fax: + 386 1 5879 295; E-mail: bojancar@onko-i.si

In January 2003, a 66-year-old patient visited the outpatient clinic at our Institute for the follow-up examination of the tumour in the inner canthus of the right eye. Biopsy of the tumour was made in November 2002 at the Department of Otorhinolaryngology and Cervicofacial Surgery of the University Medical Centre Ljubljana. Histology of the

excised sample confirmed basal cell carcinoma. The patient also told that, 10 years earlier, i.e. in 1993, he was operated on for a "lump" that developed on the same site. The patient was told that "lump" was sebaceous glad. But in a year, the "lump" reappeared and was removed again.

In 1994, the patient was operated on for squamous cell carcinoma of the ethmoidal sinus on the right, which was infiltrating into the right orbit. Ethmoidectomy was performed on the right side, with the exenteration of the right orbit. Postoperatively, the patient was treated also with telecobalt therapy and received a tumour dose (TD) 56 Gy.

On the follow-up examination in 2003, an indurated 2.5 cm long scar was still seen in the canthus of the right eye. The left cheek and orbit were covered with epithesis material (Figures 1, 2). The patient was irradiated by an orthovolt unit (Pantak), with the bulb of the irradiated eye protected; he received a TD 40 Gy. The tumour regressed completely (Figures 3, 4). These photos (Figures 3, 4) were taken on 14 January 2004.

On the last follow-up control in May 2006, no evidence of the disease recurrence was observed either in the area of ethmoid sinus or in the inner canthus of the right eye.

Radiol Oncol 2007; 41(3): 115-22. *doi:10.2478/v10019-007-0020-y*

review

Adjuvant treatment of breast cancer patients with trastuzumab

Erika Matos, Tanja Čufer

Institute of Oncology Ljubljana, Department of Medical Oncology, Ljubljana, Slovenia

Background. *Trastuzumab is a monoclone antibody directed against HER2 receptors that are overexpressed in approximately 20% of breast cancer patients. The present paper presents five clinical trials in which trastuzumab was applied in breast cancer patients in adjuvant setting. The results of all the trials consistently demonstrate a high efficacy of this target drug in the patients with HER2 positive tumours. So far, no formal guidelines for using trastuzumab in adjuvant setting for breast cancer have been approved. The reasons are many: (i) mean observation time in the studies done so far was considerably short; (ii) the drug was used according to different schedules, (iii) the overall time of treatment with trastuzumab was different in each trial, (iv) late side effects of treatment with trastuzumab are inadequately investigated, and (v) nobody can so far say for sure for which HER2 status patients therapy with trastuzumab is really beneficial.*

Conclusions. *Trastuzumab is definitely very helpful in the treatment of the HER2-positive breast cancer patients that are hormone-independent and of anatomically larger tumours; but, what the absolute benefit of trastuzumab therapy in the treatment of small hormone-dependent tumours is remains a mystery. Incidentally, it must be borne in mind that cardiotoxicity, the well known side effect, may put particularly elderly patients at risk of death, thus beating any treatment advantages down. It has also not been yet resolved at what time it would be most appropriate to start with the therapy with trastuzumab, what would be the optimal duration of the therapy and whether trastuzumab is to be administered concurrently with chemotherapy or immediately after it? What is the optimal treatment duration, one or two years or only a few months? In addition there is still a question of optimal HER2 status determination and which HER2 status predicts for trastuzumab benefit. These questions will hopefully be answered after a longer observation time of the patients included in five clinical trials that are discussed in the article.*

Key words: breast neoplasms- therapy; receptor, ERB-2 – antagonists and inhibitors; antibodies, monoclonal

Introduction

Breast cancer is the most frequent malignant disease in women. Given the clinical course, this disease is very diverse. It has now been known for some time that breast cancer may be hormone-dependent or in-

Received 12 July 2007

Accepted 26 July 2007

Correspondence to: Erika Matos, M.D., Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia; Phone: +386 1 5879 284; Fax: +386 1 5879 400; E-mail: ematos@onko-i.si

dependent and that this characteristic is one of the crucial in the course of the disease and its treatment. After recognizing new molecular characteristics of tumour cells, the diversity appears to be even greater. Tumour cell membranes as well as the inside of cells are populated with different proteins that are incorporated in the signal paths controlling the cell growth and reproduction. One of these proteins is HER2, a receptor for human epidermal growth factor. The tumours with overexpressed receptor HER2 are referred to as HER 2 positive tumours, which represent approximately 20% of all breast cancers. These tumours are biologically more aggressive. At the time of disease detection, they are usually larger than HER2 negative tumours, very often axillary lymph nodes are already involved, and in non-treated patients, the time interval to the disease recurrence is usually shorter.[1] According to recent results, these tumours are highly sensitive to anthracylines, whereas their sensitivity to hormonal therapy is less explicit. Approximately 50% of HER2 positive tumours are hormone-dependent; however, it seems that the hormonal therapy is less efficient in patients with these tumors.[1-3]

HER2 status can be determined by immunohistochemistry (ICH) or by fluorescence in situ hybridization (FISH). The former determines the quantity of HER2 protein in a cell membrane, and the latter, the HER2 gene amplification.[1]

The prognosis of the HER2-positive breast cancer patients improved significantly with the introduction of HER2-targeted agent, namely trastuzumab, in the treatment. Trastuzumab is a recombinant monoclonal antibody directed against HER2 receptor. Trastuzumab first proved to be effective in the treatment of patients with advanced breast cancer and overexpression of HER2 receptors.[4,5]

The binding of trastuzumab to HER2 receptor inhibits the signal pathways inside a tumour cell, which are essential for a cell growth, reproduction and distant metastatic spread. Trastuzumab, applied as monotherapy or in combination with cytostatics, significantly increases the survival of patients with HER2 positive metastatic breast cancer and improves disease control.[4,5] Unfortunately, metastatic breast cancer is still incurable disease. Trastuzumab was found to be effective in patients with overexpressed HER2 receptor, determined positive either immunohistochemicaly (IHC 3+) or by FISH. If IHC score is 2+, FISH test should be performed in order to determine HER2 status.[6]

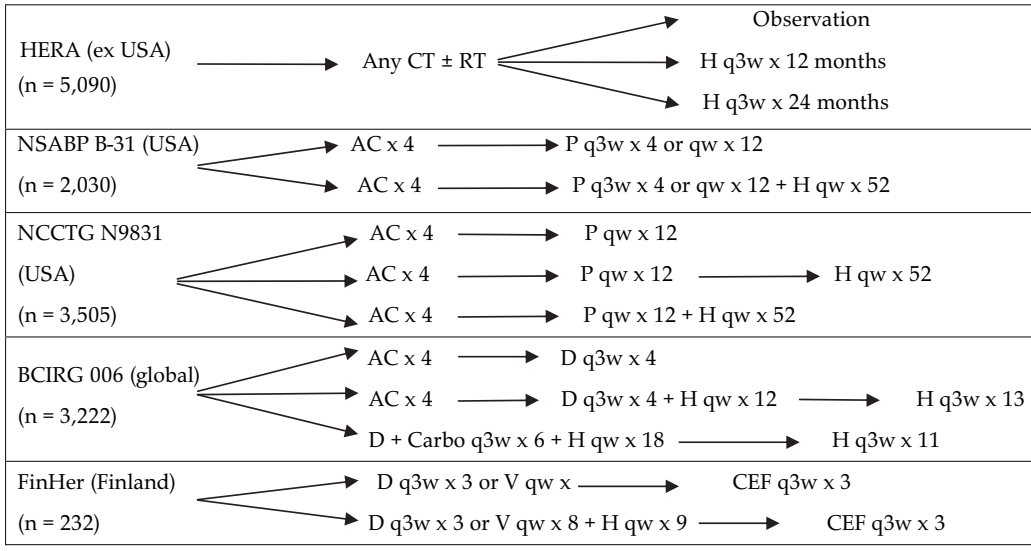
In addition to trastuzumab, targeting selectively HER2 receptor, some new target drugs are already in pre-clinical and clinical trials; according to the results of clinical trials, some have already proven to be effective in the treatment of HER2 positive breast cancer patients. One of these drugs is lapatinib, a small molecule inhibiting not only HER2 but also HER1 receptor.[1]

The role of trastuzumab in adjuvant therapy

High efficiency of trastuzumab in the treatment of metastatic breast cancer motivated researchers to further investigate the drug and use it in adjuvant setting.

So far, five big prospective clinical trials in which trastuzumab was applied as adjuvant therapy have been performed. Over 13,000 patients were included in these trials, all investigated trastuzumab applied in combination with cytostatics. The trials were carried out according to different treatment schedules (Table 1). In the HERA trial patients were administered trastuzumab only after completed adjuvant cytostatic treatment. This was the three arm trial: (i)

Table 1. Trastuzumab adjuvant trials designs



the treatment arm without trastuzumab – the comparison arm, (ii) the treatment arm with one-year trastuzumab therapy, and (iii) the treatment arm with two-year trastuzumab therapy. So far, only the results of the second arm are available, *i.e.* of one-year therapy with trastuzumab, while the results of the two-year therapy are awaited and will hopefully be available next year.[7] In both American trials (NSABP-B31 in NCCTG N9831), the patients first received chemotherapy according to AC schedule (adriablastin, cyclophosphamide), and continued with a weekly or three-weekly paclitaxel. Trastuzumab was added to paclitaxel, and after completing cytostatic therapy, the patients were receiving it as monotherapy for one year.[8,9] In the BCIRB 006 clinical trial, the patients were first treated with 4 cycles of chemotherapy according to AC schedule, followed by docetaxel with or without the addition of trastuzumab, which they were receiving for one year. The third treatment arm in BCIRG 006 was non-anthracycline one; the patients in this arm were treated with a combination of docetaxel and carboplatin to which trastuzumab was added at the very start of the therapy. The patients from this treatment arm were treated with trastuzumab for one year as well. In contrast to the two American trials in which the patients were receiving trastuzumab in weekly doses, the patients of the BCIRG 006 trial started the therapy with weekly doses of trastuzumab and were receiving it in these doses as long as they were receiving also docetaxel; after completing chemotherapy with docetaxel, they were receiving it in 3-weekly schedule.[10] The Finnish trial FinHER was slightly different from all the others. The patients received only nine weekly infusions of trastuzumab in combination with taxanes or vinorelbine, and after that the treatment with anthracyclines was following.[11]

Patients' selection

The treatment schedules in the above trials were different, but the inclusion criteria were very similar. The criterion that was common to all trials was the requirement that the patients had the HER2 positive tumour surgically removed. Another in-

clusion criterion was normal LVEF (left ventricular ejection fraction) and absence of any serious cardiologic morbidity. The trials were conducted on the patients with positive as well as those with negative axillary lymph nodes. The lowest percentage of node-positive patients (57%) was included in the HERA trial and the highest (89%) in the FinHER trial. The patients with node negative disease were also included in the trials provided that they had at least one additional unfavourable prognostic factor. This additional prognostic factor was the size of the tumour that, in HERA trial, had to be larger than 1 cm [7], whereas in the American trials, it had to be larger than 2 cm and/or 1 cm provided that the tumour was hormone-independent.[8] For the inclusion in the BCIRG 006 trial, the size of the tumour had to be larger than 2 cm; if it was smaller, it had to be hormone-independent or purely differentiated or diagnosed in a patient aged less than 35 years.[10] The Finnish trial included patients with tumours larger than 2 cm or if smaller those with negative progesterone receptors.[11] The patients with hormone-dependent as well as those with hormone-independent tumours were included in the above trials. The lowest percentage of patients with hormone-independent tumours was included in the Finnish trial (47%) and the highest in the BICRG 006 trial (54%).

Table 2. Efficacy of trastuzumab in adjuvant setting

1.) NSABP B31/NCCTG 9831 (MFU 3 years)		
DFS	HR = 0.49	p = 0.001
OS	HR = 0.63	p < 0.004
2.) HERA (MFU 2 years)		
DFS	HR = 0.64	p < 0.0001
OS	HR = 0.66	p < 0.0115
3.) BCIRG 006 (MFU 3 years)		
AC → TH		
DFS	HR = 0.61	p < 0.0001
OS	HR = 0.67	p < 0.004
TCH		
DFS	HR = 0.59	p = 0.0003
OS	HR = 0.66	p = 0.017
4.) Fin-HER (MFU 3 years)		
RFS	HR = 0.42	p = 0.01
OS	HR = 0.41	p = 0.07

DFS - disease-free survival
OS- overall survival
RFS - relapse-free survival
MFU - median follow up

Results – efficacy of trastuzumab applied in adjuvant setting

Despite different treatment schedules, the results of these trials were remarkably consistent. They definitely proved that the addition of trastuzumab to the cytostatics remarkable increases the likelihood of cure of the patients with operable HER2-positve breast cancer.

After a mean observation time of more than three years, it was noted that the use of trastuzumab decreased the risk of recurrence by approximately 50% (HR range 0.42 – 0.64) and the risk of death by approximately 40% (HR range 041 – 0.66). The differences in the disease-free survivals and overall survivals were highly statistically significant in all trials (Table 2). The addition of trastuzumab has a favourable effect regardless of the concomitantly applied cytostatic therapy. A statistically significantly improved disease-free survival and overall survival were reported also in the patients who were treated with non-anthracycline adjuvant therapy.[10] And, to our surprise in Finnish trial merely a nine-week therapy with trastuzumab improved significantly both the disease-free survival and overall survival at same extend as one year therapy in other trials.[11]

Table 3. Relative and absolute benefit of adjuvant trastuzumab according to hormonal status of tumor and anatomical spread of the disease

	Relative risk for relapse * – HERA trial (oral presentation: Gelber; SABCS 2005) (12)		Estimation of absolute benefit **	
	ER in PR neg.	ER in/ali PR poz.	ER in PR neg.	ER in/ali PR poz.
N≥4	33%	33%	16%	16%
N1-3	25%	12%	12%	6%
N0	18%	10%	9%	5%

* median observation time of 1 year

** 50%-reduced risk of relapse was estimated from the results of the above trials (8,9,10,11) with a mean observation time ranging 1-3 years. The analysis of the results showed a 40-50% relative risk reduction.

Patients' subgroup particularly benefiting from the treatment with trastuzumab

According to the results presented, trastuzumab is effective for all HER2 positive breast cancer patients, irrespective of anatomical stage (tumour size, nodal status) and of hormonal receptor status.[7,8]

Today, it is generally accepted treatment for HER2 positive early breast cancer patients. The data analysis of the HERA trial presented by Gelber at SABCS in 2005 showed that the absolute benefit was varied.[12] The patients with hormone-independent tumours or anatomically amply spread disease are benefiting more from the treatment with trastuzumab. And what is also very important that the significance of hormone-dependency diminishes with the increasing spread of the disease (Table 3).

HER2 status determined by IHC or FISH seems to be a reliable parameter for selecting metastatic breast patients who may benefit from trastuzumab therapy. But it is not known if HER2 status determined by these two methods defines well a group of patients who may benefit from adjuvant trastuzumab. A study presented at last ASCO meeting showed that a significant proportion of patients with HER2 negative tumours benefited from adjuvant trastuzumab. At the time being we are still not sure if HER2 status as it is defined now is a good predictor of benefit from adjuvant trastuzumab.[13]

Significance of early start of treatment with trastuzumab

At present, it is believed that the patients with HER2-positive tumours should start the adjuvant therapy with trastuzumab as early as possible. The above suggestion was confirmed also by the analysis of 1682 patients included in the clinical trial N9831 that compared the survival of the patients who received trastuzumab after the completed treatment with cytostatics and the survival of patients who started the therapy with trastuzumab concomitantly with paclitaxel. The latter patients who received trastuzumab earlier, *i.e.* concomitantly with paclitaxel, had significantly better survival (HR 0.63).[8]

Safety of treatment with trastuzumab

In all trials performed on trastuzumab, cardiotoxicity appears to be to the most severe side effect. From the studies on the patients with disseminated disease, it could be assumed that the combination of anthracyclines and trastuzumab, though considered to be a highly effective combination, was

Table 4. The risk of heart failure in patients treated with adjuvant trastuzumab: depends upon the age of a patients, heart function and previous anthracycline-based chemotherapy

		Age (years)	
		<50	≥50
LVEF (%) after AC (7)	50-54	3/48 (6.3%)	9/47 (19.1%)
	55-64	5/229 (2.2%)	10/194 (5.2%)
	65+	1/160 (0.6%)	2/159 (1.3%)

p (age) = 0.04, p (LVEF) < 0.0001

severely cardiotoxic. A concomitant application of both agents is therefore unacceptable in routine clinical practice. An independent analysis of cardiotoxic effects was made on 837 patients included in the trial NSABP-B31 and, from the analysis of results it was concluded that the risk for cardiotoxicity correlated with the age of patients at first administration of trastuzumab and with the functional performance of the heart assessed before treatment by the LVEF. Undesired treatment effects may be expected to be more frequent in the patients aged over 50 years and in those with lower starting LVEF. Patients with heart failure or poor functional performance of the heart were not included in the analysis (Table 4). However, it remains unclear to what extent cardiotoxicity is due to trastuzumab and to what extent to an earlier therapy with anthracyclines. An interesting conclusion drawn from the results of the trial BCIRG 006, which studied cardiotoxic side effects, was that cardiotoxicity significantly increased if trastuzumab was used after the anthracycline based chemotherapy; but, it did not appear after non-anthracyclne based chemotherapy.[14]

Other side effects of treatment, often mentioned in the studies, are also hypersensitive reactions. Severe allergic reactions *e.g.* drop of blood pressure or bronchospasm, are very rare. The pyrogene reactions unique associated with the first drug administration are more frequent. They usually appear in app. 30% of patients. Pneumonitis is also a possible, but rather rare undesired effect with the incidence of approximately 0.2% (4). So far, no firm data is available about possible late side effects of treatment with trastuzumab.

Conclusions

Trastuzumab, an inhibitor of HER2 receptor, is definitely a very effective drug for the treatment of a selected group of patients with HER2 positive breast cancer. Five large clinical trials including more than 13.000 patients uniformly confirmed the beneficial role of trastuzumab in terms of disease free survival and overall survival in all HER2 positive patients. However, the role of trastuzumab in the adjuvant therapy has not been precisely determined and the guidelines for its use have not been generally approved yet. A number of questions remain unanswered, *e.g.*: What would be the optimal treatment duration? When should it be optimal to start the therapy with trastuzumab? In which combination with cytostatics would it be optimal? When should the combination with anthracycline be applied? Which patients would be likely to benefit optimally from the treatment with trastuzumab? How to prevent undesired cardiotoxic effects of the drug? What are late side effects of treatment with trastuzumab? We believe that these questions will be answered

after a longer observation time and thorough follow-up of the patients treated with trastuzumab and included in the described clinical trials performed to prove the efficiency of trastuzumab in adjuvant setting. Only a careful observation and follow-up of patients treated with trastuzumab by experienced therapists will present benefits of such treatment for each patient individually and thereby also to other potential patients. Undoubtedly, trastuzumab is a very promising drug for a selected group of HER2 positive breast cancer patients. In addition, there are new target drugs in development. Among the drugs for treating HER2-positive breast tumours, the most promising seems to be lapatinib, a dual inhibitor of both HER1 and HER2 receptors. What will be the optimal role of trastuzumab as well as of a few dozens of other target drugs that are being tested is not yet known; but, the drug trastuzumab was the first that proved (i) that the targeted therapy is far more efficient than the empiric treatment with cytostatics, in particular when it is applied in an early stage of the disease, that means in adjuvant setting, and (ii) that the targeted therapy, if properly chosen and managed, will improve overall survival and disease control rates in breast cancer patients.

References

1. Winer EP, Piccart-Gebhart MJ, Rugo HS, Sledge GW. Management of HER2-positive breast cancer. In: Perry MC, editor. *ASCO 2006 Educational book.* Alexandria, VA: ASCO; 2006. p. 3-14.

2. Gennari A, Sormani MP, Puntoni M, *Bruzzi P*. A pooled analysis on the interaction between HER-2 expression and responsiveness of breast cancer to adjuvant chemotherapy. [Abstract 41]. *Breast Cancer Res Treat* 2006; **100(Suppl 1):**s9.

3. Lipton A, Ali SM, Leitzel K, Chinchilli V, Engle L, Harvey HA, et al. Elevated serum Her2/neu level predicts decreased response to hormone therapy in metastatic breast cancer. *J Clin Oncol* 2002; **20:** 1467-72.

4. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. *J Clin Oncol* 2005; **23:** 4265-74.

5. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783-92.

6. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology; College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *J Clin Oncol* 2007; **25:** 118-45.

7. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, et al. HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomized controlled trial. *Lancet* 2007; **369:** 29-36.

8. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1673-84.

9. Perez ES, Romond EH, Suman VJ, Jeong J, Davidson NE, Geyer CE, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer.[Abstract 512]. *2007 ASCO Annual Meeting Proceedings. J Clin Oncol 2007;* **25(Suppl I):** 6s.

10. Slamon D, Eiermann W, Robert N, *Pienkowski T, Martin M, Pawlicki M,* et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in her2 positive early breast cancer patients: BCIRG 006 study. *Breast Cancer Res and Treat* 2005; **94(Suppl 1):** s5.

11. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Bono P, Alanko T, Kataja V, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbin with or without trastuzumab for breast cancer. *N Engl J Med* 2005; **354:** 789-90.

12. Gelber RD. *HERA trial (oral presentation); SABCS 2005.*

13. Paik S, Kim C, Joeng J, Geyer CE, Romond EH, Mejia-Mejia O, et al. Benefit from adjuvant trastuzumab may not be confined to patients with 3+ and/or FISH-positive tumors: Central testing results from NSABP B-31. [Abstract 511]. *2007 ASCO Annual Meeting Proceedings. J Clin Oncol 2007;* **25(Suppl I):** 5s.

14. Tan-Chiu E, Yothers G, Romond E, Geyer CE, Ewer M, Keefe D, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23:** 7811-9.

Radiol Oncol 2007; 41(3): 123-32. *doi:10.2478/v10019-007-0021-x*

review

Ionising radiation and trans-generational instability

Ivana Vrhovac, Goran Nikšić

Faculty of Science University of Zagreb, Croatia

Background. *Indirect monitoring of the impact posed by ionising radiation to the genome instability of the descendants, consequent to the irradiation of one of their parents, boils down to the investigation of changes occurring exclusively in the mini-satellite loci of the cells constituting the gametal developmental line. The resultant mini-satellite mutations are expressed in their percentages, and equal to the ratio of the number of mutated alleles in that particular generation over the total number of alleles present. The impact of ionising radiation to the irradiated parent's offspring was first noticed on haematopoietic mouse stem-cells. Even though an irradiated cell of a female parent lacks any mutations whatsoever, daughter cells present with the increased mutation rates. The observed phenomenon of the so called trans-generational instability has been defined as the occurrence of mutations in the genome of individuals originating from the irradiated ancestors. Due to the aforementioned, one can conclude that these mutations need not be present in the irradiated parental cells, and do not necessarily vanish in the next few generations, but may result in the increase in mutation rates observed in the latter.*

Conclusions. *The results of the investigations performed on the animal model, as well as of those carried out in human population, point to the occurrence of significant changes to be found on mini-satellite loci of the descending generation, while the mechanism underlying those changes hasn't been completely clarified yet, and, therefore, calls for the further investigation.*

Key words: radiation ionizing; radiation effects; microsatellite repeats

Introduction

It has been well-recognised that ionising radiation is capable of inducing structural changes of biologically essential macromolecules, resulting in the development of malignancy within a human organism.[1] Therefore, the development and perfecting of biomonitoring methods which enable the follow-up of early indicators of cellular alterations caused by irradiation (*i.e.* the indicators of the reactions exhibited by irradiated cells), dependent on the radiation type and dose delivered, are critical. Last years have witnessed a significant advancement in the detection of effects of parental irradiation, apparent in their offspring, *i.e*. the indirect effect of irradiation expressed as the genome instability of their descendents.[2-6]

Received 28 August 2007

Accepted 10 September 2007

Correspondence to: Ivana Vrhovac and Goran Nikšić, Faculty of Science University of Zagreb, Rooseveltov trg 6, 10 000 Zagreb, Croatia; Phone +385 1 48 77 700; E-mail: ivanavrhovac@yahoo.com E-mail: marsonia2258@yahoo.com

Monitoring of the irradiation impact carried throughout a few generations subsequent to the irradiation of one of the parents, actually boils down to the investigation of changes encountered in the mini-satellite loci of the referent population, the latter being narrowed exclusively to the cells constituting the gametal developmental line.[7-10] The parameter employed in the follow-up of their frequency, the so called mutation rate, is calculated as the number of mutated alleles present in the referent generation, over the total number of alleles hosted therein, and expressed either in form of ratio, or percentage of the mutations encountered.

The impact of ionising radiation on the offspring of the first parental (F1), or the next few generations stemming from the irradiated individual, was first noticed on stem haematopoietic mouse cells. Although an irradiated cell of the female parent lacked any mutations whatsoever, the increase in the mutation rate of the daughter cells had been noticed. The phenomenon was termed the trans-generational instability, and defined as an uncommon and frequent occurrence of mutations to be found in the genome of individuals stemming from irradiated ancestors (parents, grandparents). Nevertheless, those mutations need not be present in the irradiated ancestors' cells, and do not necessarily vanish in the next generation, however, may lead to the increase in mutation rate observed in some of the descendants embraced by the next few generations.[11]

The results of experimental studies conducted on mice, and the results of the investigation carried out in persons irradiated in Chernobyl, have pointed to significant changes of mini-satellites hosted by the descendants, even though, as communicated by Dubrova affiliated with the Genetic Department of the Leicester University (United Kingdom), many issues haven't been resolved yet.[12-14]

DNA satellites

DNA satellites (micro- and mini-) are considered to be frequently-repeated segments of the cellular genome. Within this frame, micro-satellites represent shorter repeats, measuring about 500 pb in their total length, with the basic repeat of 1-4 pb.

Mini-satellites encountered in the human genome, are spots where frequent homologous recombination takes place, located adjacent to the telomere sequences that do not undergo transcription. However, there exist also mini-satellites present in non-coded inter-genetic genome sequences, *i.e.* the sequences that, following transcription, represent parts of the intron. Mini-satellites are more complex, and are constituted of repeats measuring 10-100 pb in size, and 0.1-20 kb in length. Most of the repeats host the GGGCAGGAXG pattern, within which an X can be any nucleotide whatsoever. The most frequently encountered mini-satellites are polyA and polyT, as well as CT/AG and CA/TG sequences, greatly resembling the *chi* sequence of E. coli, which represents a recombinant signal. Mini-satellites encountered in human genome are spots where homologous recombination takes place more frequently (the recombinant "hot spots"). However, as stated already, there exist also mini-satellites present in non-coded inter-genomic sequences, as well as the ones prone to exprimation, such as the *MUCI* locus, which contains the gene for the hyper-variable glycoprotein recovered from body fluids and some tissues, constituted of frequently-repeated mini-satellite sequences.[14]

Satellite DNAs are prone to mutations. Mutations of mini-satellites encountered in humans, comprise complex intra-allele rearrangements and alterations of the sequence length (mostly expansion). Mini-satellite mutations encountered in human populations, may arise spontaneously only

in cells constituting the gametal developmental line, and are characterised by the high, 0.5-13%-mutation frequency per gamete, while mutations encountered in micro-satellite sequences may be found in somatic cells as well.

Most of the mini-satellite loci (90%), are situated in the sub-telomere chromosomal regions, and had been considered irrelevant for quite a long time. They were believed to be the parts of the genome usually called "the junk DNA", although nowadays an issue of their potential influence on the alternative splicing, genome imprinting signal and regulation of gene expression, established on the transcriptional level, has been raised.[8, 15-17]

Differences in length of satellite sequences can be easily detected with gel electrophoresis subsequent to the polymerase chain reaction (PCR). The starters (probes) employed with the polymerase chain reaction, are complementary to the parts of the genome surrounding the repeats. Their hyper-variability within population, and easiness of their detection, were the exact reasons for their forensic implementation. Based on the comparison of length of a certain number of standard satellite loci, recovered from samples taken from a number of persons, positive identification can be made.[18,19] The exact determination of the loci and their mutations is accomplished by the hybridising Southern blotting method.[20]

Trans-generational instability observed with irradiated mice

The first experimental model utilised in the investigation of trans-generational instability, which made use of mini-satellite monitoring, was represented by the mice *ESTR loci*. Namely, the mini-satellites present in mice markedly differ from those present in humans, and are divided into two groups: real mini-satellites, measuring 0.5-10 kb in length, and having 14-17 bp long repeated patterns, and simple tandem repeated sequences, called the *ESTR* (*expanded simple tandem repeats*), measuring 0.5-16 kb in length, and having 4-6 bp long repeats.[12,13,15,21] Mice *ESTR loci* contain shorter repeated patterns, and their mutations occur both in somatic and gametal developmental line cells. Though in some features (length of the repeated sequence, high content of G/C base pairs, and locus length) resembling more those found in humans, mice mini-satellites do not exhibit mutations of a complex intra-allele-arranging type, and do not present with a high mutation rate that can be run across in human population.[22-25]

One of the most significant results in this research area is that of the experiment conducted in male mice of the CBA/

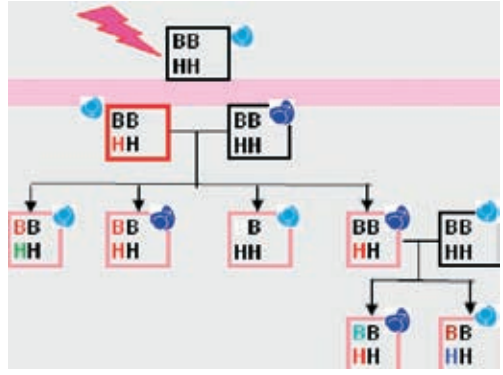


Figure 1. Model describing the inheritance of mutations in transgenic instability. Studied independent alleles are represented by the letters B and H, wild type is written in black and mutant types are written in various colours. Each colour represents a different kind of mutation. The genotype of the irradiated mouse is in the red box, of his direct offspring is in the pink boxes and in the black boxes is the genotype of non irradiated individuals. The picture shows that the mechanism of the inheritance doesn't obey the rules of Mendelian inheritance and that mutations in minisatellite alleles that weren't mutated in parents can occur. Epigenetic mechanism is the best explanation for this type of inheritance.

H strain, irradiated with various radiation types (acute X-ray irradiation, chronic gamma-irradiation, and fission high-LET neutrons).[12,13] At post-irradiation week 3, 6 and 10, irradiated males had copulated with non-irradiated females of the same strain. It has been held true that a time-period elapsed from the irradiation time-point, is of importance, since male germinative cells had stemmed from irradiated post-meiotic spermatozoids (at post-irradiation week 3), pre-meiotic spermatogonia (at post-irradiation week 6) and stem cells (at post-irradiation week 10) (Figure 1). Results obtained with all radiation types employed, had demonstrated statistically significant rise in the number of mutations emerging from the *ESTR loci* of F1 and F2 mice generation. The frequency of mutations was very similar to that of parental samples, and failed to exhibit the tendency towards diminishment. Some of the research results point at the increase in mutation rates encountered among younger generations, while genome repeats point towards trans-generational instability exhibited following ionising radiation exposure of one of the parents. These research results have reflected in a significant decrease in number of mice required for radiation experiments as compared to classical biomonitoring methods, capable of detecting genome changes solely in case a few thousands or even a few hundred thousands mice have been used. The detection of statistically significant number of mutations located on the *ESTR loci,* called for the employment of only 300-400 mice. In line with the foregoing, the investigation of mini-satellites proved better and more sensitive tool to be engaged in the monitoring of radiation impact, than classical cytological techniques did.[26]

Promising results of the first experiments conducted in mice, motivated Dubrova and associates to continue their research in an attempt to disclose the mechanism underlying the occurrence of mutations on the *ESTR loci*, the importance of gameto-generic phase in which the irradiation took place, the importance of mice strain involved, and the importance of the type of irradiation employed. In light of the foregoing, aside from CBA/H, also other mice strains, such as C57BL/6 and BALB/c, have been used. The results of the research conducted in mice of parental generation, irradiated with low-LET X-rays and low-LET fission neutrons, were engaged for the purpose of disclosing the mechanism underlying the mutation occurrence. To this goal, changes on two independent loci of mice genome, *Ms6-hm i Hm-2,* have been observed. The results revealed the origin of mutated alleles (either in a non-irradiated female, or in an irradiated male parent), to be detectable in most of the animals involved. A crucial part of the experiment was represented by the determination of mutations in gametes of the descendants whose genotype came as a result of coupling of sperms developed from irradiated post-meiotic spermatozoids (at post-irradiation week 3). As concerns the genotype of the offspring in question, the initial research results failed to reveal an increase in number of mutations, which led to the conclusion that the basic mechanism involved in trans-generational instability becomes active not sooner than the diploid gametal-generic stage. However, a further investigation yielded confusing results, since the rate of mutations found in the offspring in reference, proved higher than that observed with the offspring of the control group, *i.e*. that originating from the non-irradiated male parent (the father). Under such terms, one is tempted to conclude that the source (the cause) of genetic instability encountered in the offspring, arises in fact either from diploid zygote following impregnation, or in the early embryo-generic stage, rather than during meiosis, as first assumed. The possibility that the source of

instability lies within the very sperms was rejected based on substantial compactness and biochemical inactivity of their chromatin. Another surprising phenomenon encountered during the course of the study, was the occurrence of mutations located on the allele inherited from non-irradiated mother, which means that genome instability induced by the irradiation of the male parent, affects the alleles inherited from another parent as well.[27]

There exist two theories on the mechanism underlying trans-generational instability. According to one of them, mutation is a result of a direct damage inflicted to the DNA molecule in the area hosting one of the *ESTR* loci. If that is the case, in the offspring of an irradiated father (and their descendants), mutations located in the allele inherited from the father should be dominant. In oppose, mutations are equally encountered in both alleles of all descendants, ruling this possibility out. In addition, the number of changes encountered in 3-4 kb region, established in the population, is 100-fold greater than that statistically expected in case of a mutation arising from a direct DNA damage.[28] According to the second theory, mutations are included into a certain set of genes, such as those responsible for DNA repair. A mutation of the aforementioned kind might lead to the one engaging both alleles. If that is the case, in line with Mendel's Laws of Inheritance, each generation would witness a decrease in mutation rate based on the crossover with non-irradiated females hosting wild gene types. However, in this particular case, the mutation rate is similar in individuals of all generations. Following the rejection of these theories, the cause of trans-generational instability proposed in the literature, has been an epigenetic effect of a still non-clarified background.

The experimental research has indicated that the frequency of mutations to be seen in the offspring of irradiated mice depends on the strain used in the experiments. Within this context, the BALB/c mice strain has been demonstrated to be the most sensitive one, while the C57BL/6 turned out to be the most stable one. The importance of utilisation of various mice strains lies within the corroboration of the fact that trans-generational instability is not a strain-specific phenomenon. Alike, the research into the genetic features of mice used for experimental purposes, contributes to the comprehension of mechanisms responsible for the mutations in reference. The results obtained in mice irradiated with doses of 0.4 Gy, 1 Gy and 2 Gy, are of significance in proving that both low- and high-LET irradiation may induce trans-generational instability, and that the rate of mutations encountered in the offspring is linearly dose-dependent.

Alike human mini-satellites, mice *ESTR* sequences had been considered irrelevant and inert for a fairly long time. However, it has been proven that a number of changes encountered in the offspring of irradiated mice belonging to various strains (for instance, the increase in lung and skin tumour rate, the rate of blood cell malignancies and the decrease in ovarian cells' impregnation rate), are inherited conformant to the trans-generational instability model.[27]

Specificity of hyper-mutable mini-satellites and the transgenic model

The fact remains that, apart from human genome, there exists no other organism containing hyper-mutable mini-satellite loci in its genome. Therefore, the results of the investigation carried out on mice *ESTR* loci, could not, beyond reasonable doubt, be extrapolated to humans. Having in mind that mice mini-satellites follow the pattern similar to that in humans and resemble the

latter in mutation rates, the potential solution to the problem would be the introduction of human mini-satellite loci into the mice genome. The transgenic individuals of such kind have been irradiated insofar; however, no such thing as the rise in rates of mutations encountered on these loci, nor the occurrence of trans-generational instability, have been noted.[17]

The trans-generational instability was first noticed in transgenic yeasts (*Saccharomyces cerevisae*), in which human mini-satellite loci had been introduced. In these models, even the protein that takes control over mini-satellite expansion that occurs during meiosis (termed the *Rad 1*), had been discovered. However, the instability noted in yeasts markedly differ from that in humans; for instance, mini-satellite mutations are usually boiled down to simple arrangements, lacking any trace of complex inter- and intra-allele rearrangements that can be found in people. In addition, in mutants in whom *Rad 27* protein has been affected, complex post-mitotic mini-satellite mutations occur in somatic cells as well, while in people the latter are limited to the gametal developmental line. In some individuals, a sequence diminishment has been observed as well, as oppose to humans who presented with the preferred sequence expansions.[17] Therefore, the sole manner of monitoring and investigating mini-satellite mutations in humans, are population studies.

Population studies

The results of the investigations indicating the presence of a post-irradiation risk imposed on as many as three mice generations launched a debate on potential risks for the human population, too. It is of note that mutations occurring on human mini-satellites are exclusively narrowed down to the cells of the gametal developmental line, and are of a more complex nature, so that mice models can not be considered relevant. Although the investigation of mini-satellite mutations occurring in humans are far more difficult to explore, due to the need of having a correspondent control group, the samples had been collected among families exposed to Chernobyl catastrophe, as well as among persons included into radioactive testing conducted in the Kazakhstan region Semipalatinsk, and cancer patients receiving radiotherapy. Due to the fact that the research in question was conducted on a relatively small number of persons exposed to different radiation types, as well as due to the impossibility of determining the exact irradiation dose delivered to the exposed persons based on the timing of their irradiation within the set timeframe, this study yielded contradictory results. Owing to the short half-life of unstable radioisotopes to which the families victimised by the Chernobyl catastrophe have been exposed, doses measurable immediately after the catastrophe were not relevant after all. Realistic doses were estimated based on the number of stable and unstable chromosomal aberrations detected in the exposed persons.[29] Blood samples had been collected from the families dwelling the Mogilev County of Belarus, affected by the Chernobyl catastrophe, while British families served as controls. The mini-satellite analysis revealed the mutation rate registered in irradiated family members, to be 1.6-fold higher than that of controls. In addition, an elevated mutation rate was observed also with children coming from parents deemed as high dose recipients. However, due to the inadequacy of the controls, *i.e.* the fact that control families were of different nationality and observed a lifestyle different from that of the exposed group, the results of these investigations were given no credit. In view of solving this problem, an adequate control group was

picked up, and compared to the members of the Ukrainian families (the areas under investigation were Zhitomir and Kiev Counties). For the aforementioned purpose, blood from children conceived prior and following the nuclear catastrophe had been sampled. In subjects conceived following the nuclear accident, a 60%-rise in mutation rate had been established. In addition, the exposed persons had been subjected to the genotype analyses of the cells constituting the gametal developmental line, on the occasion of which only mutations in male cells (not in female ones) had been determined, despite the fact that both genders were exposed to equal radiation doses.[30]

Similar research had also been conducted among families dwelling Kazakhstan region of Semipalatinsk who had resided in the vicinity of the nuclear facility nearby which, starting from 1949 up to 1989, as many as 470 nuclear tests had been performed. The families in reference lived nearby the area of atmospheric, as well as underground and surface explosions. Persons of similar nationality, parental age, professions, and smoking habits, originating from the former Taldy Kurgan County of Kazakhstan, but not residing in the vicinity of the aforementioned location, served as controls. Alike the previous two, this research yielded positive results in terms of mutation rate elevation, in this particular case by as much as 70% as compared to the controls. In all of the aforementioned studies conducted in the territory of the former USSR, probes for the same mini-satellite alleles had been used.[26,29]

However, there exist also studies which failed to confirm the aforementioned results. For instance, the investigations conducted among children who managed to survive the most notorious event of an acute exposure to an enormous radiation dose, *i.e*. the Hiroshima bombing, failed to confirm the theory of trans-generational instability. Negative results of this study may serve as a proof that only certain types of radiation, or exposure (for instance, the Semipalatinsk families had been exposed to chronic, fairly uniform radiation, while the Hiroshima families had been exposed to an acute high-dose irradiation), are capable of inducing such a phenomenon. As a limitation of the studies conducted among children who managed to survive the Hiroshima bombing, the fact that most of the children under investigation were born 10 years after the nuclear attack on their parents, has often been put forward. This fact is most often taken as the main reason for negativity of the results of the study in question, together with the possibility that there exists a time-period after which the epigenetic mechanism of mutation induction "turns off". Negative results were also obtained with the analysis of sperm sampled from males diagnosed with seminoma both prior and following radiotherapy, who had been subjected to 0.4-0.8 Gy radiation, delivered in 15 fractions. The reason for the negativity of the results might be the fact that less-fractionated doses do not exhibit an additive effect. Additionally, negative results were obtained with the investigations conducted among descendants of the workers who took part in cleansing of the Chernobyl facility following the nuclear accident, and were exposed to daily radiation doses of 0.25 Gy. In confirmation of these results, the studies performed on mice managed to prove that a larger number of less fractionated doses lead to the same effect as does the single one, equal to their sum.[30,31]

Mini-satellite diseases

Mutations presented on mini-satellite loci are often put forward as causes of various diseases, for instance some tumours and

certain types of diabetes mellitus, although their genetic background remains to be somewhat unclear. The investigations of this kind have focused on the mini-satellite locus *HRAS1*, the mutations of which are incriminated to cause or contribute to the development of various diseases, *e.g*. ovarian cancer, and hereditary breast and gall bladder cancer. One of the most prominent articles in the field, had been founded on the investigations of the *HRAS1* locus, conducted in white females suffering from an ovarian cancer. Ovarian cancer is reported to be the fifth most common cause of death of US females, and the risk factors responsible for its more frequent onset are considered to be white race, older age, nuliparity and oral contraception. The mini-satellite *HRAS1* locus encountered within general population consists of 4 typical alleles and 12 atypical rare ones, the latter being trusted to emerge from the mutations of those 4 typical ones. Following the investigation of the *HRAS1* locus, performed in peripheral lymphocytes and tumour tissues of the sick women, as well as by virtue of comparison with the control samples taken from healthy white women of the similar age, a 50%-rise in share of rare alleles of the *HRAS1* locus had been noted. Statistical analyses had revealed a 1.66-fold rise in risk of developing the disease, encountered in women hosting one rare allele, and as much as 2.86-fold rise in the referent risk posed to the women hosting two of such alleles. These results prove beyond doubt that *HRAS1* locus plays a role in the onset of ovarian cancer, although the exact underlying mechanism remains to be unclear. It has been well-recognised that even as many as 4 nuclear transcript factors are bound to this allele, and that, under *in vitro* conditions, some of the alleles may pose as a transcription silencers or enhancers.[31] The diseases that might arise as a consequence of trans-generational instability induced by ionising radiation are leukaemia and Hodgkin lymphoma. Such pathology had been observed in children born nearby the Sellafield Nuclear Plant of the United Kingdom. Namely, children dwelling this area were noted to have an extraordinarily high incidence of the diseases in question. The results of the study performed as early as in 1990, pointed to an extremely high risk of developing leukaemia and/or Hodgkin lymphoma, assessed in children whose parents had, prior to the conception, worked in the power plant in question, and had been exposed to substantial radiation doses.[32]

Further investigation

The investigation conducted insofar, have demonstrated that ionising radiation is capable of influencing the genome of non-irradiated descendants, more precisely their mini-satellite loci. Further investigations, which might disclose the mechanisms underlying the occurrence of mutations on mini-satellite loci and trans-generational instability, should aim at monitoring of mini-satellite mutations to be used as a biomonitoring tool engaged in the assessment of risk of developing malignancies, present in the offspring. In addition, there exists the possibility of application of their results to the goal of designing more efficient radiotherapeutic protocols and safety-at-work measures to be observed in persons dealing with ionising radiation sources.[17] Significant improvement in understanding of the occurrence of micro-satellite mutations, is expected to be attained by the application of biophysical spectroscopic methods (for instance, NMR, circular dicroism), although the question why sequence expansions are preferred over deletions has been partially answered already, under the wing of the theory that this should be

attributed to the difference in stability of alternative DNA molecular structures.[33]

References

1. Garaj-Vrhovac V, Kopjar N, Ražem D, Vekić B, Miljanić S, Ranogajec-Komor M. Application of the alkaline comet assay in biodosimetry: assessment of *in vivo* DNA damage in human peripheral leukocites after γ-radiation incident. *Radiat Prot Dosim* 2002; **98:** 407-16.

2. Neel JV, Schull WJ, Awa AA, Satoh C, Kato H, Otake M, et al. The children of parents exposed to atomic bombs, estimates of the genetic doubling dose of radiation for humans. *Am J Hum Genet* 1990; **46:** 1053-72.

3. Sankaranarayanan K. Ionizing radiation and genetic risks X. The potential "disease phenotypes" of radiation-induced genetic damage in humans, perspectives from human molecular biology and radiation genetics. *Mutat Res* 1999; **429:** 45-83.

4. Kodaira M, Satoh C, Hiyama K, Toyama K. Lack of effects of atomic-bomb radiation on genetic instability of tandem-repetitive elements in human germ-cells. *Am J Hum Genet* 1995; **57:** 1275-83.

5. Dubrova YE, Nesterov VN, Krouchinsky NG, Ostapenko VA, Neumann R, Neil DL, et al. Human minisatellite mutation rate after the Chernobyl accident. *Nature* 1996; **380:** 683-6.

6. Byrne J, Rasmussen SA, Steinhorn SC, Connelly RR, Myers MH, Lynch CF, et al. Genetic diseases in offspring of long-term survivors of childhood and adolescent cancer. *Am J Hum Genet* 1998; **62:** 45-52.

7. Kelly R, Bulfield G, Collick A, Gibbs M, Jeffreys AJ. Characterization of a highly unstable mouse minisatellite locus: Evidence for somatic mutation during early development. *Genomics* 1989; **17:** 121-8.

8. Dubrova YE, Jeffreys AJ, Malashenko AM. Mouse minisatellite mutations induced by ionizing radiation. *Nature Genet* 1993; **5:** 92-4.

9. Sankaranarayanan K, Chakraborty R. Ionizing radiation and genetic risks XI. The doubling dose estimates from the mid- 1950s to present and the conceptual changes to the use of human data on spontaneous mutation rates and mouse data on induced mutation rates for doubling dose calculations. *Mutat Res* 2000; **453:** 107-27.

10. Vergnaud G, Denoeud F. Minisatellites, mutability and genome architecture. *Genome Res* 2000; **10:** 899-907.

11. Little JB. Radiation carcinogenesis. *Carcinogenesis* 2000; **21:** 397-404.

12. Dubrova YE, Plumb M, Brown J, Fennely J, Bois P, Goodhead D, et al. Stage specificity, dose response and doubling dose for mouse minisatellite germline mutation induced by acute radiation. *Proc Natl Acad Sci* 1998; **95:** 6251-5.

13. Dubrova YE, Plumb M, Gutierrez B, Boulton E, Jeffreys AJ. Transgenerational mutation by radiation. *Nature* 2000; **405:** 37.

14. Strachan T, Read A. *Human Molecular Genetics 2*. Oxford: BIOS Scientific Publishers Ltd; 1999.

15. Sadamoto S, Suzuki S, Kamiya K, Kominami R, Dohi K, Niwa O. Radiation induction of germline mutation at a hypervariable mouse minisatellite locus. *Int J Radiat Biol* 1994; **65:** 549-57.

16. Bois P, Stead JHD, Bakshi S, Williamson J, Neumann R, Moghadaszadeh B, et al. Isolation and characterization of mouse minisatellites. *Genomics* 1998; **50:** 317-30.

17. Bois PR. Hypermutable minisatellites, a human affair. *Genomics* 2003; **81:** 349-55.

18. Armour JAL, Brinkworth MH, Kamischke A. Direct analysis by small-pool PCR of MS205 minisatellite mutation rates in sperm after mutagenic therapies. *Mutat Res* 1999; **445:** 73-80.

19. May CA, Tamaki K, Neumann R, Wilson G, Zagars G, Pollack A, et al. Minisatellite mutation frequency in human sperm following radiotherapy. *Mutat Res* 2000; **453:** 67-75.

20. Bruce A, Roberts K, Lewis J, Raff M, Walter P, Johnson A. *Molecular biology of the cell* (4th edition): New York: Garland Pub; 2002.

21. Fan YJ, Wang Z, Sadamoto S, Ninomiya Y, Kotomura N, Kamiya K, et al. Dose-response of radiation induction of a germline mutation at a hypervariable mouse minisatellite locus. *Int J Radait Biol* 1995; **68:** 177-83.

22. Jeffreys AJ, Tamaki K, MacLeod A, Monckton DG, Neil DL, Armour JAL. Complex gene conversion events in germline mutation at human minisatellite. *Nature Genet* 1994; **6:** 136-45.

23. Jeffreys AJ, Neumann R. Somatic mutation process at a human minisatellite. *Hum Mol Genet* 1997; **6:** 129-36.

24. Tamaki K, May CA, Dubrova YE, Jeffreys AJ. Extremly complex repeat shuffling during germline mutation at human minisatellite B6.7. *Hum Mol Genet* 1999; **8:** 879-88.

25. Buard J, Collick AJ, Brown J, Jeffreys AJ. Somatic versus germline mutataion process at minisatellite CEBI (*D2S90*) in human and transgenic mice. *Genomics* 2000; **65:** 95-103.

26. Dubrova YE. Transgenerational germline instability. 33th Annual Meeting of the European Environmental Mutagen Society" Aberdeen, Great Britain 2003, Abstract pp 18.

27. Barber R, Plumb MA, Boulton E, Roux I, Dubrova YE. Elevated mutation rates in the germ line of first- and second-generation offspring of irradiated male mice. *Proc Natl Acad Sci USA* 2002; **99:** 6877-82**.**

28. Niwa O, Kominami R. Untargeted mutation of the maternally derived mouse hypervariable minisatellite allele in F1 mice born to irradiated spermatozoa. *Proc Natl Acad Sci USA* 2002; **98:** 1705-10.

29. Dubrova YE. Monitoring of radiation-induced germline mutation in human. *Swiss Medical Weekly* 2003; **133:** 474-8.

30. Dubrova YE, Grant G, Chumal AA, Stezhka VA, Karakasian AN. Elevated minisatellite mutation rate in the post chernobyl families from Ukraine. *Am J Hum Genet* 2002; **71:** 801-9.

31. Jeffreys N, Weitzel JN, Ding S, Larson GP, Nelson RA, Goodman A, et al. The HRASI minisatellite locus and risk of ovarian cancer. *Cancer Res* 2000; **60:** 259-61.

32. Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of case-control study of leukaemia and lymphoma among young people near Sellefield nuclear plant in West Cumbria. *Br Med J* 1990; **300:** 423-9.

33. Wells RD, Dere R, Hebert ML, Napierala M, Son LS. Advance in mechanisms of genetic instability related to hereditary neurological diseases. *Nucl Acids Res* 2005; **33:** 3785-798.

Radiol Oncol 2007; 41(3): 133-43. doi:10.2478/v10019-007-0022-9

3D-conformal radiotherapy for inoperable non-small-cell lung cancer – A single centre experience

Sabine Fromm[1], Andrea Rottenfusser[1], Daniel Berger[1], Robert Pirker[2], Richard Pötter[1], Boris Pokrajac[1]

[1]*Department of Radiotherapy and Radiobiology, Medical University of Vienna, Austria*
[2]*Department of Internal Medicine, Division of Oncology, Medical University of Vienna, Austria*

Background. *The purpose of this investigation was to evaluate feasibility, safety and efficacy of 3D-conformal radiotherapy (3D-RT) for inoperable non-small-cell lung cancer (NSCLC). Time to progression (TTP), including local recurrence and/or distant metastasis, local control rate (LCR), time to death (TTD) and side effects were evaluated.*

Patients and methods. *From 1997 to 2002, a total of 84 patients with inoperable NSCLC were treated with 3D-RT according to a prospective protocol at our institution. Depending on performance status, lung function and dose-volume constraints, radiation doses of either 66-70 Gy or 50-60 Gy +/- platin-based chemotherapy were applied.*

Results. *The treatment was well tolerated and the rate of side effects was low. Only one grade 4 pneumonitis was observed, the rate of grade 3 pneumonitis was 6% and 13% for grade 2. Two patients developed a grade 4 oesophagitis and no grade 3 oesophageal toxicity was observed. The analysis of dose-volume histograms (DVH) found a mean V_{20} (lung volume that receives 20 Gy) for the ipsilateral lung (IL) of 42%, a mean V_{20} for the contralateral lung (CL) of 14% and a mean lung dose IL of 25 Gy. The mean V_{20} IL in patients developing a pneumonitis grade 2-4 was 53.3%. The mean follow-up was 24 month. There was no difference in TTP (median 15 months) in the different treatment groups. Patients receiving higher radiation doses (66-70 Gy) had a benefit in an overall survival (OS) when the additional chemotherapy was applied (28 month vs. 16 month). Local control rates of mean 22% after 2 years were low.*

Conclusions. *The application of radiation doses up to 70 Gy is feasible and safe, also in combination with chemotherapy. Still, the local control and OS is poor. Thus, further trials to investigate the possibility of dose escalation in the lung without increasing lung toxicity significantly, also in more advanced tumour stages, are mandatory.*

Key words: carcinoma, non – small – cell lung – radiotherapy; radiotherapy, conformal; radiotherapy planning; computer - assisted

Received 26 September 2007
Accepted 30 September 2007

Correspondence to: Sabine Fromm, M.D., Department of Radiotherapy and Radiobiology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna; Austria; Phone: +43 1 40400 2689; Fax: +43 1 40400 2690; E-mail: sabine.fromm@akhwien.at

Introduction

In the European Union (EU) lung cancer is the most common cause of death from cancer. The estimated deaths in 1997 were 180 000, representing one-third of the total

cancer mortality in the EU.[1] In Austria, the mortality in men is declining since the 1980, whereas in women the incidence is rising in the last decades.[2]

For patients with oncological and/or functional inoperable non-small-cell lung cancer (NSCLC), 3D-conformal radiotherapy (3D-RT) has become an established treatment modality. The overall survival and distant failure rate can be improved with chemotherapy (ChT), applied sequential or concurrent to conformal radiotherapy.[3-5] Therefore, combined chemo/radiotherapy is today the standard treatment for patients with advanced inoperable NSCLC in Stage IIIA/IIIB.[6]

Still, the most common pattern of failure is local recurrence. For patients surviving 6-12 months, local tumour control results in the increased overall survival and is directly related to the applied radiation dose.[7-9] With a radiation dose ranging from 64 to 80 Gy, local control rates of 70-92% can be achieved for stage T1-T3 tumours over a period of 12 months which decreases dose-dependently to 73-43% in the following years. Thus, attempts to decrease the rate of intrathoracic recurrence have been concentrated on dose escalation and different fractionation schedules throughout the last years.[3,10-13]

The purpose of this investigation was to evaluate feasibility, safety and efficacy of 3D- conformal radiotherapy with doses up to 70 Gy +/- platinum-based chemotherapy in patients with inoperable NSCLC treated within a prospective protocol in our institution.

Patients and methods

This investigation includes 84 patients with oncological and/or functional inoperable, histologically proven NSCLC consecutively treated from 1997 to 2002 in the potential curative intent at the Radiotherapy Department of the Medical University of Vienna. According to a prospective protocol, 3D-RT with radiation doses up to 66-70 Gy was applied, depending on dose-volume-constraints for lung toxicity, performance status and lung function. All patients had a complete staging before the treatment including CT scan of the chest and upper abdomen, bronchoscopy, CT-guided biopsy or mediastinoscopy, pulmonary function test, bone scan and complete blood cell counts.

Radiotherapy

All 84 patients received 3D-conformal radiotherapy. The computed tomography (CT) for the planning was performed in inspiration while the patient was lying in a supine position with arms elevated above the head. During the treatment the patients were asked to hold the breath as maximal as possible. The planning CT scan of the entire thorax was done with a slice thickness of 8 mm. For optimal positioning, the breast-board was used. The CT images were transferred to the 3D planning system (HELAX®, MMS 6.1B). Organs at risk (lung, spinal cord, heart), gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) were delineated. The GTV contoured the primary tumour plus involved pathological lymph nodes (≥ 10mm). Patients with supraclavicular lymph node metastases were not included.

The CTV was defined by adding 10mm around the GTV including also regional lymph nodes (mediastinum and ipsilateral hilus). For the PTV an additional margin of 5mm was placed around the CTV. The dose was prescribed to the ICRU point as described in the ICRU 50 recommendations.[14] Dose volume histograms (DVH) have been calculated for both lungs and spinal cord.

For the definition of the dose-volume constraints we followed the recommendations of Graham *et al*.[15] The maximum 20 Gy volume (V_{20}) was tolerated to be 50% for ipsilateral (IL), 30% for contralateral (CL) and 40% for both lungs. The mean lung dose for the ipsilateral lung had not to be more than 25 Gy. The dose to the spinal cord was maximum 50 Gy.

The irradiation was delivered by multiple field arrangements using photons with an energy of 10-25 MV. A dose of 40 Gy was applied by AP/PA fields, followed by a field rearrangement (3-4 fields) to lower the dose to the spinal cord. For boost irradiation to the primary tumour, the shrinking field technique was used. The treatment was performed in conventional fractionation, 5 days a week, with a dose of 2 Gy per fraction.

Chemotherapy

A platinum-based chemotherapy in doublets was applied mainly sequential. Cisplatin was combined with taxotere, navelbine, etiposide, gemcitabine or ifosfamide. The majority of patients (20) received 3 cycles before radiotherapy. A maximum of 6 cycles, 3 before and 3 after irradiation was given in 7 pts. Only 4 patients had concomitant chemo/radiotherapy (Table 1).

Side effects

The diagnosis of pneumonitis was based on clinical symptoms of shortness of breath, cough, fever and in correlation with the radiographic findings on chest X-ray. Radiation pneumonitis and oeosphagitis were evaluated according to the RTOG/EORTC radiation morbidity scoring criteria:[16] grade 2 pneumonitis is defined as cough, requiring medication or mild dyspnea during exercise, grade 3 as clinical or on X-ray visible acute pneumonitis requiring steroids and maybe intermittent oxygen and grade 4 is severe respiratory insufficiency and continuous use of oxygen. Grade 2 oesophagitis is defined as mild dysphagia requiring medication, grade 3 as severe dysphagia with weight loss and dehydration, grade 4 as complete obstruction, ulceration, perforation or fistula.

Patients

Depending on DVH constraints for V_{20} and mean lung dose, forced expiratory volume in 1 second (FEV_1) and performance status, radiation doses of either 66-70 Gy or 50-60 Gy were chosen. The administration of chemotherapy depended on performance status and co-morbidity. Thus, for the retrospective analysis four different treatment groups were defined:

Patients with a Karnofsky-index (KI) of 70-100%, FEV_1 of $\geq$ 1,3 l, treated with 3D-RT in combination with chemotherapy to a total dose of 66-70 Gy were defined as group A and patients with the same KI and FEV_1 but severe co-morbidity, treated with 66-70 Gy without chemotherapy as group C. A poorer performance status and/or a $FEV_1 \leq$ 1,3 l and high values at the DVH analysis resulted in 3D-RT of 50-60 Gy with chemotherapy (group B) and in case of additional severe co-morbidity, 3D-RT (50-60 Gy) was performed without chemotherapy (group D). See details in Table 1.

Follow-up

After the treatment the patients were followed in a 3 months (mo) interval for the first 2 years (y). A thoracic CT-scan and a pulmonary function test were demanded in regularly intervals. If clinically indicated, a blood test and a CT-scan of the brain were performed. The recurrent disease was defined as appearance of new lesions on CT-scan 6 months after radiotherapy.

Table 1. Patients characteristics

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
Age (mean)	48y	61y	70y	70y
Sex (n)				
Female	13	6	5	5
Male	16	10	21	8
Histology (n)				
Squamous cell carcinoma	12	7	18	8
Adenocarcinoma	16	6	6	4
Large cell carcinoma	1	3	2	1
Stage (n)				
IA			1	
IB			5	2
IIB	1	1	6	2
IIA	5	2	8	5
IIIB	23	13	6	4
TNM (n)				
T1N0			1	
T1N2	2			
T1N3	1	1		
T2N0			5	2
T2N1			1	
T2N2	3		7	3
T2N3	2			1
T3N0	1	1	4	2
T3N2	1	3	2	2
T3N3	3	3		
T4N0	8	2	4	3
T4N1			1	
T4N2	7	5		
T4N3		1	1	
TXN3	1			
RT dose (n; Gy)				
50		7		7
60		9		6
66	15		12	
70	14		15	
ChT cycles (n)				
6	7	2		
5	1	0		
4	3	2		
3	13	8		
2	1	3		
1	0	1		
?	4	0		

RT= radiotherapy; ChT= chemotherapy; n= number of patients

Table 2. Dose volume histograms (DVH) analysis for all treatment groups (A-D), mean values and range

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
V20IL (%)	39 (23-56)	47 (25-80)	39 (10-75)	47 (37-60)
V20CL (%)	16 (2-40)	15 (0-35)	14 (1-33)	10 (1-30)
Mean lung dose IL (Gy)	23 (16-32)	25 (9-41)	27 (10-36)	24 (15-33)
Mean lung dose CL (Gy)	11 (4-25)	11 (4-24)	10 (3-18)	7 (3-12)

IL= ipsilateral lung, CL= contralateral lung

Statistical analysis

Time to progression (TTP) was defined as an interval from the date of diagnosis to the development of local recurrence and/or distant metastasis or date of the last follow-up visit. Local control rates (LCR) of 1y and 2y were evaluated. Time to death (TTD), TTP and time to pneumonitis (grade 2-4) were estimated using the Kaplan-Meier product-limit method. To test the difference between survival curves, the log-rank test was used.[17]

Results

Data have been analysed until November 2004. The evaluation included TTP, TTD, LCR, distant failure and side effects such as pneumonitis and oesophagitis. Additionally a DVH analysis was done. The mean follow up time was 24 mo (range 1-84), 2 patients were lost to the follow-up.

Although DVH were calculated for all patients at the time of treatment, in 11 patients the calculated DVH could not be retrieved retrospectively from the planning system due to a technical defect on the hard disc.

The DVH analysis showed a mean V_{20} IL of 42% with a range of 10 to 80%. The V_{20} CL was 14% (range 0-40%). The mean lung dose IL was 25 Gy (range 9-36) and CL 10 Gy (range 3-25). Although the mean values correspond to the dose volume constraints we used, in some patients it was due to the tumour volume not possible to refer to those parameters, what explains the large range of the different values. Thus, patients with higher values of V20 IL and mean lung dose IL and low FEV_1 received only 50-60 Gy as already mentioned above (Table 2).

Of all 84 patients, 1 patient (1%) developed a grade 4 pneumonitis, 5 patients (6%) a grade 3 pneumonitis and 11 patients (13%) a grade 2 pneumonitis (Table 3). The median time of the development of pneumonitis in patients who experienced a pneumonitis grade 2-4 was 2 mo, ranging from 1 to 11 mo.

The statistic analysis for all patients showed that in a mean observation time of 24 mo (1-84) the median time of pneumonitis was not reached. The proportion of patients developing a pneumonitis grade 2-4 was after 3 mo 15%, after 6 mo 18% and after 11 mo 22%. Patients with a pneumonitis grade 2-4 had a mean V_{20} IL of 53.3% (33-85) and a mean lung dose IL of 30 Gy (17.2-

Table 3. Incidence of pneumontis and oesophagitis in the different treatment groups

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
Pneumonitis				
Grade 2	4 (13%)	2 (11%)	3 (11%)	3 (23%)
Grade 3	2 (6%)	0	2 (7%)	0
Grade 4	0	0	0	1 (8%)
Oesophagitis				
Grade 2	5 (17%)	3 (17%)	2 (7%)	1 (8%)
Grade 3	0	0	0	0
Grade 4	1 (3%)	1 (6%)	0	0

37.5). The additionally calculated sigmoid dose-response curve (Figure 1) showed a risk of 60% to develop a pulmonary toxicity (> grade 1) when the mean V_{20} IL was more than 50%.

Looking at the detailed results of the different treatment groups, we found in group A a median TTP of 13 mo, with a range of 4-85 mo and a median TTD was 28 mo, ranging from 7-85 mo. The median disease specific survival (DSS) was also 28 mo. The survival after 3 and 5y was 38% and 10% respectively. The LCR was 48% after 1y and 24% after 2y. Eight patients (27%) had progressive disease after radiotherapy, 12 (41%) developed distant metastases and 2 died of other, not cancer related causes. One patient with a stage IIIB tumour, located centrally, close to the oesophagus and the trachea developed a fistula (grade 4 complication) which was treated by a stent implantation. This patient died shortly after radiotherapy due to the local tumour progression.

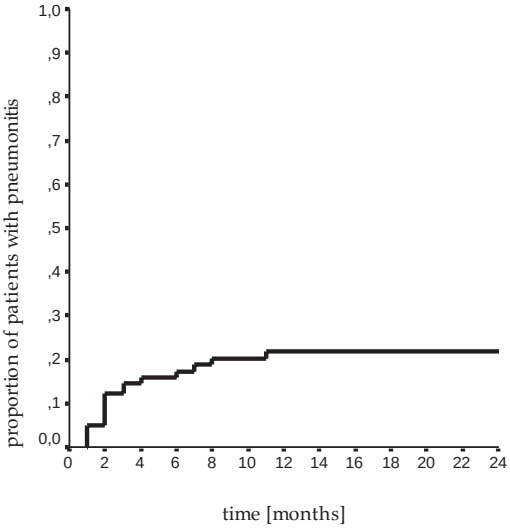


Figure 1. Sigmoid dose-response curve showing the correlation between V20 (%) IL and probability for pulmonary toxicity more than grade 1.

In group B, the median TTP was 15 mo ranging from 3-58 mo, the median TTD was 16 mo (3-27 mo), the LCR 38% after 1y and 25% after 2y. The three and 5y survival was 19% and 6% and the median DSS was 16 mo. The progressive disease after irradiation was seen in 5 patients (31%). A total of 5 patients (31%) developed distant metastases and 1 died of other causes. One 73y old patient with a T4N2 (stage IIIB) tumour developed an ulceration of the oesophageal mucosa (grade 4 complication) after irradiation, requiring hospitalisation, intravenous fluids and hyperalimentation.

In group C the median TTP was 13 mo (range 5-65 mo), the median TTD 16 mo (range 5-78 mo), the median DSS was 15 mo, the LCR was 42% after 1y and 23% after 2y. Nine patients (35%) had a tumour progression after radiotherapy, 6 (23%) had distant failure and 8 (31%) had not cancer

Table 4. Median values for time to progression (TTP), time to death (TTD), disease specific survival (DSS) and local control rate (LCR)

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
TTP (month)	13	15	13	13
TTD (month)	28	16	16	22
DSS (month)	28	16	15	16
LCR (%)				
1-year	48	53	42	38
2-year	24	25	23	15

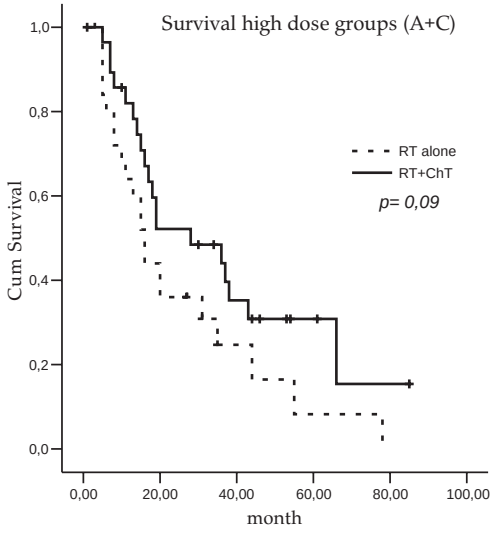


Figure 2. Kaplan-Meier overall survival curve for group A+C (66-70 Gy +/- ChT).

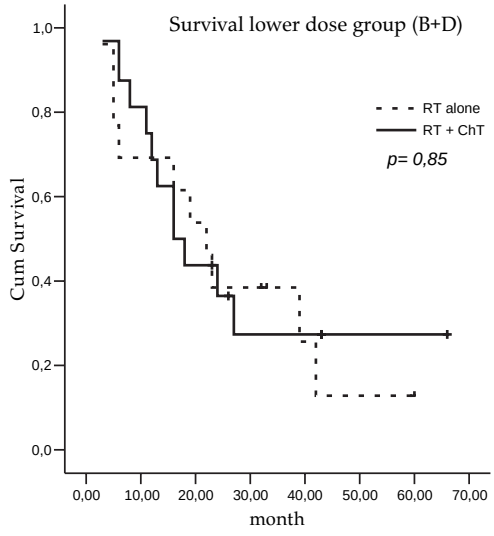


Figure 3. Kaplan-Meier overall survival curve for group B+D (50-60 Gy +/- ChT).

related death. The three and 5y survival was 11% and 8%. No grade 3 or 4 oesophageal toxicity was found.

Group D had a median TTP of 19 mo (range 3-22 mo), a median TTD of 22 mo (range 3-42 mo) and a median DSS was 16 mo. The LCR was 53% after 1y and 15% after 2y. Four patients (31%) had progressive disease after radiotherapy, no distant metastases were observed. Three patients died of other causes. The survival after 3 and 5y was 23% and 8%. No grade 3 or 4 oesophagitis was seen. One patient with a T2N2 (stage IIIA) tumour developed a grade 4 pneumonitis, requiring continuous oxygen. The ipsilateral V_{20} for this patient was 60% and the ipsilateral mean lung dose was 32 Gy. Recurrent disease was found after 10 months and death occurred 42 mo after diagnosis, without distant metastases.

Long-time survivors

For all treatment groups together a total of 14 patients survived more than 2 y with a median survival of 40 mo, ranging from 26

to 61 mo. Concerning long-time survival there was no significant difference between the different treatment groups (Figures 2, 3); however, patients receiving higher radiation doses (66-70 Gy) had a benefit in an overall survival (OS) when the additional chemotherapy was applied (28 month *vs.* 16 month).

Discussion

In the last decades, different treatment strategies were developed for locally advanced non-small cell lung cancer. For inoperable stage III NSCLC, 3D-conformal radiotherapy in combination with chemotherapy has lead to a better local control and longer survival.[7] Nevertheless, the local control remains poor, although the first results in dose escalation trials are promising.[3,13,18]

All patients included in this retrospective analysis received a 3D-conformal radiotherapy within a prospective protocol with the aim to apply a maximum dose of 70 Gy. Depending on performance status, lung function and dose volume constraints such as calculated mean lung dose and 20 Gy lung volume (V_{20}) different radiation doses ± chemotherapy have been applied on an individual basis resulting in four treatment groups. Our analysis showed that the application of radiation doses up to 70 Gy also in combination with sequential chemotherapy is feasible and safe. The treatment could be finished in all patients and no treatment related death occurred. Four grade 3 pneumonitis (9%) were found in the "higher dose" (66-70 Gy) groups (A+C) and no grade 4 pneumonitis.

The DVH analysis emphasised that the V_{20} IL in patients with grade 2-4 pneumonitis was mean 53.3%, with a mean lung dose IL of 30 Gy. Furthermore, the sigmoid dose-response curve shows that a V_{20} IL of more than 50% leads to a risk of 60% for pulmonary toxicity. This underlines the correlation of V_{20} IL with the incidence of radiation pneumonitis as reported by Graham *et al*.[15] The authors showed that a mean V_{20} of the total lung (including both lungs minus PTV) of more than 32% was significantly correlating with high grade pneumonitis (≥ grade 3). The final toxicity results of a dose-escalation study of Kong *et al.* showed that the grade 2 and 3 lung toxicity was not directly associated with the prescribed tumour dose but correlated with dosimetric parameters. The risk of pneumonitis was significantly associated with a mean lung dose ≥ 14 Gy (p = 0.002) and a V_{20} ≥ 27% (p = 0,0008).[19]

For all 84 patients, no grade 3 oesophagitis was observed. Two grade 4 oesophageal toxicities were seen in patients with central, bulky tumours close to oesophagus and trachea.

Our results also showed that in the group with higher radiation doses (66-70 Gy) the application of chemotherapy prolonged the survival compared to exclusive radiotherapy of 66-70 Gy (28 *vs.* 16 mo). Considering the DSS we found the same results (28 *vs.* 15 mo). Comparable results have been reported by Rengan *et al*.[12] In this study a group of 35 patients with stage IIIB NSCLC received 64-84 Gy plus chemotherapy with a median overall survival (OS) of 20 mo for and local failure rate of 64%. Sim *et al.*[5] reported for 152 patients with stage III NSCLC a median OS of 18 mo for the combined treatment compared to 11.7 mo for the radiotherapy alone group ($p \leq 0{,}001$).

In the lower dose (50+60 Gy) groups (B+D) there has been no benefit in OS for patients receiving ChT as it was seen in the higher dose groups (A+C). The median survival time for the lower dose groups +/- ChT (16 *vs.* 22 mo) is also comparable with results in the literature. Different studies report a median OS of 13.8-16 mo

for chemoradiotherapy and 9.7-16 mo for exclusive radiotherapy in stage III NSCLC with radiation doses between 50-63 Gy.[12,20-22] The slightly better results for the group with exclusive radiotherapy (22 mo) for OS could not be confirmed for the DSS where no difference was found (median 16 mo for both groups).

Concerning the development of distant metastases we could not obtain the same results as stated in several studies.[6,20,23] In our analysis the rate of distant failure was not lower in patients with radio-/chemotherapy as in patients receiving RT alone. The reason might be that especially in the higher dose groups, the majority of patients receiving chemotherapy had stage IIIB whereas in the exclusive radiotherapy groups, also stages I and II were included. The LCR at 1y was in all 4 treatment groups nearly the same with mean 45% and no advantage for higher radiation doses could be observed. Probably the number of patients was too small. The LCR at 2y was low in all four groups with the poorest result (15%) for the group receiving 50-60 Gy without chemotherapy.

To improve the local control, different efforts have been made in the last years. Developments in 3D-planning and new techniques like self-gated radiotherapy at deep-inspiration breath hold (DIBH) enable a better tumour targeting and sparing of normal tissue which allows an escalation of the radiation dose up to 100 Gy. Local control rates of 50-80% have been reported with radiation doses varying from 70.2 to 90 Gy.[3,8,13,17,24,25] The limiting factor for dose escalation is the surrounding normal lung tissue. Radiation doses of ≥ 90 Gy lead to severe pulmonary toxicity.[3,13] Several studies showed that intensity modulated radiotherapy (IMRT), especially if guided by PET/CT imaging, has the ability to spare more normal lung tissue and allows 25-30% higher doses than with 3D-conformal radiotherapy.[26,27] Advances in tumour staging could result in smaller treatment volumes, which would enable the application of higher radiation doses. Especially PET/CT improves the detection of lymphnode metastases and the differentiation between tumour tissue and atelectasis. De Ruysscher *et al.* showed in a planning study that the use of a combined PET/CT simulator reduced the radiation dose to normal lung tissue and oesophagus and thus allowed a significant radiation dose escalation.[28]

Still, the risk of normal tissue toxicity should not be underestimated[3,27] and new trials to evaluate a safe dose-escalation technique are obligatory.

Conclusions

The low incidence of severe side effects confirms that the application radiation doses up to 70 Gy with 3D-conformal radiotherapy is feasible and safe, taking into account 3D dose volume constraints. Our work suggests that the combination of chemotherapy and 3D-conformal radiotherapy of 66-70 Gy prolongs moderately the overall survival for patients with inoperable non-small-cell lung cancer with a low risk of severe pneumonitis.

Nevertheless, local control rates remain low, especially after 2y. Thus the possibility of further dose escalation also in more advanced tumour stages with a special regard to the long-term pulmonary and oesophageal toxicity should be investigated.

Acknowledgements

The authors would like to thank Martha Beranek for her technical support in calculating and retrieving dose-volume histograms and Brigitte Keringer and Waltraud Stepan for their secretarial assistance.

References

1. Ferlay J, Bray F, Sankila R, Parkin DM. *EUCAN: Cancer incidence, Mmortality and prevalence in the European Union 1997.* Version 4.0. IARC Cancer Base No. 4. Lyon: IARC; 1999.

2. Bray F, Tycynski JE, Parkin DM. Going up or coming down? The changing phases of lung cancer epidemic from 1967 to 1999 in the 15 European Union countries. *Eur J Cancer* 2004; **40:** 96-125.

3. Bradley J, Graham MV, Winter K, Purdy JA, Komaki R, Roa WH, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005; **61:** 318-28.

4. Semrau S, Bier A, Thierbach U, Virchow C, Ketterer P, Klautke G, et al. R. 6-Year Experience of concurrent radiochemotherapy with vinorelbine plus a platinum compound in multimorbid or aged patients with inoperable Non-Small Cell Lung Cancer. *Strahlenther Onkol* 2007; **183:** 30-5.

5. Sim S, Rosenzweig KE, Schindelheim R, Ng KK, Leibel SA. Induction chemotherapy plus three-dimensional conformal radiation therapy in the definitive treatment of locally advanced non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001; **51:** 660-5.

6. Novello S, Le Chevalier T. Use of chemo-radiotherapy in locally advanced non-small cell lung cancer. *Eur J Cancer* 2002; **38:** 292-9.

7. Ball D, Matthews J, Worotniuk V, Crennan E. Longer survival with higher doses of thoracic radiotherapy in patients with limited non-small cell lung cancer. *Int J Radiat Oncol Phys* 1993; **25:** 599-604.

8. Thirion P, Holmberg O, Collins C, O'Shea C, Moriarty M, Pomeroy M, et al. Escalated dose for non-small lung cancer with accelerated hypofractionated three-dimensional conformal radiation therapy. *Radiother Oncol* 2004; **71:** 163-6.

9. Willner J, Baier K, Caragiani E, Tschammler A, Flentje M. Dose, volume and tumor control predictions in primary radiotherapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002; **52:** 382-9.

10. Baumann M, Herrmann T, Matthiessen, Koch R, Strelocke K, Paul U. CHARTWEL-Bronchus (ARO 97-1): a randomized multicenter trial to compare conventional fractionated radiotherapy with CHARTWEL radiotherapy in inoperable non-small-call bronchial carcinoma. *Strahlenther Onkol* 1997; **173:** 663-7.

11. Catalano G, Jereczek-Fossa B, De Pas T, Leon ME, Cattani F, Spaggiari L, et al. Three-times daily radiotherapy with induction chemotherapy in locally advanced non-small cell lung cancer. *Strahlenther Onkol* 2005; **181:** 363-71.

12. Rengan R, Rosenzweig KE, Venkatraman E et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004; 60(3): 741-747

13. Rosenzweig KE, Fox JL, Yorke E, Amols H, Jackson A, Rusch V, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall lung carcinoma. *Cancer* 2005; **103:** 2118-27.

14. International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy. *ICRU Report 50.* Bethesda: International Commission on Radiation Units and Measurements; 1993.

15. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, et al. Clinical dose-volume histogram analysis of pneumonitis after 3D treatment for non small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999; **45:** 323-9.

16. Cox JD, Stretz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; **31:** 1341-6.

17. Kaplan EL, Meier P. Non parametric estimation for incomplete observations. *J Am Stat Ass* 1958; **53:** 457-81.

18. Belderbos J, Heemsbergen W, De Jaeger K, Baas P, Lebesque JV. Final results of a phase I/II dose escalation trial in non-small cell lung cancer using three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; **66:** 126-34.

19. Kong FM, Hayman JA, Griffith KA, Kalemkerian GP, Arenberg D, Lyons S, et al. Final toxicity results of a radiation-dose escalation study on patients with non-small-cell lung cancer (NSCLC): Predictors for radiation pneumonitis and fibrosis. *Int J Radiat Oncol Biol Phys* 2006; **65:** 1075-86

20. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med 1990*; **323:** 940-5.

21. Furuse K, Kubota K, Kawahara M, Kodama N, Ogawara M, Akira M, et al. Phase II study of concurrent radiotherapy and chemotherapy for unresectable stage III non small cell lung cancer. Southern Osaka Lung Cancer Study Group. *J Clin Oncol* 1995; **13:** 869-75.

22. Kubota K, Furuse K, Kawahara M, Kodama N, Yamamoto M, Ogawara M, et al. Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. *J Clin Oncol* 1994; **12:** 1547-52.

23. Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991; **83:** 417-23.

24. Barnes E, Murray B, Robinson D, Underwood LJ, Hanson J, Roa WH. Dosimetric evaluation of lung tumour immobilization using breath hold at deep inspiration. *Int J Radiat Oncol Biol Phys* 2001; **50:** 1091-8.

25. Hof H, Herfarth KK, Munter M, Essig M, Wannenmacher M, Debus J. The use of the multislice CT for the determination of respiratory lung tumor movement in stereotactic single-dose irradiation. *Strahlenther Onkol* 2003; **179:** 542-7.

26. Grills IS, Yan D, Martinez AA, Vicini FA, Wong JW, Kestin LL. Potential for reduced toxicity and does escalation in the treatment of inoperable non-small-cell lung cancer: a comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. *Int J Oncol Biol Phys* 2003; **57:** 875-90.

27. Holloway CL, Robinson D, Murray B, Amanie J, Butts C, Smylie M, et al. Results of a phase I study to dose escalate using intensity modulated radiotherapy guided by combined PET/CT imaging with induction chemotherapy for patients with non-small cell lung cancer. *Radiother Oncol* 2004; **73:** 285-97.

28. De Ruysscher D, Wanders S, Minken A, Lumens A, Schiffelers J, Stultiens C, et al. Effects of radiotherapy planning with dedicated combined PET-CT simulator of patients with non-small cell lung cancer on dose limiting normal tissues and radiation dose-escalation: a planning study. *Radiother Oncol* 2005; **77:** 5-10.

Quality of life following thoracotomy for lung cancer

Lučka Debevec, Irma Rozman

University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia

Background. *The aim of the study was to assess the preoperative and postoperative quality of life (QoL) in lung cancer patients undergoing thoracotomy and to compare the impairment of QoL in resected and exploratory thoracotomized (ET) patients.*

Patients and methods. *Forty-three patients age 31 to 82 (mean 61) thoracotomized (lobectomy 29, bilobectomy 1, pneumonectomy 8, ET 5) for non-small cell lung cancer were assessed using the EORTC QLQ-LC30 and QLQ-LC13 questionnaire preoperatively and a mean of 45±17 days after the thoracotomy and before eventual chemotherapy and radiation therapy.*

Results. *After thoracotomy there were significantly impaired functional scales (physical functioning, role functioning, social functioning) and symptom scales (fatigue, constipation, appetite loss, dyspnoea, pain). The remaining symptoms (nausea/vomiting, insomnia, diarrhoea, coughing), global health status, functional scales (emotional functioning, cognitive functioning) and financial difficulties were impaired non-significantly. However, haemoptysis significantly improved and completely disappeared after thoracotomy. There were no significant differences between resected and ET patients.*

Conclusions. *The study established significant impairment of QoL in the first two months after thoracotomy, but no significant differences between resected and ET patients.*

Key words: lung neoplasms – surgery; thoracotomy; quality of life

Introduction

Surgery is the treatment of choice for technical and medical operable non-small cell lung cancer (NSCLC). However, thoracotomy impairs quality of life (QoL) in the case of resection or exploration without resection. Exploratory thoracotomy (ET) as the only method for tumour verification is currently very rare. In the period 1990 to 1999 the ET rate was 9.1% among 1808 thoracotomized lung cancer patients at the Department of Thoracic Surgery, Clinical Centre Ljubljana, Slovenia.[1] Of 131 evaluable ET patients, only one underwent surgery without preoperative verification. ET is mostly caused by unresectability. This was the case in 119/131 patients. Incidental ET (open and closed thoracotomy) could be a consequence of intraoperative complications (1/131 patient) or necessity for pneumonectomy in the case of poor pulmonary function (11/131 patients). In any case, one

Received 14 August 2007

Accepted 29 August 2007

Correspondence to: Assist. Lučka Debevec, MD, PhD, University Clinic of Respiratory and Allergic Diseases Golnik, SI-4204 Golnik, Slovenia; Phone: +386 4 2569 100; Fax: +386 4 2569 117; E-mail: lucka.debevec@klinika-golnik.si

must take into account a certain percent of ET in every large group of thoracotomized lung cancer patients.

During the last ten years, QoL has become an important issue in the treatment of cancer. Especially in clinical trials it is considered an aspect as important or even more important than traditionally used endpoints such as remission rate, disease-free survival and time to progression.[2] QoL assessment is a way to obtain objective data in order to "measure" a patient's condition and to evaluate the global impact of therapies administered to improve a patient's situation.[3] QoL is multidimensional and according to the WHO is a definition of health composed of physical, mental and social function. To measure QoL, the symptoms of a certain tumour are assessed in a semi-quantitative manner. For lung cancer patients the most popular questionnaire is the EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 and its QLQ-LC13 module.[4] Altogether it has 43 questions that are answered by patients. For converting the answers into percent-values, a special scoring procedure is used[5] and can be performed in connection with statistical analysis by common computer programs.

The aim of the present study was twofold: (1) to assess preoperative and postoperative QoL in lung cancer patients undergoing thoracotomy and (2) to compare the impairment of QoL in resected and ET patients.

Table 1. Characteristics of the patients and tumours

Variable	Value
Number of patients	43
Age (years) – mean	61 (range 31-82)
Male/Female	33/10
Histology	
squamous cell	21
adenocarcinoma	16
large cell	5
non-small cell	1
Forced expiratory volume in one second (FEV_1 %) -mean	81 ± 20
Carbon monoxide lung diffusion capacity (DLCO %) - mean	77 ± 19
Clinical stage	
IA	12
IB	14
IIB	10
IIIA	7
Operation	
lobectomy	29
bilobectomy	1
pneumonectomy	8
ET	5
Postsurgical stage	
IA	13
IB	9
IIA	3
IIB	8
IIIA	5
IIIB	4
IV	1

Patients and methods

From February 2004 to July 2005, 78 patients diagnosed at the University Clinic for Respiratory and Allergic Diseases Golnik, Slovenia, underwent surgery for NSCLC with intention to cure. These patients completed the EORTC QLQ-C30 and QLQ-LC13 preoperatively. All ET patients (5 of 78 patients) and 38 resected patients completed the questionnaire postoperatively again, at 45±17 days after thoracotomy, before eventual chemotherapy or radiation therapy. So 43 patients were eligible for the study.

The diagnostic procedure of lung tumour consisted in all patients of chest X-ray, CT

scan of the chest and upper abdomen, bronchoscopy, pulmonary function testing and arterial blood gas analysis. Cervical mediastinoscopy was performed in 5 patients. Tumour was microscopically confirmed before surgery in all patients.

All patients had the ECOG performance status ≤ 1. Other characteristics of the patients and tumors are shown in Table 1.

Thirty four patients underwent the anterolateral, 8 axillar, and 1 posterolateral thoracotomy, with a partial rib resection in 12 patients. Pain management postoperatively included epidural analgesia for 2 to 7 (mean 4) days.

The resection was curative without a residue of tumor (R0 stage) in 39 patients, stage R1 in 3, and stage R2 in 1 patient. As postsurgical stage in Table 1 was designated pathological stage in resected patients and surgical stage in ET patients.

The causes of ET were as follows: pleural carcinomatosis in 2, invasion of heart in 1, extensive invasion of mediastinal lymph nodes in 1, and not permissible pneumonectomy due to poor pulmonary function in 1 patient.

Statistical analysis was carried out using SPSS (Statistical Package for the Social Sciences for Windows, Chicago, IL) version 13.0. The difference was confirmed by paired-samples *t* test and independent-samples *t* test respectively. The level of significance was $p < 0.05$.

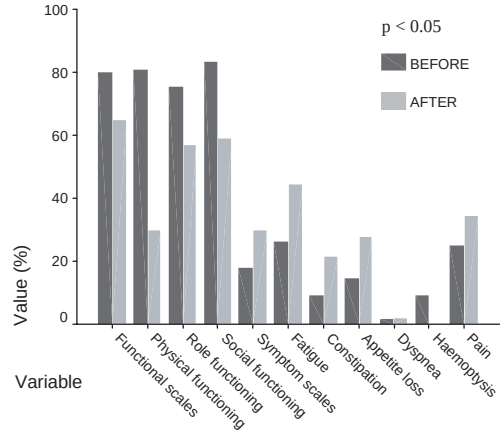


Figure 1. Preoperative and postoperative quality of life in 43 thoracotomized lung cancer patients – significant differences.

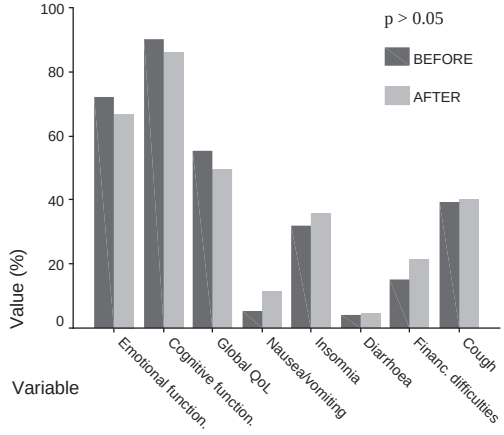


Figure 2. Preoperative and postoperative quality of life in 43 thoracotomized lung cancer patients – non significant differences.

Results

Preoperative and postoperative QoL is presented in Figure 1 and in Figure 2. Functional scales (physical, role and social functioning) and symptom scales (fatigue, constipation, appetite loss, dyspnoea and pain) significantly worsened (Table 2). In thoracotomized patients it is very important to define the pain. According to presence, level and location of pain, impairment was significant in unspecified pain ($p = 0.030$), pain interfering with daily activities ($p = 0.000$) and chest pain ($p = 0.039$). There was no significance in the impairment of pain in the arm or shoulder ($p = 1.000$) or of pain in other parts ($p = 0.133$).

QoL was not significantly impaired according to the remaining symptoms (nausea/vomiting, insomnia, diarrhoea, coughing), global health status, functional scales

Table 2. EORTC QLQ-C30 and QLQ-LC13 scores in 43 patients before and after thoracotomy

Variables	Item numbers	Before thoracotomy Mean±SD	After thoracotomy Mean±SD	p-value
Functional scales	1–7, 20–27	80.0±17.4	64.8±22.2	**0.000**
Physical functioning	1 – 5	80.9±20.8	59.8±33.2	**0.000**
Role functioning	6, 7	75.6±30.7	57.0±30.9	**0.003**
Emotional functioning	21–24	72.2±18.8	66,9±34.0	NS
Cognitive functioning	20, 25	90.3±16.8	86.0±18.2	NS
Social functioning	26, 27	83.3±24.1	59.3±40.0	**0.001**
Global QoL	29, 30	55.2±25.6	49.4±20.7	NS
Symptom scales/items	8 –19, 28	18.1±15.3	30.0±16.3	**0.000**
Fatigue	10,12,18	26.4±25.1	44.4±21.8	**0.000**
Nausea/vomiting 14, 15	5.0±10.0	11.6±23.2	NS	
Insomnia	11	31.8±35.6	35.7±29.5	NS
Constipation	16	9.3±25.5	21.7±25.5	**0.041**
Diarrhoea	17	3.9±16.6	4,7±13.8	NS
Appetite loss	13	14.7±26.5	27.1±33.5	**0.025**
Financial difficulties	28	15.1±28.7	21.4±32.8	NS
Dyspnoea	8, 33-35	1.6±0.6	1.9±0.6	**0.001**
Coughing	31	39.5±25.5	40.3±22.5	NS
Haemoptysis	32	9.3±16.8	0.0±0.0	**0.001**
Pain	9,19,40-42	24.8±20.8	34.7±23.0	**0.009**

(emotional, cognitive) and financial difficulties. However haemoptysis significantly improved, and completely disappeared after thoracotomy.

In order to compare QoL in resected and ET patients, the differences (impairments or improvements) of single items before and after thoracotomy were computed. Afterwards the resected and ET group were compared according to these QoL differences. Table 3 shows that there were no significant differences between resected and ET patients except in haemoptysis, appearing only preoperatively in resected patients.

Discussion

Assessing QoL means measuring either the absolute value or relative alteration of quality, and in the case of expressive impairment items may attain a negative value. The goal of the study was the alteration of

Table 3. The difference of quality of life alteration after thoracotomy in resected and exploratory thoracotomized (ET) patients

Variables	Item numbers	ET pts Mean±SD	Resected pts	p-value Mean±SD
Functional scales	1-7, 20-27	16.9±23.0	15.0±21.7	NS
Physical functioning	1-5	36.0±62.6	19.1±28.0	NS
Role functioning	6, 7	36.0±27.4	18.4±40.2	NS
Emotional functioning	21-24	5.0±19.2	7.7±33.6	NS
Cognitive functioning	20, 25	-3.3±7.5	5.3±19.0	NS
Social functioning	26, 27	10.0±25.3	25.9±48.4	NS
Global QoL	29, 30	6.7±18.0	5.7±24.2	NS
Symptom scales/item	8-19, 28	-8.7±20.0	-12.3±19.0	NS
Fatigue	10,12,18	-8.9±34.6	-19.3±29.2	NS
Nausea/vomiting	14,15	-6.7±25.3	-6.6±26.1	NS
Insomnia	11	-13.3±29.8	-2.6±35.8	NS
Constipation	16	-26.7±43.5	-10.5±38.0	NS
Diarrhoea	17	0.0±0.0	-0.9±23.9	NS
Appetite loss	13	0.0±40.8	-14.0±34.3	NS
Financial difficulties	28	-6.7±14.9	-6.3±30.3	NS
Dyspnoea	8, 33-35	-5.0±16.2	-11.4±19.8	NS
Coughing	31	0.0±23.6	-0.9±27.4	NS
Haemoptysis	32	0.0±0.0	10.5±17.5	**0.001**
Chest pain	40	-13.3±38.0	-20.2±62.3	NS

QoL due to establishing the value of items prior to and 1-2 month after a thoracotomy. Further change of QoL in ET patients is not clearly a consequence of surgery. This might be due to tumor progress or radiation and chemotherapy.

As expected, thoracotomy significantly impaired physical, role, and social functioning, and it increased dyspnoea and chest pain. Any thoracotomy results in a decline in vital capacity of approximately 25%, independent of lung resection, which returns to normal after 6 to 8 weeks.[6,7] The major effects result from changes in chest wall compliance and an increase in the work of breathing due to the surgical wound and postoperative pain.[8]

It was somewhat surprising that there was no significant change in emotional functioning and financial difficulties. These confirmed both patients' optimism and the good social support in Slovenia. Postoperative constipation could be a consequence of poorer nutrition due to appe-

tite loss or an effect of some medicines, especially analgesics.

In the literature there are not many articles about the influence of thoracotomy on the QoL in lung cancer patients and we have found no published data on QoL in ET.

Win *et al.*[9] assessed the effect of thoracotomy in 110 potentially curatable lung cancer patients using the EORTC QLQ-C30 and QLQ-LC13 before surgery and again at 1, 3 and 6 months postoperatively. Eight ET patients were excluded. Global QoL had deteriorated significantly 1 month after surgery but had returned to preoperative levels by 3 months. Symptoms had worsened significantly at 1 month after surgery but returned to baseline levels by 6 months. Low values of the preoperative QoL were not significantly associated with a poor surgical outcome. However, patients with low preoperative QoL functioning scales and high preoperative symptom scores were more likely to have poor postoperative (6 months) QoL. The only lung function measurement to show a marginally statistically significant association with QoL at 6 months after surgery was the percentage of predicted carbon monoxide transfer factor (DLCO).

Handy *et al.*[10] measured QoL in 103 lung cancer patients with the Short-Form 36 Health Survey (SF-36) and Ferrans and Powers Quality-of-Life Index (QLI) preoperatively and 6 months after surgery. Pain and impairment of functional health status persisted for 6 months after resection. DLCO, not forced expiratory volume in one second (FEV_1), predicted postoperative QoL. Preoperative chemoradiation, the extent of resection, postoperative complications, and adjuvant therapy did not adversely affect functional health status or QoL 6 months after surgery.

Dales *et al.*[11] investigated QoL in 91 resected lung cancer patients using the Clinical Dyspnea Index (CDI), Pneumoconiosis Research Unit Index (PRU), QL-Index (QLI) and Sickness Impact Profile (SIP). QoL was measured preoperatively and 1, 3, 6 and 9 months postoperatively. Dyspnoea significantly increased postoperatively at 1 and 3 months, but returned at 6 and 9 months. Similarly, activities of daily life were significantly impaired at 1 month, and returned to baseline at 6 and 9 months.

Zieren *et al.*[12] assessed QoL in 20 lung cancer patients 1 day before surgery, postoperatively on the day of discharge from hospital and at 3-month intervals thereafter until the end of the first postoperative year (6 times) using the EORTC QLQ-C30. The external evaluation was made by a psychologist using the Spitzer Index. After surgery QoL was mainly affected by restrictions related to physical activities, job and household tasks, and disease symptoms, whereas limitations in emotional, social and financial domains were found to be less frequent and less severe. Tumour recurrence was determined to have a significant and negative influence on postoperative QoL. When compared to preoperative assessment, QoL had deteriorated on discharge from hospital but was restored within 3–6 months postoperatively in disease-free patients.

Paull *et al.*[13] measured QoL prior to resection, at 0 to 3 months following resection, and at more than 3 months after resection in 37 patients with early-stage NSCLC using Functional Assessment of Cancer Therapy-Lung (FACT-L). Preoperative dyspnoea and postoperative chemotherapy were associated with worse postoperative QoL.

Fiedler *et al.*[14] measured QoL in 36 patients 40 months (range 7–147) after pneumonectomy for lung cancer using the EORTC QLQ-C30. Restricted QoL was mainly caused by reduction of lung function due to the loss of parenchyma. Further adjuvant therapy at least 6 months after surgery did not reduce either impairment of lung function or the impairment of QoL.

Balduyck *et al.*[15] assessed QoL in 100 patients undergoing major pulmonary surgery for malignant disease preoperatively and 1, 3, 6 and 12 months postoperatively. Pneumonectomy was signficantly associated with a less favorable QoL score evolution when compared with lobectomy. Comparing antero- and posterolateral thoracotomy, significant differences in pain and dyspnea were seen in favor of the anterolateral technique.

Pompeo *et al.*[16] analyzed QoL in 16 patients undergoing tailored combined surgery for stage I lung cancer and severe emphysema using the SF-36 questionnaire. Significant improvements occurred for up 36 months in the general health domain and for 24 months in physical functioning, role physical and general health SF-36 domains. They concluded that selected lung cancer patients with severe emphysema may benefit in terms of long-term QoL.

Myrdal *et al.*[17] compared QoL in 112 resected lung cancer patients and 121 patients that underwent coronary bypass surgery using the SF-36 health questionnaire and Hospital Anxiety and Depression Scale (HADS). Lung cancer patients had poorer function because of reduced pulmonary function but showed no sign of increased anxiety or depression. Those that continued to smoke after surgery had impaired mental health.

Li *et al.*[18] compared 24 patients resected at thoracotomy and 27 VATS (video–assisted thoracic surgery) resected lung cancer patients 6 months or more after surgery using the EORTC QLQ-C30 and QLQ-LC13. Although VATS patients tended to score higher on the QoL and functioning scales and to report relatively fewer symptoms, there were no significant differences.

Hoang *et al.*[19] analyzed the importance of returning to work after thoracic surgery. Return to work is not a trivial component of global post-surgical QoL. Patients have indicated that they value being able to return to work as highly as their overall health.

Following the statements above, the greatest impairment of QoL due to thoracotomy was established immediately and in the first 3 months after surgery. QoL improved 6 to 9 months after surgery, but dyspnoea continued in the case of extensive resection and chest pain in some patients. In the case of tumour recurrence or metastatic spread, QoL depends mainly on these. The results of this study agree with the studies cited. The non-significant difference in dyspnoea impairment in pnemonectomized and ET patients was probably due to the small number of patients in each group.

We are aware of shortcomings of the current study. Due to organizing difficulties it was not possible to assess the QoL in all patients at quite the same interval after thoracotomy. The small number of ET patients and the heterogeneity of characteristics in the patients and tumours reduce the reliability of the results. Nevertheless the study is the first essay comparing the QoL following the thoracotomy in ET and resected lung cancer patients.

Conclusion

This study established a significant impairment of QoL, of functional scales (physical, role and social functioning) and symptom scales (fatigue, constipation, appetite loss, dyspnoea, pain) 1-2 months after thoracotomy, but no significant differences between resected and ET patients.

References

1. Debevec L, Eržen J, Debeljak A, Crnjac A, Kovač V. Exploratory thoracotomy and its influence on the survival of patients with lung cancer. *Wien Klin Wochenschr* 2006; **118:** 479-84.

2. Beitz J, Grecco C, Justice R. Quality-of-life and points in cancer clinical trials: the U.S. Food and Drug Administration perspective. *J Natl Cancer Inst Monogr* 1996; **30:** 7-9.

3. Sculier JP, Mancini I, Paesmans M, Klastersky J. Quality of life and supportive care. In: Hansen HH, editor. *IASLC Textbook of Lung Cancer*. London: Martin Dunitz; 2000. p. 337-48.

4. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85.** 365-76.

5. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A; on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual.* 3rd Edition. Brussels: European Organisation for Research and Treatment of Cancer; 2001.

6. Bollinger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. *J Thorac Cardiovasc Surg* 1998; **11:** 198-212.

7. Ferguson MK, Reeder LB, Mick R. Optimizing selection of patients for major lung resection. *J Thorac Cardiovasc Surg* 1995; **109:** 275-81.

8. Lin J, Martinez FJ, Iannettoni MD. The medical evaluation and management of the lung cancer patient pre-treatment. In: Pass HL, Carbone DP, Johnson DH, Minna JD, Turrisi AT, editors. *Lung Cancer. Principles and Practice*. Philadelphia: Lippincott Williams Wilkins; 2005. p. 400-25.

9. Win T, Sharples L, Wells FC, Ritchie AJ, Munday H, Laroche CM. Effect of lung cancer surgery on quality of life. *Thorax* 2005; **60:** 234-38.

10. Handy JR, Skokan L, Brooks G, Ott GY. What happens to patients undergoing lung cancer surgery? Outcomes and quality of life before and after surgery. *Chest* 2002; **122:** 21-30.

11. Dales RE, Belanger R, Shamji FM, Leech J, Crepeau A, Sachs HJ. Quality-of-life following thoracotomy for lung cancer. *J Clin Epidemiol* 1994; **l47:** 1443-9

12. Zieren HU, Mueller JM, Hamberger U, Pichlmaier H. Quality of life after surgical therapy of bronchogenic carcinoma. *Eur J Cardio-thorac Surg* 1996; **10:** 233-7.

13. Paull DE, Thomas ML, Meade GE, Updyke GM, Arocho MA, Chin HW, et al. Determinants of quality of life in patients following pulmonary resection for lung cancer. *Am J Surg* 2006; **192:** 565-71.

14. Fiedler R, Neef H, Hennig H, Rosendahl W, Lautenschlaeger C. Lebensqualitaet nach pneumonektomie wegen bronchialkarzinom. *Zentralbl Chir* 1997; **122:** 327-31.

15. Balduyck B, Hendriks J, Lauwers P, Van Schil P. Quality of life evolution after lung cancer surgery: A prospective study in 100 patients. *Lung Cancer* 2007; **56:** 423-31.

16. Pompeo E, De Dominicis E, Ambrogi V, Mineo D, Elia S, Mineo TC. Quality of life after tailored combined surgery for stage I non-small-cell lung cancer and severe emphysema. *Ann Thorac Surg* 2003; 76: 1821-7.

17. Myrdal G, Valtysdottir S, Lambe M, Stahle E. Quality of life following lung cancer surgery. *Thorax* 2003; 58: 194-7.

18. Li WW, Lee TW, Lam SS, Ng CS, Sihoe AD, Wan IY, et al. Quality of life following lung cancer resection. Video-assisted thoracic surgery vs thoracotomy. *Chest* 2002; **122:** 584-9.

19. Hoang CD, Osborne MC, Maddaus MA. Return to work after thoracic surgery: an overlooked outcome measure in quality-of-life studies. *Thorac Surg Clin* 2004; **14:** 409-16.

Diagnostic and treatment problems with parosteal osteosarcoma. A clinical and a histological study of 7 cases and review of the literature

Milan Samardziski[1], George Zafiroski[1], Cveta Tolevska[2], Slavica Konstadinova-Kunovska[3], Violeta Vasileva[4]

[1]University Clinic for Orthopedic Surgery-Skopje, [2]Institute for Radiotherapy and Oncology-Skopje, [3]Pathology Institute-Skopje, [4]University Surgical Clinic "St. Naum Ohridski" – Skopje

Background. *Parosteal osteosarcoma is a rare low-grade bone tumour. The operation material must undergo a careful patohistological analysis, because the extent of invasion of the medullar cavity and most probably the extent of dedifferentiated areas determines the prognosis and occurrence of local recurrence and metastases.*

Patients and methods. *In this retrospective clinical study, 7 cases of parosteal osteosarcoma of the bone have been analyzed. Six patients were with parosteal osteosarcoma and one with periosteal osteosarcoma. The study was performed at the Clinic for Orthopedic Surgery in Skopje, Macedonia, from 1995 to 2006. This tumour represents 1.5% of all 467 patients with primary bone tumours treated at the Clinic in the 12 year period. The age of 7 patients (3 female and 4 male) ranged from 8 to 39 years (median 27). The history analysis of the patients showed the misinterpreted diagnosis in 57% of the cases, with 71.4 % rate of local recurrence, 28.7% of metastases and 28.7% of mortality. The follow-up varied from 7 months to 9 years (median 37 months).*

Results. *The clinical and histopathological findings of this study (same as those reviewed in the literature) confirmed the occurrence of two biologically different types of parosteal osteosarcoma: the predominant type is originally "benign" but has a definite malignant potential, causing metastases after the long symptom-free interval. The other type is highly malignant from the beginning.*

Conclusions. *The compartmental, radical "en bloc" resection, followed by the regular review of the patients, is recommended for the low malignant type, however, the radical surgery, followed by chemotherapy, is recommended for the highly malignant tumours.*

Key words: osteosarcoma – diagnosis – therapy; periosteum

Received 1 August 2007

Accepted 7 August 2007

Correspondence to: Milan Samardziski MD, MSc, University Clinic for Orthopaedic Surgery, University "St. Cyril and Methodius", Vodnjanska 17, 1000 Skopje, Macedonia; Phone/Fax: + 389 23176 672; E-mail: milan_samardziski @ yahoo.com

Introduction

Parosteal osteosarcoma is a rare low-grade bone tumour. It was apparently described for the first time in 1951 by Geschickter and Copeland, regarding the initial confusion

with the terminology.[1,2] It occurs between the 2nd and 7th decade of life and it represents 1,6 to 2% of all malignant bone tumours.[3] The most frequent location is the distal dorsal femur. Until clearly proven otherwise, a bone-forming tumour in this localisation must be regarded as parosteal osteosarcoma. To determine the histopathological diagnosis could be "tricky". The tumour is characterised by hyalinized fibrous stroma with low cell content without substantial nucleus polymorphism and variably dense bony trabeculae. The operation material must undergo a careful patohistological analysis, because the extent of invasion of the medullar cavity and most probably the extent of dedifferentiated areas determines the prognosis and occurrence of local recurrence and metastases.[4,5]

As most authors report, a wide margin of excision ensures the adequate surgical treatment of parosteal osteosarcoma in any surgical grade or stage. No evidence for the development of primary tumour satellite nodules or of "skip" metastases were seen, so it would seem that truly radical or compartmental surgery is rarely indicated. The significant incidence of pulmonary metastasis among those patients with Grade III parosteal osteosarcoma and involvement of the medullar cavity, suggests that, for them, adjuvant chemotherapy should be considered.[3,4,6,7] The primary wide excision may be less effective for the local recurrence where there has been a previous inadequate biopsy or surgical treatment, because of the contamination and spread of the tumour into the surrounding tissues.[7]

The tumour is most commonly misinterpreted as osteochondroma or heterotrophic ossification and even large institutions have limited experience of its diagnosis and management.[4] Parosteal osteosarcoma shows, like no other tumour, the necessity of close cooperation of all involved disciplines for diagnosis and therapy and should be treated only in specialized institutions for bone tumour surgery.

Patients and methods

At the re-examination of the records at the Clinic for Orthopedic Surgery in Skopje, during the last 12 years (from 1995 to 2006), 7 cases of juxtracortical osteosarcoma were found. Five of them were patients with parosteal osteosarcoma and one patient was with periosteal osteosarcoma. Parosteal osteosarcoma represented 1.5% of all 467 patients with malignant bone tumours treated in this time at the Clinic.

Reviewing the records, bone scans with Technetium 99m, radiographs, arteriography, CT, MRI and histopathology findings showed 6 patients with the confirmed diagnosis of parosteal osteosarcoma and one was with a high grade chondroblastic type of periosteal osteosarcoma. Four of them were diagnosed and treated at the Clinic for Orthopedic Surgery in Skopje and 3 patients started their treatment elsewhere and were misdiagnosed for osteochondroma. Another three started their treatment as unspecified malignant tumour of distal femur and only one was primarily suspected to be parosteal osteosarcoma.

Results

The clinical details of all 7 patients are summarized in Table 1.

Age and sex

The age ranged from 8 to 39 years (median 27). There were 3 female and 4 male patients.

Site of the tumour

In 4 cases the site of tumour was the posterior surface of the distal femur. In 1 case primary site of tumour was postero-medial surface of the proximal femur. In 1 case the site of tumour was proximal humerus and

Table 1. Clinical details of the 7 cases

Case / initials	Sex	Age	Site of the tumor	Duration of symptoms (months)	Symptoms
1. VM	F	28	Proximal tibia	13	Painless tumour
2. BT †	M	27	Distal femur	15	Blunt pain and tumour
3. BS †	M	8	Distal femur	9	Blunt pain and tumour
4. SV	F	39	Distal femur	17	Painless tumour
5. ID	M	24	Proximal femur	13	Painless tumour
6. JM	M	17	Proximal humerus	8	Severe pain tumour and reduction of movements
7. RM	F	32	Distal femur	11	Blunt pain and tumour
median		27	median	**13**	

Legend
MSTSS - Musculoskeletal Tumor Society Score[7];
MMA - reconstruction of the defect with metilmet-acrilate (bone cement);
Resection arthrodesis- reconstruction with intramedular nail and MMA;
STE - special tumour endoprosthesis;
† - lethal outcome.

in 1 case the site of tumour was the posterior surface of the proximal tibia**.**

Symptoms

The most frequent sign on admission at the Clinic was localized painless swelling present in 3 patients, progressively increasing blunt pain and swelling was present in 3 patients and severe "night pain", swelling and restriction of movements was present in 1 patient. The duration of the symptoms varied from 8 to 17 months (median 13).

Radiological findings

In 4 cases the radiographs showed a densely ossified and lobulated mass on the posterior mataphysial cortex of the distal femur (Figure 1a). Similar dense and lobulated tumours were seen at the other sites. Tumours were attached to the bone by broad base (Figure

Treatment	Chemotherapy	Local recurrence	Metastases	Follow-up (months)	Outcome (MSTSS)
1. radical resection +MMA	After Oper.	After 6 months	No	23	25
1. resection 2. reresection 3. amputation	After Oper.	After 3 months	Lungs after 23 months	37 †	† 30
1.resection arthrodesis 2. recurrence excision	Neo- adjuvant	After 3 months	Lungs after 16 months	21 †	† 37
1. resection arthrodesis 2. STE.	After Oper.	After 32 months	No	71	39
1. resection and STE. 2. disarticulation after masive local recurrence	Neo- adjuvant	After 61 months	No	67	31
1. radical resection + nonvascular fibular graft	No	No	No	109	33
1. "en bloc" resection 2. radical resection + STE	Neo- adjuvant	No	No	7	38
	median	**6**	**19.5**	**37**	**33**

1a, 1c). In one case, after the recurrence, two thirds of the circumference of the distal femoral metaphysis were involved (Figure 1b). This patient was considered to have medullar involvement on CT scans (Figure 3a).

Pathological findings

The tumours were ossified with occasional soft areas, all of them infiltrating the surrounding soft tissues. Most of them had typical histological appearance of a low grade parosteal osteosarcoma, with spindle cells and collagen fibers embedding osseous trabeculae. The spindle cell stroma was scarcely cellular, with low to moderate atypia of the cells, as well as low mitotic activity. The trabeculae were rather regularly arranged, but missing the osteoblastic rimming. Two of the cases also showed cartilaginous islands in the mainly fibroblastic tumour tissue (Figure 2a). Most of the cases had well (G1) to moderate (G2) degree of differentiation (Figure 2b).

Only one presented a high grade chondroblastic (G3) surface osteosarcoma. It was presented as a high grade surface chondroblastic osteosarcoma (case 3, Table 1), with scarce and hard to find foci of osteoid and wide areas of malignant cartilage. The tumour cells showed marked polymorphism and high mitotic index (Figure 2c). Recurrent lesions usu-

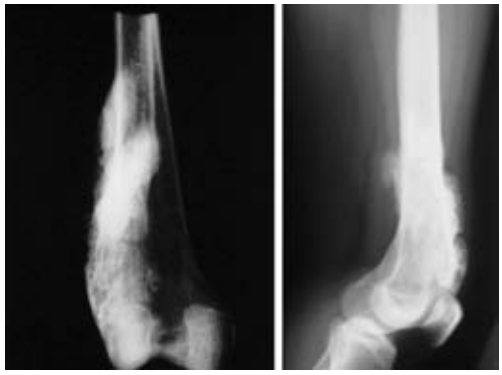


Figure 1a. Frontal and lateral radiography of the parosteal osteosarcoma of right distal femur (case 2).

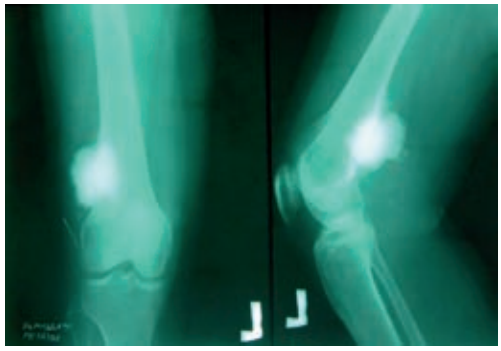


Figure 1b. Frontal and lateral radiography of the parosteal osteosarcoma of right distal femur (case 7).

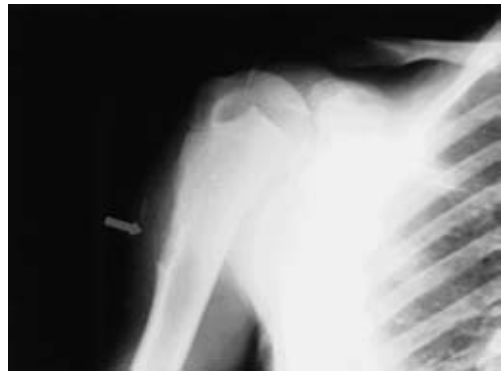


Figure 1c. X-ray of parosteal osteosarcoma of the right proximal humerus (case 6).

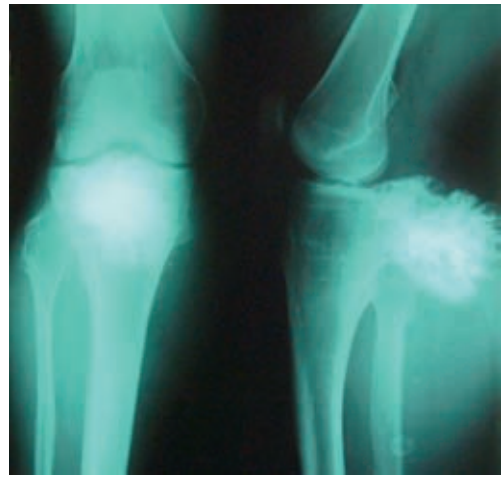


Figure 1d. X-rays of parosteal osteosarcoma of the proximal tibia (case 1).

ally showed less differentiation than the primary tumours.

Medullar involvement

In 7 patients managed, 1 had the initial histological medullar involvement and 2 patients had the medullar involvement after the local recurrence (Figure 3a). For two patients who were treated out of the Clinic for Orthopaedic Surgery in Skopje initially, it was not possible to tell due to the lack of evidence (Figure 3b, 3c). Only one patient didn't have the medullar involvement at all (case 6).

Discussion

Parosteal osteosarcoma is a rare malignant bone tumour first described by Geschickter and Copeland in 1951.[1,2,8, 9] Up to date, there are reports of parosteal osteosarcoma even in human pets.[10] Larsson and Lorentcon found only 206 cases (including sixteen cases from their study) to be reported until 1980 in the world literature.[11] The annual incidence in Sweden, as they reported, corresponds to one case per 8 000 000 inhabitants and were accounted for about 2% of all primary malignant

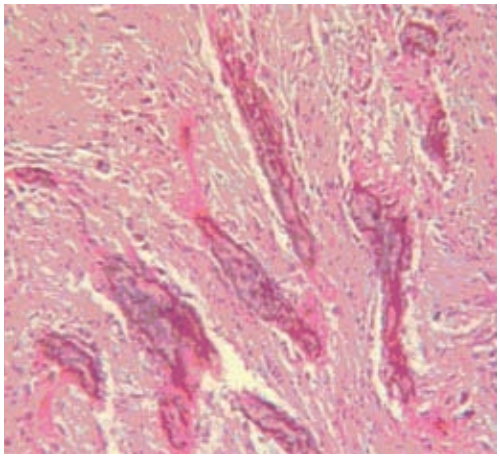


Figure 2a. Parosteal osteosarcoma showing parallel osteoid trabeculae embedded in fibroblastic stroma. HE, x100.

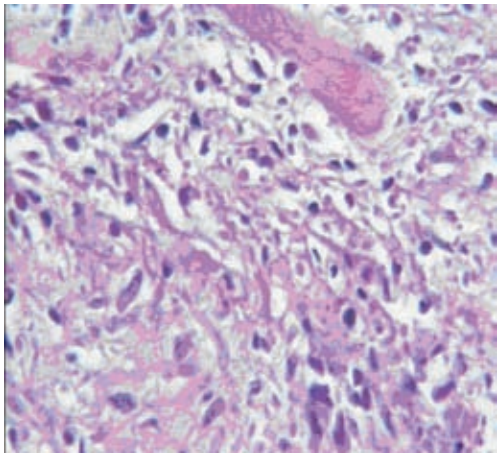


Figure 2b. Focus of a moderate grade of differentiation (G2) in a well differentiated osteosarcoma. HE, x200.

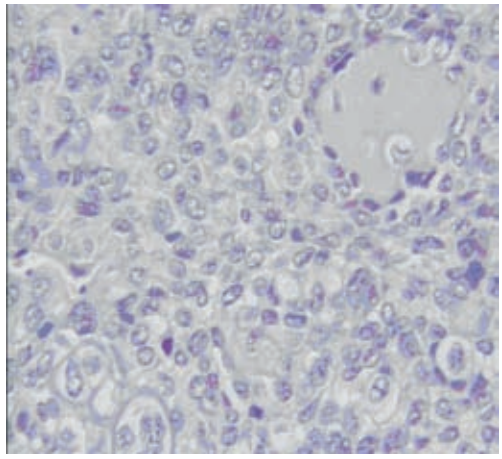


Figure 2c. Osteoid deposits in high grade chondroblastic osteosarcoma. HE, x400.

tumours of bone and 6.2% of all osteosarcomata. In comparison, Dahlin reported that parosteal osteosarcoma constituted only 3.7% of all osteosarcomata from Mayo Clinic.[3,11,12]

Most of the world studies documented difficulties in the diagnosis of parosteal osteosarcoma. The inability to diagnose the lesion correctly often leads to inadequate initial operative procedures. The differential diagnosis may include diverse entities such as: myositis ossificans, fracture callus, ossifying haematoma, osteochondroma, extraosseus osteosarcoma, parosteal chondroma, desmoplastic fibroma and osteoma.[3,4,5,7,13]

The clinical characteristic of patients who have a parosteal osteosarcoma is distinctly different from that of patients who have conventional osteosarcoma.[2,13] The most common complain was "painless swelling", the same as reviewed in the literature, presented with 3 patients.[3,4,7,8,12] Two of our patients had "blunt pain with swelling" and one had "night pain". Most of our patients had the symptoms of prolonged duration more than one year before admitting at the Clinic.

The site of the parosteal osteosarcoma in our study correlates with the reported sites of the literature. A predilection for anatomic site was a characteristic feature of the patients in the study and showed that 50% of the patients in our study had the involved posterior part of distal metaphysis of the femur.[4,6,9,14, 15]

The well described concept of dedifferentiated parosteal osteosarcoma with higher incidence of development of metastases

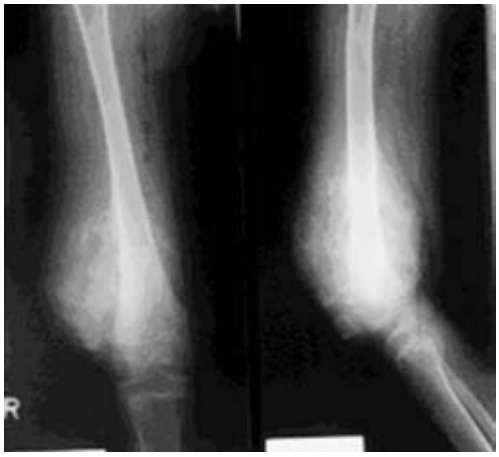


Figure 3a. frontal and lateral radiography of local recurrence of "high grade" chondroblastic type periosteal osteosarcoma (case 3).

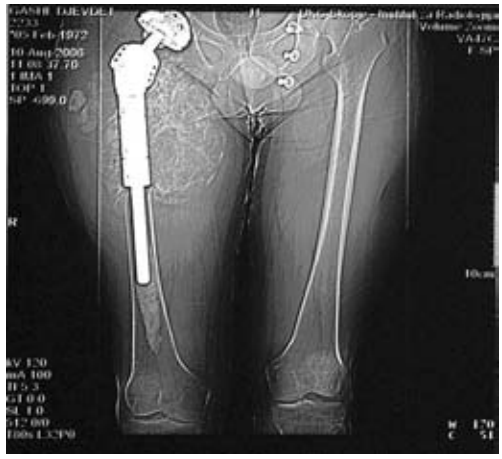


Figure 3c. Radiograph of the recurrence of parosteal osteosarcoma at the proximal femur after limb salvage operation with special tumor endoprosthesis (case 5).

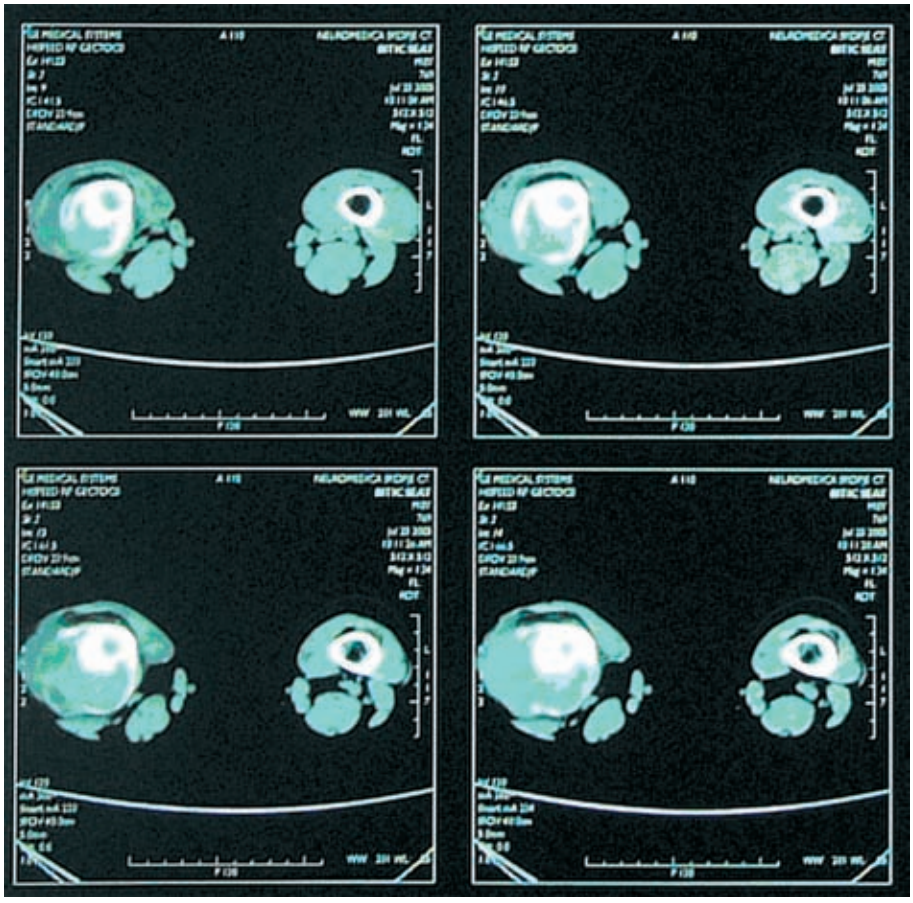


Figure 3b. CT of distal femur showing the extent of medullar involvement of the bone (case 3).

is also applicable in our study.[3,5,16,17] The dedifferentiation of the tumour showed the high incidence with pulmonary metastases in one of our patients. A long-term follow up is essential for assessing the real malignant potential of parosteal osteosarcoma since the recurrence can be considerably delayed.[18]

The results of various types of therapy are always difficult to evaluate in retrospect. A review of the literature shows that the local excision of the tumours has almost invariably resulted in recurrence.[3,6,9,13,17,18] The local recurrence was not related to the medullar involvement of the tumour but to the number or adequacy of biopsies and surgical margins of the resection of the tumour.[14,19] Two of the patients had more than one, and one patient had three inadequate placed biopsies. Further more, three of the patients in our study had the intralesional or inadequate marginal resection of the tumour during the primary surgical treatment. Over all results were poor to fair and varied from 25 to 39 points of MSTS score.[20]

Conclusions

The findings of this study followed the theory that two distinct types of parosteal osteosarcoma exist: one type, which is primarily highly malignant and the other one, which is originally benign but with the inherent malignant potential. Only two patients of our study had modern chemotherapy and this did not allow any definite conclusion. In most of the cases the histopathological diagnosis was a problem at the beginning of the treatment. For well delineated tumours with a well-differentiated histological appearance, the radical (en block) resection of the tumour and surrounding soft tissue is strongly recommended. In patients with advanced tumours containing pleomorphic areas and/or inadequate placed biopsies or prior inadequate surgical treatment, the amputation should be undertaken. Parosteal osteosarcoma shows, like no other tumour, the necessity of the close cooperation of all involved disciplines for the diagnosis and therapy and should be treated only in specialized institutions for bone tumour surgery.

References

1. Geschickter CF, Copeland MM. Parosteal osteosarcoma of bone: a new entity. *Ann Surg* 1951; **133:** 579-83.

2. Gross SW. The classic: sarcoma of the long bones: based upon a study of one hundred and sixty-five cases. 1879. *Clin Orthop Relat Res* 2005; **438:** 9-14.

3. Lorentzon R, Larsson SE, Boquist L. Parosteal (juxtracortical) osteosarcoma. A clinical and histopathological study of 11 cases and review of the literature. *J Bone Joint Surg Br* 1980; **62-B:** 86-92.

4. Campanacci M, Picci P, Gherlinzoni F, Guerra A, Bertoni F, Neff JR. Parosteal Osteosarcoma. *J Bone Joint Surg Br* 1984; **66:** 313-21.

5. Deling, D, Werner M. Pathomorphologie des parossalen osteosarcoms. Erfahrungen an 125 fällen des Hamburger Knochentumor-Registers. *Orthopäde* 2003; **32:** 74-81.

6. Bacci G, Picci P, Ferrari S, Sangiorgi L, Mercuri M, Bertoni F, et al. Neoadjuvant chemotherapy for the treatment of osteosarcoma of the extremities: excellent response of the primary tumor to preoperative treatment with methotrexate, cisplatin, adriamycin, and ifosfamide. Preliminary results. [English, Italian]. *Chir Organi Mov* 1995; **80:** 1-10.

7. Bertoni F, Boriani S, Campanacci M. Periosteal osteosarcoma and periosteal chondrosarcoma. Two distinct entities. *J Bone Joint Surg Br* 1982; **64:** 370-6.

8. Lichtenstein L. *Bone tumors.* 4th edition. Saint Louis: CV Mosby Company; 1972.

9. Scaglietti O, Calandriello CB. Ossifying parosteal osteosarcoma. Parosteal osteoma or juxtacortical osteogenic sarcoma. *J Bone Joint Surg Am* 1962; **44-A:** 635-47.

10. Thomas WB, Daniel GB, McGavin MD. Parosteal osteosarcoma of the cervical vertebra in a dog. *Vet Radiol Ultrasound* 1997; **38:** 120-3.

11. Larsson SE, Lorentzon R. The geographic variations of the incidence of malignant primary bone tumors in Sweden. *J Bone Joint Surg Am* 1974; **56-A:** 592-600.

12. Pritchard DJ, Finkel MP, Reilly CA Jr. The etiology of osteosarcoma. A review of current considerations. *Clin Orthop Relat Res* 1975; (111): 14-22.

13. Okada K, Frassica FJ, Sim FH, Beabout JW, Bond JR, Unni KK. Parosteal osteosarcoma. A clinicpathological study. *J Bone Joint Surg Am* 1994; **76:** 366-78.

14. Kavanagh TG, Cannon SR, Pringle J, Stoker DJ, Kemp HB. Parosteal osteosarcoma. Treatment by wide resection and prosthetic replacement. *J Bone Join Surg Br* 1990; **72:** 959-65.

15. Kumm DA.; Rütt J. Hakenbroch MH. Parosteal osteosarcoma of the tarsus. *Arch Orthop Trauma Surg* 1997; **116:** 437-9.

16. Haeckel C, Ayala AG, Radig K, Raymond AK, Roessner A, Czerniak B. Protease expression in dedifferentiated parosteal osteosarcoma. *Arch Pathol Lab Med* 1999; **123:** 213-21.

17. Ritschl P, Wurnig C, Lechner G, Roessner A. Parosteal osteosarcoma. 2-23-year follow-up of 33 patients. *Acta Othop Scand* 1991; **62:** 195-200.

18. Lau TW, Wong JW, Yip DK, Chien EP, Shek TW, Wong LL. Local recurrence of parosteal osteosarcoma adjacent to a prosthesis after 20 years: a case report. *J Orthop Surg* 2004; **12:** 263-6.

19. Lewis VO, Gebhardt MC, Springfield DS. Parosteal osteosarcoma of the posterior aspect of the distal part of the femur: oncological and functional results following a new resection technique. *J Bone Joint Surg Am* 2000; **88-A:** 1083-8.

20. Enneking WF, Dunham W, Gephardt MC, Malawar M, Prichard DJ. A system for functional evaluation of reconstructive procedures after surgical treatment of tumours of the musculoskeletal system, *Clin Orthop* 199; **286:** 241-6.

Radiol Oncol 2007; 41(3): 99-106.

CT- perkutana transtorakalna tankoigelna biopsija pljučnih sprememb. Dvoletne izkušnje na Kliničnem inštitutu za radiologijo v Ljubljani

Kocijančič I, Kocijančič K

Izhodišča. Prvo perkutano pljučno biopsijo je leta 1883 opisal Layden, o prvem primeru pljučne biopsije pod nadzorom računalniške tomografije (CT) pa sta leta 1976 poročala Haaga in Alfidi. Danes je odvzem tkiva iz sprememb v pljučih potreben, kadar z uporabo endobronhialnih tehnik sprememb ne moremo vzročno opredeliti ter kadar citološki izvid lahko spremeni stadij bolezni ali vpliva na odločitev o zdravljenju.
Citološki pregled vzorca, odvzetega s tankoigelno biopsijo potrdi etiologijo sprememb v pljučih v 80 – 95% primerov. Postopek odvzema je varen, saj so resni zapleti zelo redki.
Z našo retrospektivno analizo smo želeli določiti osnovne podatke o diagnostični zanesljivosti te preiskave ter o pogostosti pnevmotoraksa pri naših bolnikih.
Metode. Po namestitvi bolnika smo izvedli spiralno CT preiskavo prsnega koša z nameščeno metalno značko, ki nam je omogočila optimalni transkutani pristop. Po ponovni preverbi lokalizacije sprememb v pljučih in po subkutani anesteziji smo pri CT- vodeni tankoigelni aspiracijski biopsiji uporabili koaksialne 18G Gallini igle. Njihovo dolžino smo izbrali glede na globino tarčne spremembe.
Rezultati. Od januarja 2005 do januarja 2007 smo pri 43 bolnikih (24 moških in 19 ženskah), ki so bili stari od 26 do 79 let, izvedli CT- perkutano transtorakalno tankoigelno biopsijo pljučnih sprememb. Pri enem bolniku smo verificirali dve spremembi, vsako posebej. Retrospektivno smo tako pregledali bolnišnično dokumentacijo 44 posegov pri 43 bolnikih.
Diagnostična zanesljivost preiskave je bila 93,2%, pnevmotoraksov je bilo 27,2%, pri 4,5% bolnikov pa je bilo potrebno pnevmotoraks zdraviti z vstavitijo plevralnega drena.
Zaključki. Dvoletne izkušnje na Radiološkem inštitutu v Ljubljani potrjujejo, da je CT-vodena perkutana transtorakalna tankoigelna biopsija zanesljiva in varna metoda za diagnostiko neopredeljenih sprememb v pljučih.

Radiol Oncol 2007; 41(3): 107-12.

Obstruktivna ileocekalna intususcepcija pri odraslem bolniku

Žokalj I, Magaš Z, Pavčec Z, Saghir H, Pal A, Kolarić Z, Marotti M

Izhodišča. Prikazujemo primer odraslega bolnika z obstruktivno ileocekalno intususcepcijo zaradi karcinoma cekuma.

Prikaz primera. 44 letnega moškega smo sprejeli v bolnišnico s hudimi bolečinami v zgornjem delu trebuha, bruhanjem in povišano vrednostjo serumske amilaze (154 U/L, normala 23-91 U/L pri 37°C). Deveti dan po sprejemu se je bolnikovo stanje nenadoma močno poslabšalo, prisotni so bili klinični in radiološki znaki zapore črevesa. Naredili smo nujno CT preiskavo, predhodno pa smo bolnika opazovali ter njegovo stanje sledili s preglednim rentgenskim slikanjem trebuha ter UZ preiskavami trebuha. CT je pokazal mehkotkivno strukturo, obdano z več koncentričnimi obroči, ki se je na pokontrastnih posnetkih dobro obarvala – videz tarče. Bolnika smo operirali, naredili smo desno hemikolektomijo s terminolateralno ileotransverzoanastomozo. Ob operaciji smo našli več vijug tankega črevesa, zataknjenega v cekum in ascendentni kolon ter karcinom kolona (Dukes B, Astler-Coller B2), ki je predstavljal glavni vzrok intususcepcije.

Zaključki. Intususcepcija pri odraslih je redek vzrok trebušne bolečine, vendar pa je ena izmed diferencialno diagnostičnih možnosti, zlasti kadar je bolečina občasna in so prisotni klinični in radiološki znaki črevesne zapore. Opisan primer potrjuje CT preiskavo kot slikovno metodo izbora v primerih intususcepcije pri odraslem.

Radiol Oncol 2007; 41(3): 115-22.

Dopolnilno zdravljenje bolnic z rakom dojke s transtuzumabom

Matos E, Čufer T

Izhodišča. Trastuzumab je monokolonsko protitelo, usmerjeno proti HER2 receptorejm, ki so prekomerno izraženi pri približno 20% bolnic z rakom dojke. Članek predstavlja pet kliničnih raziskav, v katerih so trastuzumab uporabljali v okviru dopolnilnega zdravljenja raka dojke. Rezultati vseh opisanih raziskav kažejo na visoko učinkovitost tega tarčnega zdravila pri bolnicah s HER2 pozitivnimi tumorji. Splošno sprejetih priporočil za uporabo trastuzumaba za dopolnilno zdravljenje raka dojke še ni. Vzrokov je več: navedene klinične raziskave imajo kratek srednji čas opazovanja, zdravilo je bilo uporabljeno v različnih shemah, različen je bil skupni čas zdravljenja s trastuzumabom, pozni neželeni učinki zdravljenja so še slabo opredeljeni.

Zaključki. Še vedno ne vemo, katerim HER2 pozitivnim bolnicam zdravljenje s trastuzumabom res koristi. Prav gotovo je korist velika pri pravih HER2 pozitivnih rakih dojk, ki so hormonsko neodvisni, in pri anatomsko večjih rakih. Kakšna pa je absolutna dobrobit pri majhnih, hormonsko odvisnih rakih, ostaja odprto vprašanje. Vedeti moramo, da neželeni učinek – kardiotoksičnost – lahko življenjsko ogrozi predvsem starejše bolnice in morebitno izniči dobrobit zdravljenja. Ne vemo še, kakšen je optimalen čas pričetka in trajanja zdravljenja s trastuzumabom. Ali naj poteka zdravljenje s trastuzumabom sočasno s kemoterapijo ali takoj za njo, ali naj zdravljenje traja eno leto, dve leti ali samo nekaj mesecev. Poleg tega ostaja še vedno odprto vprašanje optimalnega določanja HER2 statusa in kateri HER2 status napoveduje korist od zdravljenja s trastuzumabom. Na ta vprašanja nam bo dalo odgovor daljše opazovanje bolnic, vključenih v petih velikih prikazanih kliničnih raziskavah.

Radiol Oncol 2007; 41(3): 123-32.

Ionizirajoče sevanje in transgeneracijska nestabilnost

Vrhovac I, Nikšić G

Izhodišča. Posredno preučevanje vpliva ionizirajočega sevanja na nestabilnost genoma naslednikov kot posledice obsevanja njihovih staršev, lahko skrčimo na preiskovanje sprememb, ki se pojavljajo samo na minisatelitnih lokusih celic, ki sestavljajo razvojno linijo gamet. Minisatelitne mutacije, ki so rezultat tega obsevanja, so izražene kot njihov odstotek in so enake razmerju števila mutiranih alelov v določeni generaciji glede na celotno število prisotnih alelov. Vpliv ionizirajočega sevanja na potomce obsevanih staršev so prvič opazili na mišjih krvotvornih matičnih celicah. Kljub temu, da je obsevana celica matere brez mutacij, ima hčerinska celica povečan nivo mutacij. Ta fenomen, ki so ga poimenovali transgeneracijska nestabilnost, je definiran kot mutacija v genomu posameznikov, ki so potomci obsevanih prednikov. Glede na zgoraj omenjeno, lahko zaključimo, da te mutacije niso nujno prisotne v obsevanih starševskih celicah, niti ni nujno, da izginejo v nekaj naslednjih generacijah, temveč se lahko pokažejo kot povečano število mutacij pri potomcih.

Zaključki. Rezultati raziskav, ki so bile narejene na živalskem modelu, kot tudi raziskav na človeški populaciji, kažejo na značilne spremembe, ki jih najdemo na minisatelitnih lokusih v generacijah potomcev. Mehanizmi, ki so odgovorni za te spremembe, še niso znani in so torej nove raziskave na tem področju potrebne.

Radiol Oncol 2007; 41(3): 133-43.

Radiotherapija s trodimenzionalnim planiranjem pri bolnikih z inoperabilnim nedrobnoceličnim rakom pljuč – izkušnje v posamični ustanovi

Fromm S, Rottenfusser A, Berger D, Pirker R, Pötter R, Pokrajac B

Izhodišča. Namen raziskave je bil ovrednotiti primernost, varnost in učinkovitost radioterapije s trodimenzionalnim planiranjem (3D-RT) pri bolnikih z inoperabilnim nedrobnoceličnim rakom pljuč (NSCLC). Zanimali so nas čas, ki je potekel do napredovanja obolenja (TTP), vključno s časom do lokalne ponovitve bolezni in/ali oddaljenih zasevkov, lokalna kontrola bolezni (LCR), čas do smrti (TTD) in stranski učinki zdravljenja.

Bolniki in metode. Od 1997 do 2002 smo s 3D-RT zdravili 84 bolnikov z inoperabilnim NSCLC. Upoštevali smo prospektivni protokol, ki smo ga naredili na Radioterapevtskem oddelku Klinične bolnišnice na Dunaju. Glede na stanje splošne zmogljivosti, pljučno funkcijo in glede na omejitev, ki ga je določalo razmerje med dozo in volumnom obsevanja, smo bolnike obsevali s 66-70 Gy ali 50-60 Gy, nekateri pa so bili zdravljeni tudi s sekvenčno ali pa hkratno kemoterapijo, ki je vsebovala cisplatin.

Rezultati. Bolniki so zdravljenje dobro prenašali, stranski učinki zdravljenja pa so bili majhni. Samo pri enem bolniku smo ugotovili pneumonitis stopnje 4, pri 6% bolnikov pneumonitis stopnje 3 in pri 13% stopnje 2. Pri dveh bolnikih smo ugotovili esofagitis stopnje 4 in pri nobenem stopnje 3. Analiza histograma doza-volumen (DVH) je pokazala, da je 42% pljuč na strani, kjer je bil tumor, prejelo 20 Gy (V_{20}), druga stran pljuč pa le 14% te doze. Srednja vrednost obsevalne doze pljuč na strani, kjer je bil tumor, je bila 25 Gy, srednja vrednost pri tistih bolnikih, kjer se je razvil pneumonitis stopnje 2-4, pa je bila 53,3%.
Srednja vrednost sledenja bolnikov je bila 24 mesecev. Glede na različno obsevalno dozo nismo našli razlike v času do napredovanja bolezni (srednja vrednost 15 mesecev). Tisti bolniki, ki so ob višji obsevalni dozi (66-70 Gy) prejeli tudi kemoterapijo, pa so imeli statistično značilno daljše preživetje (28 mesecev ***vs.*** 16 mesecev). Po dveh letih smo le pri 22% bolnikov dosegli lokalno kontrolo bolezni.

Zaključki. Zdravljenje z obsevalno dozo do 70 Gy je primerno, varno in ga lahko kombiniramo tudi s kemoterapijo. Kljub temu sta stopnja lokalne kontrole bolezni in celokupno preživetje sorazmerno nizki. Predlagamo nadaljnje klinične raziskave z višjo obsevalno dozo, ki ne bo povzročala povečane toksičnosti, tudi ne pri bolnikih z napredovalo boleznijo.

Radiol Oncol 2007; 41(3): 144-51.

Kvaliteta življenja bolnikov s pljučnim rakom po torakotomiji

Debevec L, Rozman I

Izhodišča. Namen raziskave je bil oceniti kvaliteto življenja (KŽ) bolnikov s pljučnim rakom pred torakotomijo in po njej ter primerjati poslabšanje KŽ po resekciji in po eksplorativni torakotomiji.

Bolniki in metode. Zaradi nedrobnoceličnega pljučnega raka je bilo torakotomiranih 43 bolnikov, starih od 31 do 82 (povprečno 61) let in opravljenih 29 lobektomij, 1 bilobektomija, 8 pnevmonektomij in 5 eksplorativnih torakotomij. KŽ smo ocenjevali z vprašalnikom EORTC QLQ-LC30 in QLQ-LC13 pred operacijo in povprečno 45±17 dni po njej, še pred morebitno kemoterapijo in radioterapijo.

Rezultati. Po torakotomiji so se značilno poslabšali fukcionalna sposobnost (telesna zmogljivost, sposobnost za dnevna opravila in družbeno udejstvovanje) in simptomi: utrujenost, zaprtje, inapetenca, dispneja, bolečine. Neznačilno so bili slabši drugi simptomi (slabost oz. bruhanje, nespečnost, driska, kašelj), splošno zdravstveno stanje, funkcionalna sposobnost (razpoloženje, spoznavna sposobnost) in denarne težave. Hemoptize pa so se značilno izboljšale in jih po torakotomiji ni bilo več. Med bolniki, pri katerih je bil tumor reseciran, in bolniki, pri katerih je bila narejena samo eksplorativna torakotomija, ni bilo značilnih razlik.

Zaključki. V raziskavi smo ugotovili značilno poslabšanje KŽ v prvih dveh mesecih po torakotomiji, ni pa bilo značilnih razlik med reseciranimi in eksplorativno torakotomiranimi bolniki.

Radiol Oncol 2007; 41(3): 152-60.

Diagnosticiranje in zdravljenje parostealnega osteosarkoma. Klinična in patohistološka raziskava 7 primerov ter pregled literature

Samardziski M, Zafiroski G, Tolevska C, Konstadinova-Kunovska S, Vasileva V

Izhodišča. Parosteal osteosarkom je redek nizkomaligni kostni tumor. Po kirurškem posegu je potreben skrben patohistološki pregled, ker stopnja tumorske invazije v kostni mozek in stopnja dediferenciranosti določata napoved poteka bolezni ter pogostnost lokalne ponovitve bolezni in metastaziranja.

Bolniki in metode. V retrospektivni raziskavi smo analizirali 7 bolnikov s kostnim parostealnim osteosarkomom; 6 bolnikov je imelo parostealni in 1 periostealni osteosarkom. Obravnavali smo bolnike, ki so bili zdravljeni na Ortopedski kliniki v Skopju, Makedonija, od 1995 do 2006. V 12-letnem obdobju smo ugotovili med 467 bolniki s primarnimi kostnimi tumorji 1,5% parostealnih osteosarkomov. Med 7 bolniki so bile 3 ženskega spola in 4 moškega, starosti od 8 do 39 let (srednja starost 27). Analiza je pokazala, da je kar 57% bolnikov imelo sprva napačno diagnozo, pri 71,4% se je pojavil lokalni recidiv, pri 28,7 % metastaze, smrtnost pa je bila 28,7%. Bolnike smo sledili od 7 mesecev do 9 let (srednja vrednost 37).

Rezultati. Klinični in histopatološki izsledki pričujoče raziskave so podobno kot podatki iz literature potrdili obstoj dveh biološko različnih tipov parostealnega osteosarkoma. Prevladuje tip, ki je sprva benigni, a ima vseeno maligni potencial in povzroča zasevke po daljšem prostem intervalu. Drugi tip je visokomaligni od začetka.

Zaključki. Pri bolnikih, ki imajo prevladujoči nizkomaligni parostealni osteosarkom, priporočamo radikalno *"en bloc"* resekcijo tumorja s skrbnim sledenjem bolnika, pri visokomalignem tipu osteosarkoma pa radikalno operacijo s kemoterapijo.

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.*

Radiotherapy

October21-25, 2007
The ESTRO teaching course "Physics for Clinical radiotherapy" will take place in Limassol, Cyprus.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Prevention of tobacco

November 2-4, 2007
The "6th Conference of the International Society for Prevention of Tobacco Induced Diseases" will take place in Little Rock, Arkansas; USA.
E-mail Carolyn.dresler@ksg03.harvard.edu

Radiation oncology

November 11-16, 2007
The ESTRO teaching course "Evidence Based Radiation Oncology: Methodological Basis & Clinical Application" will take place in Athens, Greece.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Prostate cancer

November 15-17, 2007
The ESTRO multidisciplinary prostate cancer meeting will be offered.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Molecular markers in cancer

November 15-17, 2007
The "EORTC-NCI-ASCO Annual Meeting on Molecular Markers in Cancer" will be held in Brussels.
E-mail ENASCO2007@eortc.be; or see http://www.eortc.be/seminar/ENASCO2007/

Lung cancer

December 5-7, 2008
The "3rd Asia Pacific Lung Cancer Congress" will be offered in India.
E-mail: purvish@rediffmail.com

Lung cancer

December 7-8, 2007
The CELCC-ESMO workshop '' Predictive Factors in Lung Cancer'' will take place in Vienna, Austria.
E-mail: robert.pirker@meduniwien.ac.at or see www.mondial-congress.com/celcc2007

Radiotherapy

December 9-13, 2007
The ESTRO teaching course "Image-Guided Radiotherapy in Clinical Practice" will take place in Brussels, Belgium.
Contact ESTRO office, Avenue E. Mounierlaan, 83/12, B-1200 Brussels, Belgium; or call +32 2 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Oncology

February 21-23, 2008
The "8th Targeted Therapy Meeting" will take place in Santa Monica, CA, USA-
See http://www. iaslc.org

Oncology

March 5-9, 2008
The NCCN 13th Annual Conference "Clinical Practice Guidelines & Quality Cancer Care™" will be offered in Hollywood, Florida, USA
See http://www.nccn.org

Lung cancer

April 23-26, 2008
The first lung cancer conference in Europe will be held in Geneva, Switzerland.
E-mail pia.hirsch@uchsc.edu

Lung cancer

April 24-26, 2008
The "IASLC/ESMO Lung Cancer Conference" will be offered in Geneva, Switzerland.
See http://www.iaslc.org

Lung cancer

June 12-14, 2008
The "11th Central European Lung Cancer Conference" will be offered in Ljubljana, Slovenia.
Contact Conference secretariat, Ms. Ksenia Potocnik, Department of Thoracic Surgery, Medical Centre Ljubljana, Slovenia; or call +386 1 522 2485; or fax +386 1 522 3968; or e-mail ksenia.potocnik @kclj.si; or see http://www.ce-lung2008.org/

Oncology

October 9-10, 2008
The ''3rd Latin American Cancer Conference'' will take place in Vina del Mar, Chile.
E mail nisehy@uol.com.br or rodrigo.arriagada@ki.se

Oncology

November 13-15, 2008
The Chicago/IASLC/ASCO/ASTRO symposiums "Malignancies of the Chest and Head and Neck" will be offered in Chicago.
E-mail: evokes@medicine.bsd.uchicago.edu

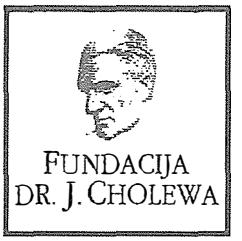
Lung cancer

August 21-24, 2009
The "13th World Conference on Lung Cancer" will be offered in San Francisco, USA.
Contact Conference Secretariat; e-mail WCLC2007@ ncc.re.kr; or see http://www.iaslc.orgIumages/ 12worldconfannounce.pdf

Oncology

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

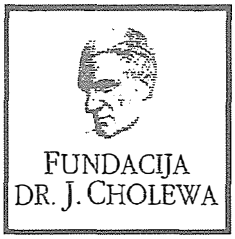
As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.



FUNDACIJA "DOCENT DR. J. CHOLEWA"
JE NEPROFITNO, NEINSTITUCIONALNO IN NESTRANKARSKO ZDRUŽENJE POSAMEZNIKOV, USTANOV IN ORGANIZACIJ, KI ŽELIJO MATERIALNO SPODBUJATI IN POGLABLJATI RAZISKOVALNO DEJAVNOST V ONKOLOGIJI.

DUNAJSKA 106
1000 LJUBLJANA

ŽR: 02033-0017879431



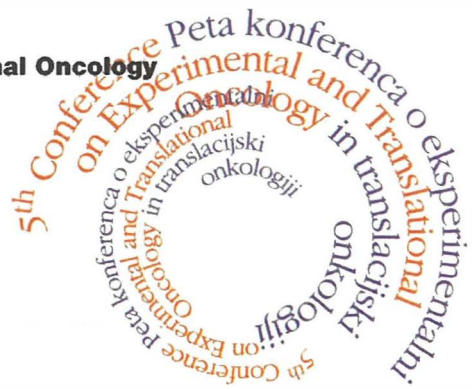
Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the third quarter of 2007

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to focus its activities and attention to cancer research and education in Slovenia and continues to deal carefully and with the requests and proposals for research grants and scholarships. The Foundation members with clinical and research experience in cancer and members with important experience in finance will continue to be instrumental in this activity.

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to support the regular publication of "Radiology and Oncology" international medical scientific journal in 2007. This journal is edited, published and printed in Ljubljana, Slovenia. This support emphasizes the spread of information and knowledge about advances in cancer among professionals and to many interested individuals in lay public and others in Slovenia and elsewhere. The Foundation also pays special attention to the support of the publication of the results from cancer research in Slovenia in respectable international scientific journal worldwide.

The Foundation salutes the start of usage of new premises of the Institute of Oncology in Ljubljana, Slovenia, a fine tribute to its coming 70th anniversary.

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



5th Conference on Experimental and Translational Oncology

Kranjska gora, Slovenia, March, 26-30, 2008

Organized by: Janko Kos, Tamara Lah and Gregor Serša

Topics:

- Carcinogenesis
- Mechanisms of Tumour Progression
- Stem Cells in Cancer
- Tumour Markers
- Delivery Systems in Cancer Therapy
- New Drugs and Therapeutic Markers

Location:
Hotel Kompas
Kranjska gora, Slovenia
http://www.hoteli-kompas.si

Correspondence:
Phone: +386 1 241 29 70
Fax: +386 1 241 29 80
Email: ceto@nib.si
http://www.onko-i.si/ceto

Organized under patronage of Association of Radiology and Oncology

LABORMED

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

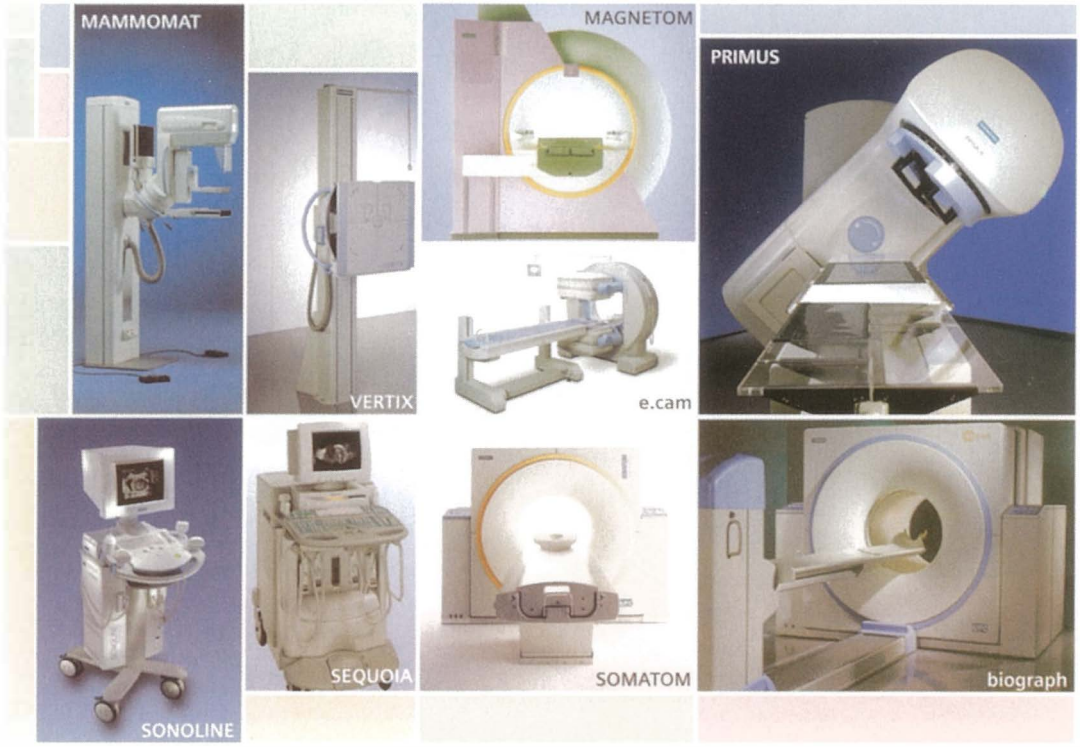
LABORMED d.o.o.
Bežigrajski dvor
Peričeva 29, Ljubljana
Tel.: (0)1 436 49 01
Fax: (0)1 436 49 05

info@labormed.si

www.labormed.si

SIEMENS

SiemensMedical.com/oncology



SEEK-FIND-ACT-FOLLOW - the Continuum of Oncology Care™

Siemens oncology portfolio comprises comprehensive workflow solutions integrating the full spectrum of care from screening/early detection and diagnosis through therapy and follow-up. All from one provider — with over 100 years history of innovation in medical technology.

Siemens proven clinical methods can help you to achieve more successful outcomes. How? Through industry-leading technology, increased productivity measures for maximized utilization potential, and patient-friendly design and features.

Every day in the United States alone, 29,000 cancer patients receive radiation therapy delivered by Siemens linear accelerators. As clinical protocols transition to include IMRT and IGRT, Siemens seamlessly integrates the diagnostic and treatment modalities. That's what we call Best Practice Oncology Care.

Siemens medical
Solutions that help

Arimidex®

anastrozol

Takojšnje dopolnilno zdravljenje

pri bolnicah po menopavzi z zgodnjim hormonsko odvisnim invazivnim rakom dojke

Kratka informacija o zdravilu

Ime zdravila
Arimidex 1 mg filmsko obložene tablete

Sestava
Ena tableta vsebuje 1 mg anastrozola.

Indikacije
Adjuvantno zdravljenje žensk po menopavzi, ki imajo zgodnji invazivni rak dojke s pozitivnimi estrogenskimi receptorji. 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
1 tableta po 1 mg peroralno, enkrat na dan.
Pri zgodnjem raku je priporočljivo trajanje zdravljenja 5 let.

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 drugo sestavino zdravila.

Posebna opozorila in previdnostni ukrepi
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.

Povzetek glavnih neželenih učinkov
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)
Arimidex znižuje nivo estrogena v obtoku, zato lahko povzroči zmanjšanje mineralne kostne gostote, kar pomeni za nekatere bolnike zvečano tveganje za zlome.

Medsebojno delovanje z drugimi zdravili
Zdravila, ki vsebujejo estrogen, ne smete dajati sočasno z Arimidexom, ker bi se njegovo farmakološko delovanje izničilo. Tamoksifena se ne sme uporabljati skupaj z Arimidexom, ker lahko pride do zmanjšanja njegovega delovanja.

Režim izdajanja zdravila
Rp/Spec

Datum priprave informacije
Februar 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 55, Ljubljana

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

AstraZeneca

ONKOLOGIJA

ARI 01/07 P

Za področja:

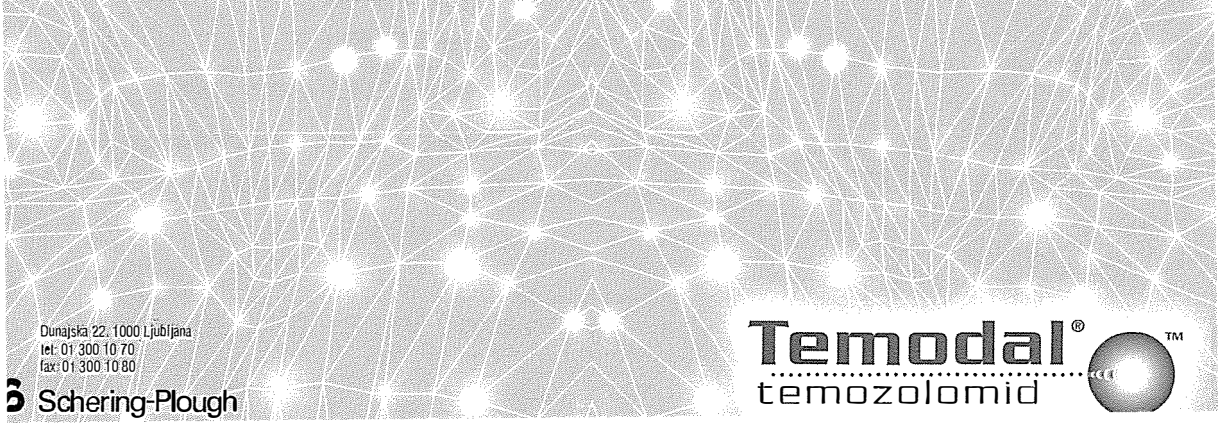
- bioznanosti **SYNGENE, INVITROGEN**: **DYNAL, ZYMED, MOLECULAR PROBES, CALTAG**
- diagnostike **MINERVA, MEDAC, BIOTEK**
- gojenja celičnih kultur **INVITROGEN-GIBCO**, **TPP, GREINER** in **SANYO**
- merjenja absorbance, fluorescence in luminiscence **BIOTEK**
- pipetiranja **BIOHIT** in **BIOTEK**
- laboratorijske opreme **SANYO**
- čiste vode za laboratorije **ELGA LABWATER**
- HPLC in GC kolon, vial in filtrov **PHENOMENEX** in **CHROMACOL/NATIONAL SCIENTIFIC**

KEMOMED
Prinašamo rešitve

SVETOVANJE, TRGOVINA, TRŽENJE d.o.o. • Kališka 9 • PE: Stritarjeva 5 • 4000 KRANJ • Slovenija
T: +386 4 20 15 050 • F: +386 4 20 15 055 • e-mail: info@kemomed.si • www.kemomed.si

emodal 20 mg; 100 mg, 250 mg. Sestava zdravila Vsaka kapsula zdravila Temodal vsebuje 20 mg, 100 mg ali 250 mg temozolamida.**Terapevtske indikacije** Temodal apsule so indicirane za zdravljenje bolnikov z: - za zdravljenje novo diagnosticiranega glioblastoma multiforme, sočasno z radioterapijo in kasneje kot monoterapija, - nalignim gliomom, na primer multiformnim glioblastomom ali anaplastičnim astrocitomom, ki se po standardnem zdravljenju ponovi ali napreduje. **Odmerjanje in način porabe** 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/m² na dan 42 dni, sočasno z žariščno radioterapijo (60 Gy, danih v 30 delnih odmerkih). Odmerka e boste zmanjševali, vendar se boste vsak teden odločili o morebitni odložitvi jemanja temozolomida ali njegovi ukinitvi na podlagi kriterijev hematološke in ehematološke toksičnosti. Zdravilo Temodal lahko bolnik jemlje ves čas 42-dnevnega obdobja sočasne terapije do 49 dni, če so izpolnjeni vsi od naslednjih pogojev: bsolutno število nevtrofilcev $\geq$ 1,5 x 10^9/l, število trombocitov $\geq$ 100 x 10^9/l, skupni kriteriji toksičnosti (SKT) za nehematološko toksičnost $\leq$ 1. stopnje (z izjemo opecije, slabosti in bruhanja). Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko. **Faza monoterapije** Štiri tedne po zaključku faze očasnega zdravljenja z zdravilom Temodal in radioterapijo naj bolnik jemlje zdravilo Temodal do 6 ciklov monoterapije. V 1. ciklu (monoterapija) je odmerek zdravila 150 g/m² enkrat na dan 5 dni, temu pa naj sledi 23 dni brez terapije. Na začetku 2. cikla odmerek povečajte na 200 mg/m², če je SKT za nehematološko toksičnost za 1. cikel opnje $\leq$ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (AŠN) $\geq$ 1,5 x 10^9/l in število trombocitov $\geq$ 100 x 10^9/l. Če odmerka niste povali v 2. ciklusu, ga v naslednjih ciklusih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m² na dan v prvih 5 dneh vsakega naslednega ciklusa, razen če nastopi toksičnost. Med zdravljenjem morate pregledati celotno krvno sliko na 22. dan (21 dni po prvem odmerku zdravila Temodal). **Ponavljajoči e 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/m² enkrat na dan prvih 5 dni, temu pa naj sledi 23-dnevni premor (skupaj 28 dni). Pri bolnikih, ki so že bili zdravljeni s kemoterapijo, je četni odmerek 150 mg/m² enkrat na dan, v drugem ciklusu pa se poveča na 200 mg/m² enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov. **Pediatrični olniki** Pri bolnikih, starih 3 leta ali starejših, posamezen ciklus zdravljenja traja 28 dni. Temodal naj jemljejo peroralno v odmerku 200 mg/m² enkrat na dan prvih 5 dni, otem pa naj sledi 23-dnevni premor (skupaj 28 dni). Otroci, ki so že bili zdravljeni s kemoterapijo, naj prejmejo začetni odmerek 150 mg/m² enkrat na dan 5 dni, s ovečanjem na 200 mg/m² enkrat na dan 5 dni v naslednjem ciklusu, če ni bilo hematoloških toksičnih učinkov. **Bolniki z motnjami v delovanju jeter ali ledvic** Pri olnikih z blagimi ali zmernimi motnjami v delovanju jeter je farmakokinetika temozolomida podobna kot pri tistih z normalnim delovanjem jeter. Podatki o uporabi ravila 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 trebna previdnost pri uporabi zdravila Temodal pri teh bolnikih. **Starejši bolniki** Analiza farmakokinetike je pokazala, da starost ne vpliva na očistek temozolomida. Kljub mu je potrebna posebna previdnost pri uporabi zdravila Temodal pri starejših bolnikih. **Način uporabe** Temodal mora bolnik jemati na tešče. Temodal kapsule mora olnik pogoltniti cele s kozarcem vode in jih ne sme odpirati ali žvečiti. Predpisani odmerek mora vzeti v obliki najmanjšega možnega števila kapsul. Pred jemanjem ravila Temodal ali po njem lahko bolnik vzame antiemetik. Če po zaužitju odmerka bruha, ne sme še isti dan vzeti drugega odmerka. **Kontraindikacije** Temodal je ntraindiciran pri bolnikih, ki imajo v anamnezi preobčutljivostne reakcije na sestavine zdravila ali na dakarbazin (DTIC). Temodal je kontraindiciran tudi pri bolnikih s hudo elospresijo. Temodal je kontraindiciran pri ženskah, ki so noseče ali dojijo. **Posebna opozorila in previdnostni ukrepi** Pilotno preskušanje podaljšane 42-dnevne sheme ravljenja je pokazalo, da imajo bolniki, ki so sočasno prejemali zdravilo Temodal in radioterapijo, še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s *eumocystis carinii* (PCP). Profilaksa proti tovrstni pljučnici je torej potrebna pri vseh bolnikih, ki sočasno prejemajo zdravilo Temodal in radioterapijo v okviru 42-dnevne eme zdravljenja (do največ 49 dni), ne glede na število limfocitov. Če nastopi limfopenija, mora bolnik nadaljevati s profilakso, dokler se limfopenija ne povrne na opnjo $\leq$ 1. **Antiemetična terapija:** Z jemanjem zdravila Temodal sta zelo pogosto povezana slabost in bruhanje. **Laboratorijske vrednosti** Pred jemanjem zdravila orata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC mora biti $\geq$ 1,5 x 10^9/l in število trombocitov $\geq$ 100 x 10^9/l. Na 22. dan (21 dni po prvem odmerku) 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 10^9/l in število trombocitov nad 100 10^9/l. Če med katerimkoli ciklusom ANC pade na $<$ 1,0 x 10^9/l ali število trombocitov na $<$ 50 x 10^9/l, morate odmerek zdravila v naslednjem ciklusu zmanjšati za eno merno stopnjo. Odmerne stopnje so 100 mg/m², 150 mg/m² in 200 mg/m². Najmanjši priporočeni odmerek je 100 mg/m². **Moški bolniki** Temozolomid lahko deluje notoksično, zato morate moškim, ki se zdravijo z temozolomidom svetovati, da naj ne zaplodijo otroka še šest mesecev po zdravljenju. **Interakcije** Sočasna uporaba ravila Temodal in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali monometiltriazenoimidazol karboksamida (MTIC). Jemanje zdravila Temodal rano je povzročilo 33 % zmanjšanje Cmax in 9 % zmanjšanje površino pod krivuljo (AUC). Ker ne moremo izključiti možnosti, da bi bila sprememba Cmax lahko ično pomembna, naj bolniki jemljejo zdravilo Temodal brez hrane. Analiza populacijske farmakokinetike v preskušanjih druge faze je pokazala, da sočasna uporaba ksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka temozolomida. Sočasno anje z valprojsko kislino je bilo povezano z majhnim, a statistično značilnim zmanjšanjem očistka temozolomida. Uporaba zdravila Temodal v kombinaciji z drugimi elosupresivnimi učinkovinami lahko poveča verjetnost mielosupresije. **Nosečnost** Študij na nosečih ženskah ni bilo. Predklinične študije na podganah in kuncih z merkom 150 mg/m2 so pokazale teratogenost in/ali toksičnost za plod. Zato naj noseče ženske načeloma ne bi jemale zdravila Temodal. Če pa je uporaba v času sečnosti nujna, morate bolnico opozoriti na možne nevarnosti zdravila za plod. Ženskam v rodni dobi svetujte, naj med zdravljenjem z zdravilom Temodal preprečijo nositev. **Dojenje** Ni znano, ali se temozolomid izloča v materino mleko, zato ženske, ki dojijo, ne smejo jemati zdravila Temodal. **Neželeni učinki V** kliničnih preskušanjih bili najpogostnejši neželeni učinki, povezani z zdravljenjem, prebavne motnje, natančneje slabost (43 %) in bruhanje (36 %). Oba učinka sta bila ponavadi 1. ali 2. opnje (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 slabsti 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 oma. Zaradi njiju je bila potrebna hospitalizacija in/ali prekinitev zdravljenja z zdravilom Temodal pri 8 % in. 4 % bolnikov. Mielosupresija je bila predvidljiva (ponavadi 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 nulative mielosupresije. Trombocitopenija lahko poveča tveganje za pojav krvavitev, nevtropenija ali levkopenija pa tveganje za okužbe.**Imetnik dovoljenja za pro-t** SP Europe 73, rue de Stalle B-1180, Bruselj, Belgija. **Način in režim izdaje** Zdravilo se izdaja samo na recept, uporablja pa se pod posebnim nadzorom zdravnika ecialista ali od njega pooblaščenega zdravnika. **Datum priprave informacije** september 2007 Podrobnejše informacije o zdravilu Temodal dobite na sedežu podjetja.

rava informacije Schering-Plough, september 2007.



Dunajska 22, 1000 Ljubljana
tel: 01 300 10 70
fax: 01 300 10 80

Schering-Plough

Temodal®™
temozolomid

resnični napredek

Pri na novo odkritem glioblastomu multiforme in malignih gliomih, ki se ponovijo ali napredujejo.

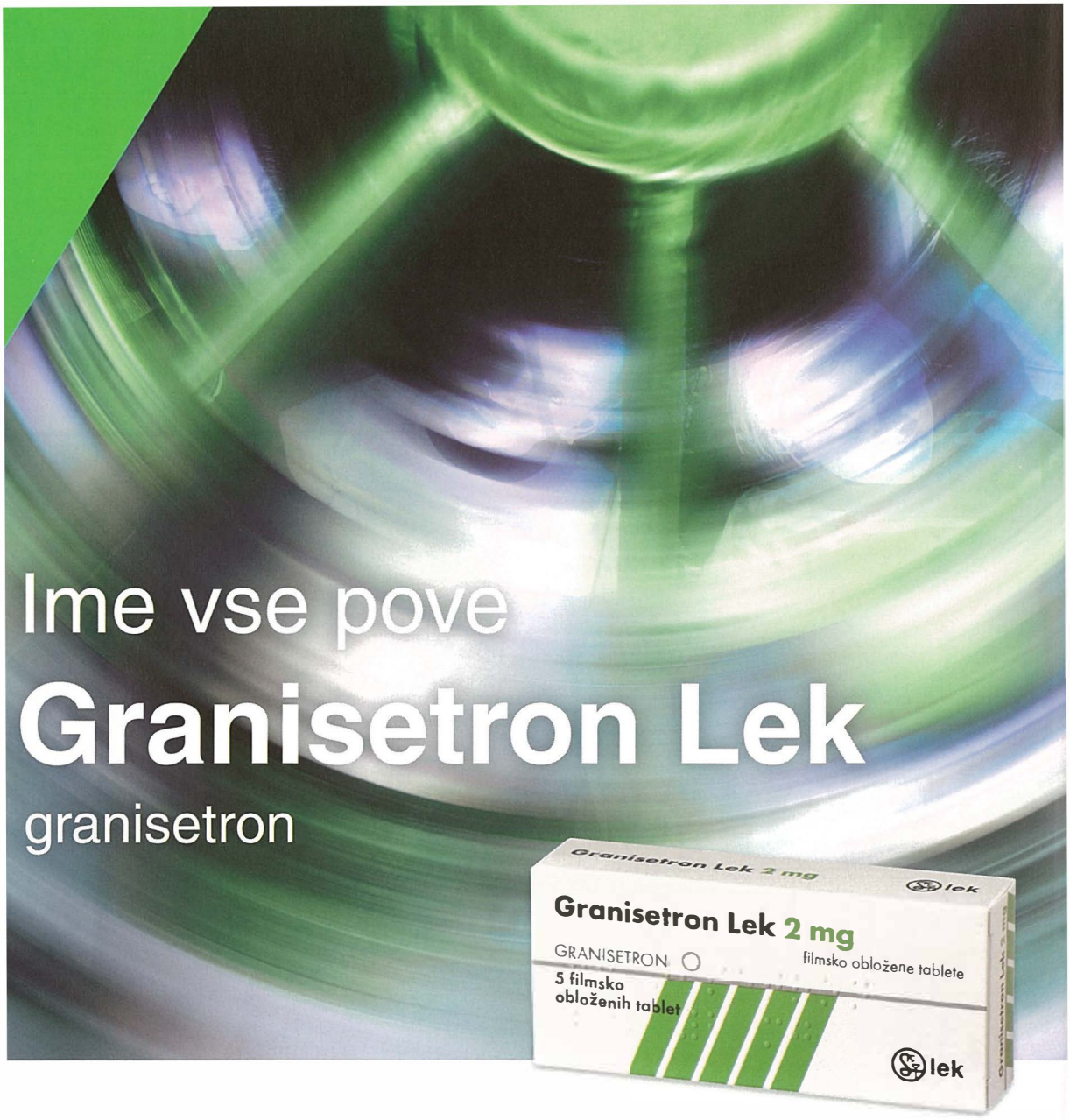
odmerjanje po barvi

nove barve kapsul Temodal, omogočajo lažje odmerjanj

Dunajska 22, 1000 Ljubljana
tel: 01 300 10 70
fax: 01 300 10 80

Schering-Plough

Temodal®
temozolomid



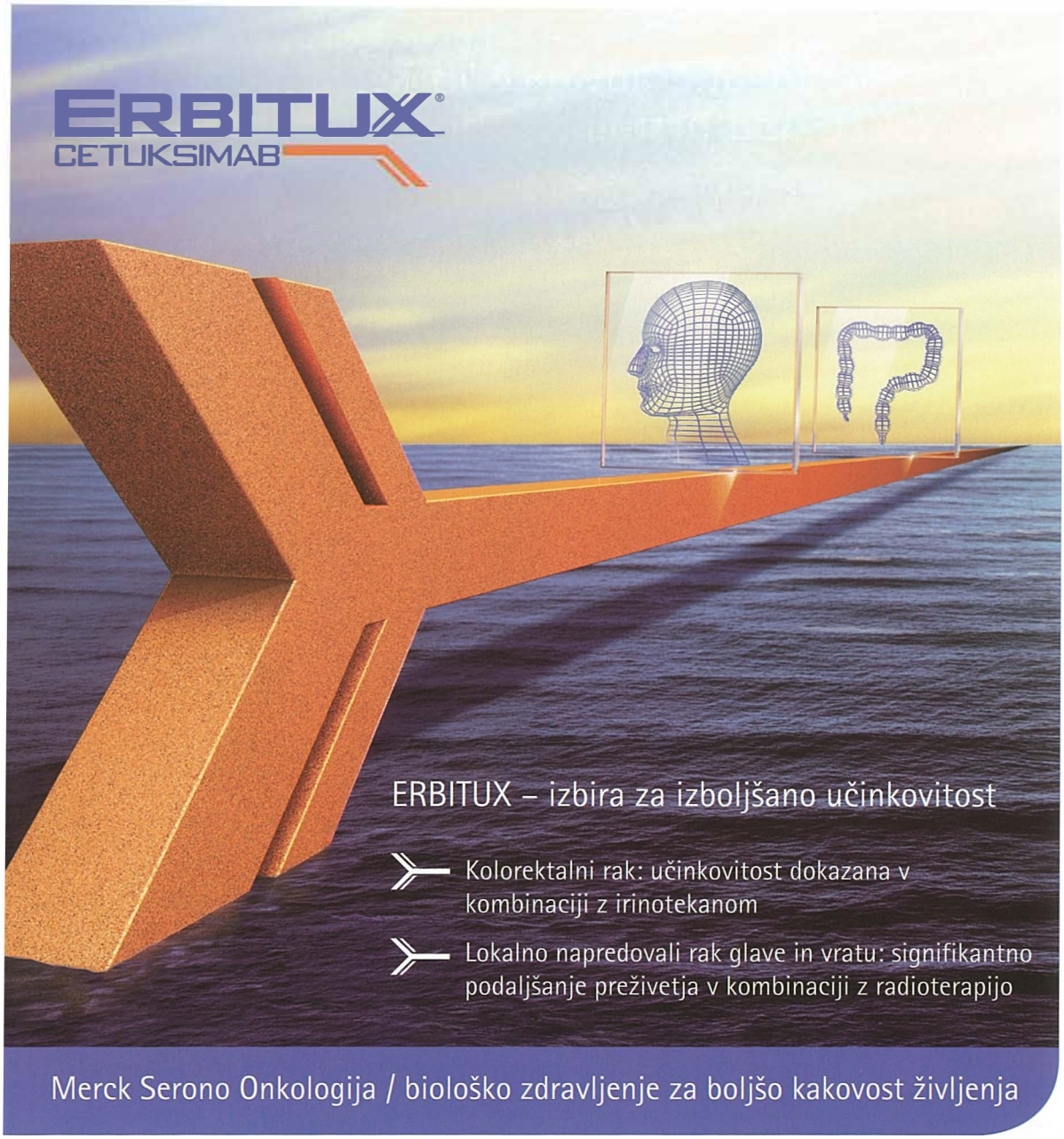
POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Granisetron Lek 2 mg filmsko obložene tablete. SESTAVA: 1 filmsko obložena tableta vsebuje 2 mg granisetrona v obliki granisetronijevega klorida. **TERAPEVTSKE INDIKACIJE:** Preprečevanje akutne slabosti in bruhanja, ki sta posledica zdravljenja s citostatiki (kemoterapije in radioterapije). Bolnik mora zdravilo vzeti na dan zdravljenja s citostatiki. **ODMERJANJE IN NAČIN UPORABE: Odrasli in otroci, stari več kot 12 let in težki več kot 50 kg:** Odmerek zdravila je 1 mg dvakrat na dan ali 2 mg enkrat na dan, na dan zdravljenja s citostatiki. Odmerek (prvi) je treba vzeti eno uro pred začetkom zdravljenja s citostatiki. **Kombinacija s kortikosteroidi:** Učinkovitost zdravila zvečamo z intravenskim dodatkom kortikosteroida. **Največji odmerek in trajanje zdravljenja:** Največji odmerek, ki ga bolniki lahko vzamejo peroralno, je 9 mg granisetrona v enem dnevu. **Starejši in bolniki z motenim ledvičnim in/ali jetrnim delovanjem:** Odmerek je enak kot pri odraslih. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilno učinkovino granisetron, sorodne učinkovine ali katerokoli pomožno snov. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Zdravilo lahko zmanjša motiliteto črevesja, zato je treba bolnike, ki imajo znake subakutne črevesne zapore, med jemanjem zdravila Granisetron Lek skrbno nadzorovati. 5-HT3 antagonisti, kot je granisetron, so lahko vpleteni v nastanek aritmij ali nepravilnosti EKG-ja. To je lahko klinično pomembno pri bolnikih z že obstoječimi aritmijami ali motnjami konduktivnosti srca ali pri bolnikih, ki se zdravijo z antiaritmiki ali zaviralci adrenergičnih receptorjev beta. Zdravila Granisetron Lek ne smemo dajati bolnikom z redkimi dednimi boleznimi, kot so intoleranca za galaktozo, glukoza-galaktoza malabsorpcijski sindrom, pomanjkanje Lapp laktaze. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Granisteron se presnavlja s pomočjo jetrnega citokroma P450; zaviralci ali spodbujevalci tega encima lahko spremenijo očistek in posledično razpolovni čas granisetrona. Pri ljudeh je indukcija jetrnih encimov s fenobarbitalom povzročila zvečanje celotnega plazemskega očistka granisetrona (za približno 25 %), danega intravensko. Do sedaj niso opazili znakov medsebojnega delovanja granisetrona in drugih pogosto predpisanih antiemetikov, kot so benzodiazepini, nevroleptiki in antiulkusni pripravki. Tudi med granisetronom in emetogenimi kemoterapevtiki ni bilo opaženih interakcij. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Podatki, da bi Granisetron vplival na sposobnost vožnje, niso znani. **NEŽELENI UČINKI:** Zelo pogosti (> 1/10): glavobol, slabost, zaprtje. Pogosti (< 1/10, >1/100): zmanjšan apetit, driska, bruhanje, bolečine v trebuhu, astenija, bolečine, vročina. Redki (< 1/1.000, >1/10.000): aritmija, bolečine v prsih, patološko delovanje jeter, zvečanje jetrnih transaminaz. **VRSTA OVOJNINE IN VSEBINA:** Škatla s 5 filmsko obloženimi tabletami. **NAČIN IZDAJE ZDRAVILA:** Na zdravniški recept. **IMETNIK DOVOLJENJA ZA PROMET:** Lek farmacevtska družba d.d., Verovškova 57, Ljubljana, Slovenija. **INFORMACIJA PRIPRAVLJENA:** april 2007

lek

član skupine Sandoz

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



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

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

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

www.oncology.merck.de

MERCK SERONO

A therapeutic advance in second-line NSCLC and first-line pancreatic cancer

Prolongs your patients life[1,2]

Tarceva is indicated for:

- Treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.
- Tarceva in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.

For additional information please consult your local Roche office.

Tarceva®
erlotinib HCl

Roche

Reference:

1. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005 Jul 14;353(2):123-32.
2. Moore MJ, Goldstein D, Hamm J et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007 May 20;25(15) 1960-6.

Roche farmacevtska družba d.o.o.
Vodovodna cesta 109
1000 Ljubljana
www.roche.si

Editorial policy

Editorial policy of the journal *Radiology and Oncology* is to publish original scientific papers, professional papers, review articles, case reports and varia (editorials, reviews, short communications, professional information, book reviews, letters, etc.) pertinent to diagnostic and interventional radiology, computerized tomography, magnetic resonance, ultrasound, nuclear medicine, radiotherapy, clinical and experimental oncology, radiobiology, radiophysics and radiation protection. The Editorial Board requires that the paper has not been published or submitted for publication elsewhere: the authors are responsible for all statements in their papers. Accepted articles become the property of the journal and therefore cannot be published elsewhere without written permission from the editorial board. Papers concerning the work on humans, must comply with the principles of the declaration of Helsinki (1964). The approval of the ethical committee must then be stated on the manuscript. Papers with questionable justification will be rejected.

Manuscript written in English should be submitted to the Editorial Office in triplicate (the original and two copies), including the illustrations: *Radiology and Oncology*, Institute of Oncology, Zaloska 2, SI-1000 Ljubljana, Slovenia; (Phone: +386 (0)1 5879 369, Tel./Fax: +386 (0)1 5879 434, E-mail: gsersa@onko-i.si). Authors are also asked to submit their manuscripts electronically, either by E-mail or on CD rom. The type of computer and word-processing package should be specified (Word for Windows is preferred).

All articles are subjected to editorial review and review by independent referee selected by the editorial board. Manuscripts which do not comply with the technical requirements stated herein will be returned to the authors for correction before peer-review. Rejected manuscripts are generally returned to authors, however, the journal cannot be held responsible for their loss. The editorial board reserves the right to ask authors to make appropriate changes in the contents as well as grammatical and stylistic corrections when necessary. The expenses of additional editorial work and requests for reprints will be charged to the authors.

General instructions·• Radiology and Oncology will consider manuscripts prepared according to the Vancouver Agreement (*N Engl J Med* 1991; **324:** 424-8, *BMJ* 1991; **302:** 6772; *JAMA* 1997; **277:** 927-34.). Type the manuscript double spaced on one side with a 4 cm margin at the top and left hand side of the sheet. Write the paper in grammatically and stylistically correct language. Avoid abbreviations unless previously explained. The technical data should conform to the SI system. The manuscript, including the references may not exceed 20 typewritten pages, and the number of figures and tables is limited to 8. If appropriate, organize the text so that it includes: Introduction, Material and methods, Results and Discussion. Exceptionally, the results and discussion can be combined in a single section. Start each section on a

new page, and number each page consecutively with Arabic numerals.

Title page should include a concise and informative title, followed by the full name(s) of the author(s); the institutional affiliation of each author; the name and address of the corresponding author (including telephone, fax and e-mail), and an abbreviated title. This should be followed by the *abstract page*, summarising in less than 200 words the reasons for the study, experimental approach, the major findings (with specific data if possible), and the principal conclusions, and providing 3-6 key words for indexing purposes. The text of the report should then proceed as follows:

Introduction should state the purpose of the article and summarize the rationale for the study or observation, citing only the essential references and stating the aim of the study.

Material and methods should provide enough information to enable experiments to be repeated. New methods should be described in detail. Reports on human and animal subjects should include a statement that ethical approval of the study was obtained.

Results should be presented clearly and concisely without repeating the data in the tables and figures. Emphasis should be on clear and precise presentation of results and their significance in relation to the aim of the investigation.

Discussion should explain the results rather than simply repeating them and interpret their significance and draw conclusions. It should review the results of the study in the light of previously published work.

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

References· must be numbered in the order in which they appear in the text and their corresponding numbers quoted in the text. Authors are responsible for the accuracy of their references. References to the Abstracts and Letters to the Editor must be identified as such. Citation of papers in preparation, or submitted for publication, unpublished observations, and personal communications should not be included in the reference list. If essential, such material may be incorporated in the appropriate place in the text. References follow the style of Index Medicus. All authors should be listed when their number does not exceed six; when there are seven or more authors, the first six listed are followed by "et al". The following are some examples of

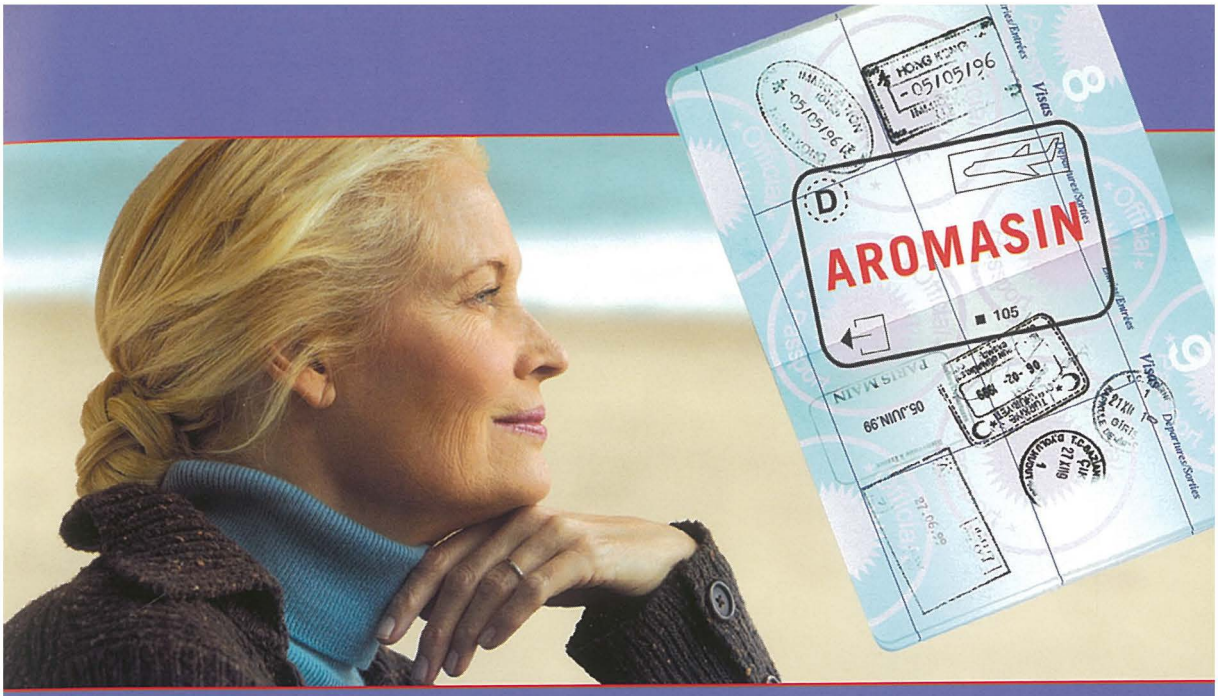
references from articles, books and book chapters:

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

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.

Page proofs will be faxed or sent by E-mail to the corresponding author. It is their responsibility to check the proofs carefully and fax a list of essential corrections to the editorial office within 48 hours of receipt. If corrections are not received by the stated deadline, proof-reading will be carried out by the editors.



PRAVI TRENUTEK ZA NOV ZAČETEK

Odobrena indikacija za prehod med adjuvantnim zdravljenjem

AROMASIN®
eksemestan

BISTVENE INFORMACIJE IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA
AROMASIN® 25 mg obložene tablete
Sestava in oblika zdravila: obložena tableta vsebuje 25 mg eksemestana. **Indikacije:** adjuvantno zdravljenje žensk po menopavzi, ki imajo invazivnega zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji in so se uvodoma vsaj 2 leti zdravile s tamoksifenom. Zdravljenje napredovalega raka dojke pri ženskah z naravno ali umetno povzročeno menopavzo, pri katerih je bolezen napredovala po antiestrogenski terapiji. Učinkovitost še ni bila dokazana pri bolnicah, pri katerih tumorske celice nimajo estrogenskih receptorjev. **Odmerjanje in način uporabe:** 25 mg enkrat na dan, najbolje po jedi. Pri bolnicah z zgodnjim rakom dojke je treba zdravljenje nadaljevati do dopolnjenega petega leta adjuvantnega hormonskega zdravljenja oz. do recidiva tumorja. Pri bolnicah z napredovalim rakom dojke je treba zdravljenje nadaljevati, dokler ni razvidno napredovanje tumorja. **Kontraindikacije:** znana preobčutljivost na učinkovino zdravila ali na katero od pomožnih snovi, ženske pred menopavzo, nosečnice in doječe matere. **Posebna opozorila in previdnostni ukrepi:** predmenopavzni endokrini status, jetrna ali ledvična okvara, bolniki z redkimi prirojenimi motnjami, kot so fruktozna intoleranca, malabsorpcija glukoze-galaktoze ali insuficienca saharoze-izomaltase. Lahko povzroči alergijske reakcije ali zmanjšanje mineralne gostote kosti. Ženskam z osteoporozo ali tveganjem zanjo je treba izrecno izmeriti gostoto kosti s kostno denzitometrijo, in sicer na začetku zdravljenja in nato redno med zdravljenjem. **Medsebojno delovanje z drugimi zdravili:** sočasna uporaba zdravil - npr. rifampicina, antiepileptikov (npr. fenitoina ali karbamazepina) ali zeliščnih pripravkov s šentjaževko - ki inducirajo CYP 3A4, lahko zmanjša učinkovitost Aromasina. Uporabljati ga je treba previdno z zdravili, ki se presnavljajo s pomočjo CYP 3A4 in ki imajo ozek terapevtski interval. Kliničnih izkušenj s sočasno uporabo zdravila Aromasin in drugih zdravil proti raku ni. Ne sme se jemati sočasno z zdravili, ki vsebujejo estrogen, saj bi ta izničila njegovo farmakološko delovanje. **Vpliv na sposobnost vožnje in upravljanja s stroji:** po uporabi zdravila je lahko psihofizična sposobnost za upravljanje s stroji ali vožnjo avtomobila zmanjšana. **Neželeni učinki:** neželeni učinki so bili v študijah ponavadi blagi do zmerni. *Zelo pogosti (> 10 %)*: vročinski oblivi, bolečine v sklepih, utrujenost, slabost, nespečnost, glavobol, močnejše znojenje, blago zvišanje alkalne fosfataze. **Način in režim izdajanja**: zdravilo se izdaja le na recept, uporablja pa se po navodilu in pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Luksembourg SARL, 283, route d'Arlon, L-8011 Strassen, Luksemburg. **Datum zadnje revizije besedila:** 9.12.2005
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Pfizer

Podrobnejše informacije o zdravilu so na voljo pri:
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Letališka cesta 3c, 1000 Ljubljana