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- *ALIMTA je v kombinaciji s cisplatinom indicirana za zdravljenje bolnikov z neresektabilnim malignim plevralnim mezoteliomom, ki jih še nismo zdravili s kemoterapijo.*[1,2]
- *ALIMTA je indicirana kot monoterapija za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom po predhodni kemoterapiji.*[1,3]

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RAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
MTA 500 mg prašek za koncentrat za raztopino za infundiranje **Sestava** Vsaka viala vsebuje 500 mg pemetrekseda (v obliki dinatrijevega pemetrekseda). Pomožne snovi: manitol, klorovodikova kislina, natrijev hidro
kacije ALIMTA je v kombinaciji s cisplatinom indicirana za zdravljenje bolnikov z neresektabilnim malignim plevralnim mezoteliomom, ki jih še nismo zdravili s kemoterapijo. ALIMTA je indicirana kot monoterapi
vljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom po predhodni kemoterapiji. **Odmerjanje in način uporabe** ALIMTO smemo dajati le pod nadzorom zdravnika, usposob
a uporabo kemoterapije za zdravljenje raka. Maligni plevralni mezoteliom Priporočeni odmerek ALIMTE je 500 mg/m² telesne površine (TP), dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21-dnevnega cik
obnocelični pljučni karcinom Priporočeni odmerek ALIMTE je 500 mg/m² TP, dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21 dnevnega ciklusa. **Kontraindikacije** Preobčutljivost za pemetreksed ali katero
ožno snov. Med zdravljenjem s pemetreksedom je treba dojenje prekiniti. Sočasno cepljenje proti rumeni mrzlici. **Opozorila** Pri bolnikih moramo biti med zdravljenjem pozorni na morebiten pojav mielosupresije, pemetrek
olnikom ne smemo dajati, dokler se absolutno število nevtrofilcev (ANC) ne povrne na ≥ 1500 celic/mm³ ter število trombocitov na ≥ 100.000 celic/mm³. Bolnikom, zdravljenim s pemetreksedom, moramo naročiti
jejo folno kislino in vitamin B12 kot preprečevalni ukrep za zmanjšanje toksičnosti, povezane z zdravljenjem. Predhodno zdravljenje z deksametazonom (ali drugim ustreznim kortikosteroidom) lahko zmanjša incidenc
ost kožnih reakcij. Uporabe pemetrekseda pri bolnikih z očistkom kreatinina < 45 ml/min ne priporočamo. Bolniki z blagim do zmernim popuščanjem delovanja ledvic (očistek kreatinina od 45 do 79 ml/min) naj se izogi
nju nesteroidnih protivnetnih zdravil (NSAID), denimo, ibuprofena in acetilsalicilne kisline (> 1,3 g dnevno) 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Vsi bolniki, ki jih l
vimo s pemetreksedom, naj se izogibajo jemanju NSAID-ov z dolgimi razpolovnimi časi izločanja vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Pri bolnikih s klir
embno tekočino tretjega prostora moramo razmisliti o drenaži izliva pred dajanjem pemetrekseda. Bolnike moramo pred prejemanjem terapije in/ali po njej ustrezno hidrirati ter prejeti zadostno antiemetično zdravlj
sno so v kliničnih študijah pemetrekseda, običajno ob sočasnem dajanju z drugo citotoksično učinkovino, poročali o resnih srčnožilnih dogodkih, vključno z miokardnim infarktom in možganskožilnimi dogodki. Odsvetuj
abo živih oslabljenih cepiv (razen za rumeno mrzlico). Spolno zrelim moškim odsvetujemo zaploditev otroka v času zdravljenja in še 6 mesecev zatem. Zaradi možnosti, da zdravljenje s pemetreksedom povzroči tr
odnost, naj se moški pred začetkom zdravljenja posvetujejo o shranjevanju semena. Ženske v rodni dobi morajo v času zdravljenja s pemetreksedom uporabljati učinkovito kontracepcijo. **Medsebojno delovanje z dru**
vili in druge oblike interakcij Sočasno dajanje nefrotoksičnih zdravil (denimo, aminoglikozidov, diuretikov zanke, spojin platine, ciklosporina) lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Sočasno daj
, ki se tudi izločajo s tubulno sekrecijo (denimo, probenecid, penicilin), lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Pri bolnikih z normalnim delovanjem ledvic (očistek kreatinina ≥ 80 ml/min) lahko vi
erki nesteroidnih protivnetnih zdravil (NSAID-i, denimo, ibuprofen > 1600 mg dnevno) in acetilsalicilna kislina v visokih odmerkih (≥ 1,3 g dnevno) zmanjšajo eliminacijo pemetrekseda in tako lahko povečajo pojav
enih učinkov pemetrekseda. Pri bolnikih z blagim do zmernim popuščanjem delovanja ledvic (očistek kreatinina 45 - 79 ml/min) se moramo izogibati sočasnemu dajanju pemetrekseda z NSAID-i (denimo, ibuprofenom
salicilno kislino v visokih odmerkih 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Sočasnemu dajanju NSAID-ov z daljšimi razpolovnimi časi s pemetreksedom se moramo izog
5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Velika različnost med posamezniki v koagulacijskem statusu v času bolezni ter možnost medsebojnega delovanja med peroral
oagulacijskimi učinkovinami ter kemoterapijo proti raku zahtevata povečano pogostnost spremljanja INR. Kontraindicirana sočasna uporaba: Cepivo proti rumeni mrzlici: tveganje za smrtno generalizirano bolezen po ceplje
etovana sočasna uporaba: Živa oslabljena cepiva (razen proti rumeni mrzlici): tveganje za sistemsko, potencialno smrtno bolezen. **Neželeni učinki** Klinične študije maligne plevralnega mezotelioma Zelo pogosti: zni
ofilci/granulociti, znižani levkociti, znižan hemoglobin, znižani trombociti, slabost, bruhanje, stomatitis/faringitis, anoreksija, diareja, zaprtje, utrujenost, nevropatija-senzorična, povišan kreatinin, znižan očistek kreatin
čaj, alopecija Pogosti: konjuktivitis, dispepsija, dehidracija, disgevzija Klinične študije nedrobnoceličnega pljučnega karcinoma Zelo pogosti: znižan hemoglobin, znižani levkociti, znižani nevtrofilci/granulociti, slab
ksija, bruhanje, stomatitis/faringitis, diareja, utrujenost, izpuščaj/luščenje Pogosti: znižani trombociti, zaprtje, povišana telesna temperatura, povišanje SGPT (ALT), povišanje SGOT (AST), srbenje, alopecija Občasni: r
žilni in možganskožilni dogodki, vključno z miokardnim infarktom, angino pektoris, cerebrovaskularnim insultom in prehodnimi ishemičnimi atakami Redki: primeri potencialno resnega hepatitisa, pancitopenija Po uv
ila na trg so pri bolnikih poročali o redkih primerih kolitisa. **Imetnik dovoljenja za promet** Eli Lilly Nederland B.V., Grootslag 1 5, NL 3991 RA, Houten, Nizozemska **Datum zadnje revizije bese**
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Editoral

RADIOLOGY AND ONCOLOGY celebrates its esteemed 40 years of existence. The journal has evolved from *Radiologia Iugoslavica,* a regional journal of the former Yugoslavia into an international journal that is published quarterly in English language.

Its international involvement is reflected in the esteemed membership of Editorial Board and many published papers by the authors from Central European countries. We greatly acknowledge the work of the former editorial board and we would like to thank them for their contribution in the development of the journal. In order to bring new momentum into the journal, we have asked some of the new members to actively participate in the development of the journal in the future. We also welcome new Editors of the journal. With joined efforts we would like to make the journal more recognizable in the scientific community of radiologists and oncologists.

With this goal in mind we have also decided to make some technical changes in the journal RADIOLOGY AND ONCOLOGY. We decided to publish Web based journal on Meta Press technology that will enable us to be indexed in international data bases. This will enable an open access of the journal to all the readers. We believe that this is the way how to make the journal more visible and more attractive.

Everybody is welcome to publish in RADIOLOGY AND ONCOLOGY. We believe that with mutual efforts we will in a few years reach broader international recognition and become an esteemed journal. We thank also our supporters, especially Research Agency of Slovenia that has financially supported regular publishing of RADIOLOGY AND ONCOLOGY.

Gregor Serša
Editor-in-Chief of
Radiology and Oncology

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review

Computed tomography and magnetic resonance colonography

Sandra Vegar-Zubović, Irmina Sefić-Pašić, Lidija Lincender, Dunja Vrcic, Melika Klancevic, Una Delic

Institute of Radiology, Clinical Center University of Sarajevo, Bosnia and Herzegovina

Background. *Colon cancer is the second leading cause of cancer death in the western world. Adenomatous colorectal polyps, which are found in 30-50% of Americans more than 50 years old, are recognized as important precursors of malignancy. Probably most of the invasive colon carcinomas arise from polyps. For this reason an early detection of these polyps and their complete removal is a recognized strategy for the prevention of colon cancer. So far no single method for an early diagnosis of colon polyps or colon cancer offers high sensitivity and specificity along with low cost and good patient acceptance. Endoscopic colonoscopy allows the accurate detection of very small lesions and has since almost completely replaced fluoroscopy. Cross-sectional imaging techniques, including magnetic resonance imaging (MRI) and computed tomography (CT), are increasingly being considered imaging modalities for the detection of colorectal polyps.*
Conclusions. *CT and MR colonography are new techniques for imaging of the colon. In symptomatic patients, these new techniques show promising results for the detection of polyps equal to or larger than 1 cm in diameter.*

Key words: colonic neoplasms-diagnosis, tomography, X-ray computed; magnetic resonance imaging

Introduction

Colon cancer is the second leading cause of cancer death in the western world.[1] Several risk factors predispose a person to develop colon cancer.[2] Adenomatous colorectal polyps, which are found in 30-50% of Americans more than 50 years old, are recognized as important precursors of malignancy. Probably most of the invasive colon carcinomas arise from polyps. An early polyp removal has been shown to reduce mortality from colon cancer by 25-50%. For this reason the early detection of these polyps and their complete removal is a recognized strategy for the prevention of colon cancer.[3,4] So far no single method for an early diagnosis of colon polyps or colon cancer including faecal occult blood testing (FOBT), proctosigmoidoscopy, double contrast barium enema (fluoroscopy) or conventional endoscopy offers high sensi-

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tivity and specificity along with low cost and good patient acceptance. Endoscopic colonoscopy allows the accurate detection of very small lesions and has almost completely replaced fluoroscopy. Furthermore, biopsies are easily harvested and polypectomy is also feasible. Although providing means for an early diagnosis of colon polyps and therapeutic intervention, endoscopic colonoscopy is a costly procedure which depends on the skill of the examiner and carries a low but not negligible risk of bowel perforation. Therefore, the indication to perform colonoscopy should be restricted to symptomatic patients or persons with an increased risk of cancer development. Furthermore, colonoscopy fails to reach the caecum in 5-10% of average risk-patients and in even higher percentages of patients with obstructing cancer.[5]

Cross-sectional imaging techniques, including magnetic resonance imaging (MRI) and computed tomography (CT), are increasingly being considered imaging modalities for the detection of colorectal polyps.[6,7] Using thin section axial images and assigned software both techniques allow the generation of three-dimensional views of the colon, simulating those obtained with conventional colonoscopy. Since CT-colonography is relatively safe and minimally invasive, it has the potential to become an attractive alternative to existing tests for an early diagnosis of colorectal cancer.[8]

Major advantages over endoscopy are its shorter examination time, non-invasiveness, and relative independence from the examiner. Thus, patient acceptance for this new method may be improved. Inherent advantages of CT-colonography, compared to endoscopy, include the visualization of the colon proximal and distal to constricting lesions, the ability to quantify local morphometric characteristics of the colon such as wall thickness and tumour extension in the extraluminal space, and the accurate localization of other abnormalities. It has to be stressed, however, that CT-colonography requires bowel cleansing and bowel distension by air insufflation similar to barium enema or conventional colonoscopy. Therefore, the patient's discomfort still remains a problem. Currently MRI CT-colonography is restricted by limited availability of scanners and high procedural costs. MRI as well as single-slice CT suffers from restrictions in spatial resolution and from motion artefacts, which explain insufficient detection rates for masses smaller than 10 mm.[6,7]

Single-slice CT requires several breath holds or a slice thickness exceeding 4 mm in order to scan the entire colon. A recent study comparing single-slice CT-colonography and conventional colonoscopy suggests a similar efficacy for the detection of polyps 6 mm or more in diameter (82-91%). However, restrictions in spatial resolution resulted in a low sensitivity for polyps smaller 6 mm (55%) and frequent false positive findings.[6] Recently introduced multi-slice CT (MSCT) scanners represent a significant improvement in CT technology, combining high-resolution thin slice imaging with high-speed volume coverage,[9] resulting in multiple advantages over single-slice-CT which has been documented for CT-angiography or lesion detection in the liver.[10,11] MSCT has already been shown to enhance the quality of CT-colonography due to the improved colonic distension and reduction of respiratory motion artefacts compared to single slice CT.[12]

Methods of colon investigation

Currently, there are four methods for the investigation of the entire colon. These are double-contrast barium enema (DCBE), colonoscopy, CT colonography, and MR colonography. Fischer described the DCBE technique in 1923.[13] It was refined in the

late 1960s and became the radiologic technique of choice for colon imaging in the mid-1970s.[14,15] Recently, the DCBE technique was reviewed.[16] It was concluded that performing a high-quality DCBE study requires tailoring of the examination to the clinical history, patient, and fluoroscopic findings. Each colonic segment should be viewed in detail with spot radiographs or magnified digital images. The order in which these are obtained is flexible, as long as each loop of colon has adequate barium coating and distention and is demonstrated en face. Overhead views such as left and right side–down *decubitus* views and a prone-angled view of the rectosigmoid junction are helpful in piecing together the spot images.[16]

Colonoscopy was first described in 1965 by three independent Japanese groups in the same journal.[17-19] Since then, technical developments made scopes smaller, easier to manipulate around angles, and improved the quality of the visualization methods.

Compared to DCBE studies and colonoscopy, CT and MR colonography (MRC) have a short history and are still being developed. CT colonography was described in 1994 by Vining *et al.*[20] and MR colonography in 1997 by Luboldt *et al.*[21] Both are cross-sectional methods that generate numerous images in the axial plane (CT) or any desired plane (MR imaging), preferably during one breath-hold. To efficiently read these images, postprocessing on a workstation is necessary. Such workstations should be able to handle the data quickly and, therefore, should have adequate hardware and software to allow fast interaction with the data set. These data sets can consist of up to 700 images with relatively high spatial resolution.

Reading the source images is the first step. These images need to be viewed carefully for filling defects and, if applicable, enhancing lesions. Postprocessing is an important feature of image interpretation. The most simple and important postprocessing technique for CT and MR colonography is multiplanar reformatting (MPR).[22,23] Furthermore, volume rendering techniques, such as tissue transition projection or endoscopic three-dimensional (3D) viewing (virtual endoscopy), can be performed. These require a great deal of computer power; endoscopic 3D viewing is especially time-consuming. Other 3D rendering techniques such as maximum-intensity projection (MIP) and shaded surface display (SSD) are easy to perform but only a small part of the entire data set is used in these techniques. Thus, much important information is lost and this makes these techniques unsuitable for the polyp detection. Postprocessing techniques will be discussed in detail. The purpose of this article is to describe scanning techniques in CT and MR colonography, discuss the currently available postprocessing methods, and discuss the accuracy of these techniques for the polyp detection compared with colonoscopy and DCBE.

CT colonography

Computed tomography (CT) colonography (virtual colonoscopy) is a promising new method for detecting colorectal polyps and cancers. Although multiple articles on this issue have been published since the mid-1990s, it remains an important discussion topic in current radiology and gastroenterology societies. Regarding its clinical role, there is no doubt that this imaging technique is best suited and highly recommended for those patients who are unable or unwilling to undergo conventional colonoscopy. Its role as a general screening tool for colon cancer is obvious for many, equivocal for some, and doubtful for others.

CT colonography uses multidetector-row CT to generate data, which is then

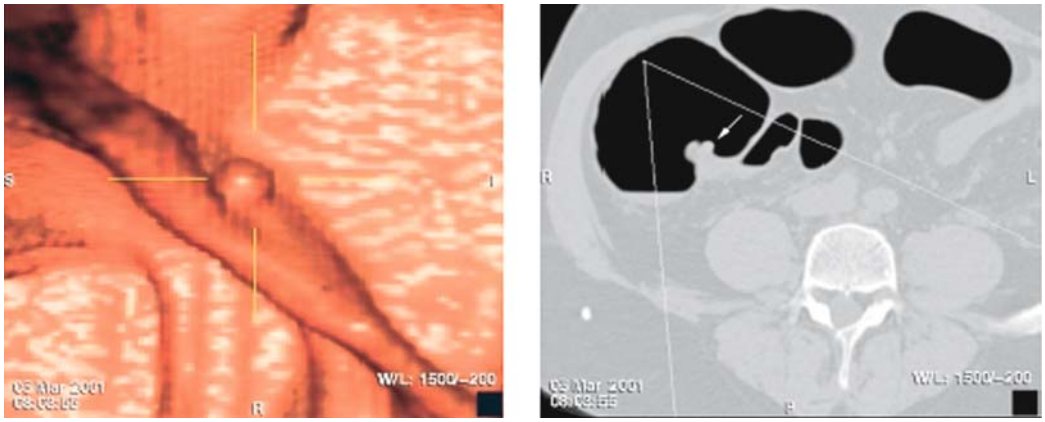

Figure 1. Multislice CT colonography.

converted by computer software into 2-dimensional (2D) and 3-dimensional (3D) displays of the colon. CT colonography has several advantages over conventional colonoscopy: No sedation is needed, it is only minimally invasive, and the examination is less time-consuming than conventional colonoscopy. However, there is still a need for bowel cleansing and insufflation of gas to expand the colon. Moreover, exposure to radiation is inherent to CT, and there is no possibility of biopsy, polypectomy, or treatment during the examination (Figures 1, 2).

MSCT has the potential to significantly improve the detection rate for colorectal polyps due to its better z-axis resolution, improved 3D-image quality and faster data acquisition. The detection and the subsequent removal of colorectal polyps remain the most important approaches for the reduction of colon cancer related mortality (Figures 3, 4, 5).

Studies

A meta-analysis of data from 14 studies with a total of 1324 patients reported the sensitivity and specificity of CT colonography for the detection of polyps, using conventional colonoscopy as the reference standard. The pooled per-patient sensitivity for polyps 10 mm or larger was 88% (95% confidence interval [CI], 84–93%), for polyps 6–9 mm it was 84% (95% CI, 80–89%), and for polyps 5 mm or smaller it was 65% (95% CI, 57–73%). The pooled per-polyp sensitivity for polyps 10 mm or larger was 81% (95% CI, 76–85%), for polyps 6–9 mm it was 62% (95% CI, 58–67%), and for polyps 5 mm or smaller it was 43% (95% CI, 39–47%). The overall specificity for the detection of polyps 10 mm or larger was 95% (95% CI, 94–97%).

A study involving 1233 asymptomatic adults reported that the per-patient sensitivity for polyps 10 mm or larger was 94% (95% CI, 83–99%) for CT colonography and 88% (95% CI, 75–95%) for conventional colonoscopy. The per-patient sensitivity for polyps 6 mm or larger was 89% (95% CI, 83–93%) for CT colonography and 92% (95% CI, 87–96%) for conventional colonoscopy.

A study of 615 patients reported per-patient sensitivities of 55% (95% CI, 40–70%) for polyps 10 mm or larger and 39% (95% CI, 30–48%) for polyps 6 mm or larger. Another study of 614 patients reported that CT colonography was significantly more sensitive than barium enema but less sensitive than colonoscopy.

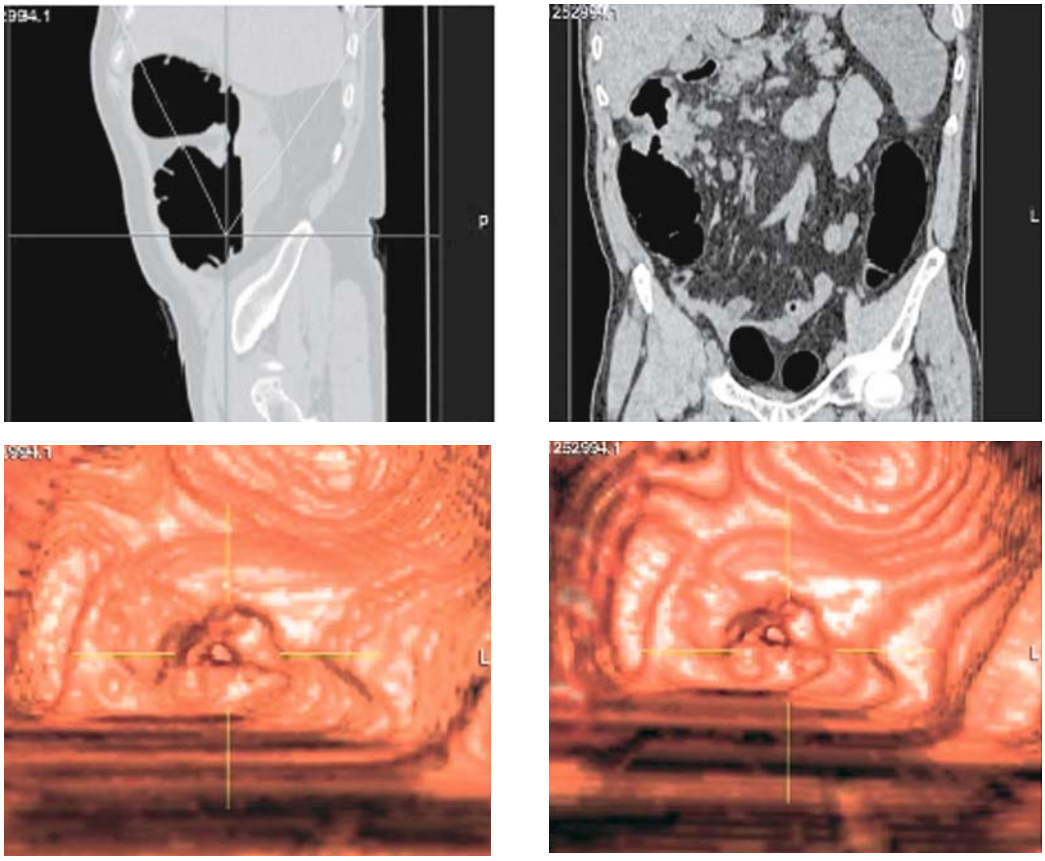

Figure 2. Multislice CT colonography. Colon tumour in 67-year old patient.

Figure 3. Shaded surface display of inflammatory stenosis.

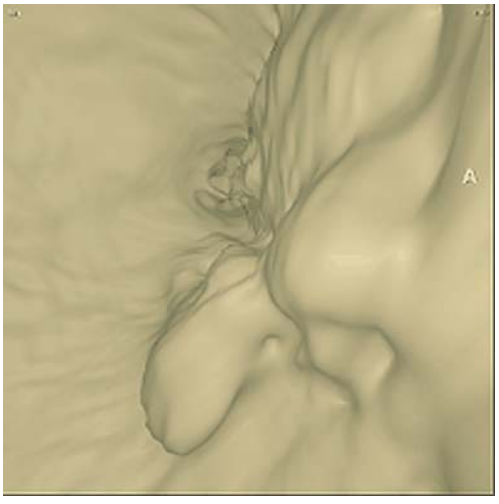

Figure 4. Virtual colonoscopic view of polypoid lesion.

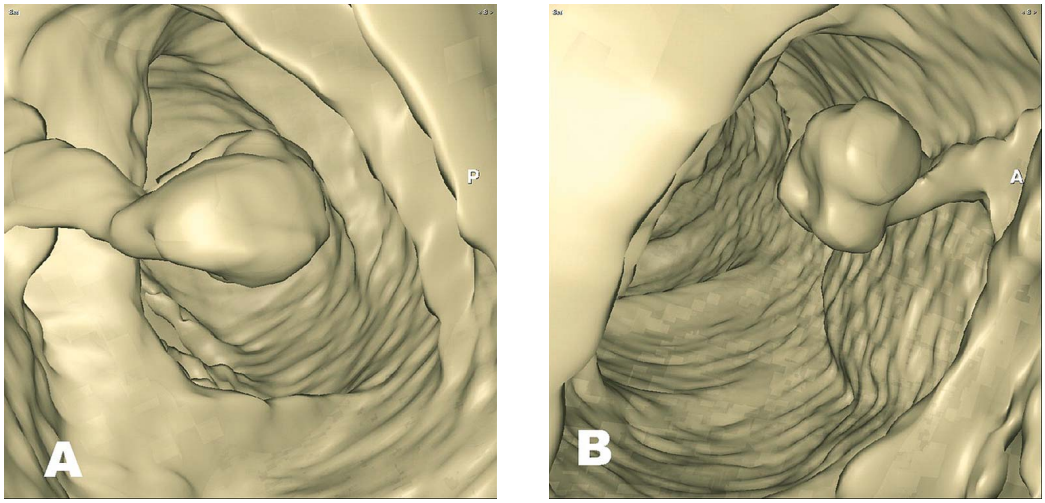

Figure 5. Virtual colonoscopy. (A) Retrograde and (B) antegrade views of polyp.

A study of 203 patients that used faecal tagging reported an overall per-patient sensitivity of 90% (95% CI, 86–94%).[24]

MR colonography

Currently two techniques are being evaluated for MR colonography . Based on the signal within the colonic lumen, they can be differentiated as "bright lumen" and "dark lumen" MRC (Figure 6).

Bright lumen MRC

Similar to contrast enhanced 3D MR angiography, MRC is based on the principles of ultra fast, T1 weighted 3D GRE acquisitions collected within the confines of a single breath hold.[25] This requires the use of an MR scanner equipped with high performance gradients. To permit the homogenous signal transmission and the reception over the entire colon with high CNR values, a combination of phased array surface coils should be used. The size of the coil must permit a coverage of the entire colon. As colonic lesions can often not be differentiated from stool, the patient has to undergo bowel cleansing in a manner similar to that required for conventional colonoscopy. Before the examination the patient should be screened for contraindications to MRI such as severe claustrophobia, presence of metallic implants in critical regions such as the eyes, spinal chord or brain, or cardiac pacemakers. The presence of hip prostheses, which normally is not regarded a contraindication to MRI, impedes a complete analysis of the rectum and sigmoid colon. Therefore, patients with hip prosthesis should also not be examined by MRC.

After the placement of a rectal enema tube, the colon is filled with the patient in the prone position using 1000 to 2000 ml of a water based enema, spiked with paramagnetic contrast (1:100). The enema is administered using 100 cm–150 cm of hydrostatic pressure. To reduce bowel motion and alleviate colonic spasm, the use of intravenously administered spasmolytic agents (for example, scopolamine or glucagon) before and during the bowel filling is helpful. In contrast with conventional colonoscopy sedative or analgesic agents do not have to

be applied. To ensure safe and optimal bowel filling and distension, the filling process is monitored with a non-slice select 2D acquisition, collecting one image every three seconds. Once the enema has reached the *caecum*, a 3D dataset of the abdomen encompassing the entire colon is collected. To compensate for the presence of residual air exhibiting "filling defects" similar to polyps within the colonic lumen, 3D datasets are collected in both the prone and supine patient positions. Here-after the enema bag is placed on the floor for facilitated emptying of the colon and the patient is removed from the scanner.

The acquired 3D MR datasets consist of coronal sections, ranging in thickness between 1.5 mm and 2 mm. The sequence is based on the use of short repetition (TR 1.6 ms–3.8 ms) and echo times (0.6 ms – 1.6 ms). The achievable minimum TR should be shorter than 5 ms; otherwise, the acquisition of a 3D dataset cannot be collected within the confines of a single breathhold. In conjunction with a field of view of 400 x 400 mm and an imaging matrix of 460 x 512, the spatial resolution includes an interpolated voxel size of about 1 mm x 1 mm x 1.6 mm.

On the 3D GRE datasets only the colonic lumen containing the enema is bright, whereas all other tissues remain low in signal intensity. The resulting contrast between the colonic lumen and surrounding structures is the basis for the subsequent virtual colonographic viewing. The MRC protocol can be further amplified by the acquisition of 2D gradient echo datasets after the intravenous application of a gadolinium containing contrast compound. This permits a more comprehensive assessment of parenchymal abdominal organs and increases the ability to detect hepatic metastases.

Bright lumen MRC can be completed within 20 minutes, including the time for patient positioning, image planning, and data acquisition. The 3D datasets are subsequently processed using commercially available software and hardware. A complete analysis of an MRC examination still requires 15 minutes of interactive image viewing on a high performance work station. In the first step MRC images should be interpreted in the multiplanar reformation mode scrolling through the prone 3D dataset in all three orthogonal planes. In regions containing larger pockets of residual air, the assessment needs to be supplemented by views of the supine dataset. In the second step the data should be assessed based on virtual endoscopic renderings displaying the inside of the colonic lumen. A virtual endoscopic fly through allows the observer to concentrate on the colon facilitating the depiction of small structures protruding into the colonic lumen. Furthermore, the three dimensional depth perception permits the assessment of haustral fold morphology, thereby increasing the observer's ability to distinguish polyps from haustra. To assure the complete visualisation of both sides of haustral folds, the virtual fly through should be performed in an antegrade as well as retrograde direction.

Dark lumen MRC

The detection of colorectal lesions with "bright lumen" MRC relies on the visualisation of filling defects. Differential considerations for such a filling defect beyond polyps include air bubbles as well as residual faecal material. To permit differentiation datasets are collected in both the prone and supine patient position: air and faecal material move, while polyps remain stationary. While effective in most instances, the technique can introduce errors. Thus, polyps with a long stalk may move sufficiently to impress as a moving air bubble or more probably residual stool, while stool adherent to the colonic wall may not move at all and, thus,

falsely impress as a polyp. In addition to obviating the need for the second, time consuming 3D data acquisition "dark lumen" MRC facilitates the identification of polyps.

"Dark lumen" MRC focuses on the colonic wall. It is based on the contrast generated between a brightly enhancing colonic wall and a homogeneously dark colonic lumen.[26] The technique differs from "bright lumen" MRC in the following manner:

1. Instead of gadolinium containing enema only tap water is rectally applied rendering low signal on heavily T1 weighted 3D GRE acquisitions.
2. The colonic filling process is monitored with a fluoroscopic T2w sequence, rather than a T1w sequence.
3. To obtain a bright colonic wall paramagnetic contrast is applied intravenously. 3D datasets are collected before the application and after a 75 second delay.
4. As residual air exhibits no signal in the colonic lumen, the examination needs to be performed only in the prone patient position.

Compared with "bright lumen" MRC that has been extensively evaluated in the past, "dark lumen" MRC harbours considerable advantages including the reduced examination and post-processing times, as only one 3D dataset needs to be collected. Furthermore, the "dark lumen" technique copes with the problem of residual stool in a simple manner: if the lesion enhances, it is a polyp; if it does not enhance, it represents stool. Suspicious appearing lesions are analysed by comparing signal intensities on the pre-contrast and post-contrast images. If analyses were limited to the post-contrast dataset, bright stool could be misinterpreted as a polyp. A comparison with the pre-contrast images records the lack of contrast enhancement, which assures the correct diagnosis.

The enhancement of colorectal masses following the intravenous administration of contrast has been reported in conjunction with MRC[22] and CT colonography.[23] The use of intravenously administered contrast material significantly improves the reader confidence in the assessment of bowel wall conspicuity and the ability to depict medium sized polyps in suboptimally prepared colons. The enhancement observed within polyps exceeds the increase determined within the colonic wall. This may aid in differentiating even very small polyps from thickened haustral folds.

A further advantage of "dark lumen" MRC relates to the fact that it permits a direct analysis of the bowel wall. This might facilitate the evaluation of inflammatory changes in patients with inflammatory bowel disease. Increased contrast uptake and bowel wall thickening, as recorded on contrast enhanced T1 weighted images, have already been shown to correlate well with the degree of inflammation in the small bowel.[27] Hence, the "dark lumen" approach may indeed amplify the list of indications for MRC in the future to encompass also inflammatory bowel disease.

Finally, the intravenous application of paramagnetic contrast permits a more comprehensive assessment of parenchymal abdominal organs contained within the field of view. By combining pre-contrast and post-contrast T1 weighted imaging, the liver can be accurately evaluated regarding the presence and type of concomitant disease. Dark lumen MRC also offers new perspectives regarding the optimisation of bowel distension. Although the administration of water as a rectal enema does not adversely affect patient comfort in most cases, a modified strategy could be based on the application of gases like carbon dioxide.[28] The gas is signalless and would thus easily permit delineation of the contrast enhanced colonic wall and masses.

The diagnostic performance of bright lumen MRC was assessed in several stu-

Table 1. Sensitivity and specificity of bright lumen MR colonography (MRC)[29]

All lesions	
Sensitivity	27/58 = 47%
Specificity	48/59 = 81%
PPV	27/38 = 71%
NPV	48/79 = 61%
Lesions >10 mm	
Sensitivity	13/14 = 93%
Specificity	102/103 = 99%
PPV	13/14 = 93%
NPV	102/103 = 99%

PPV = Positive predictive value
NPV = Negative predictive value

dies using conventional colonoscopy as the standard of reference. While most mass lesions smaller than 5 mm in size were missed, almost all lesions exceeding 10 mm were correctly identified (Table 1).[29] In a study by Pappalardo *et al*. MRC even detected a higher total number of polyps exceeding 10 mm in size than conventional colonoscopy. MRC identified additional polyps in regions of the colon not reached by colonoscopy (Figure 6).

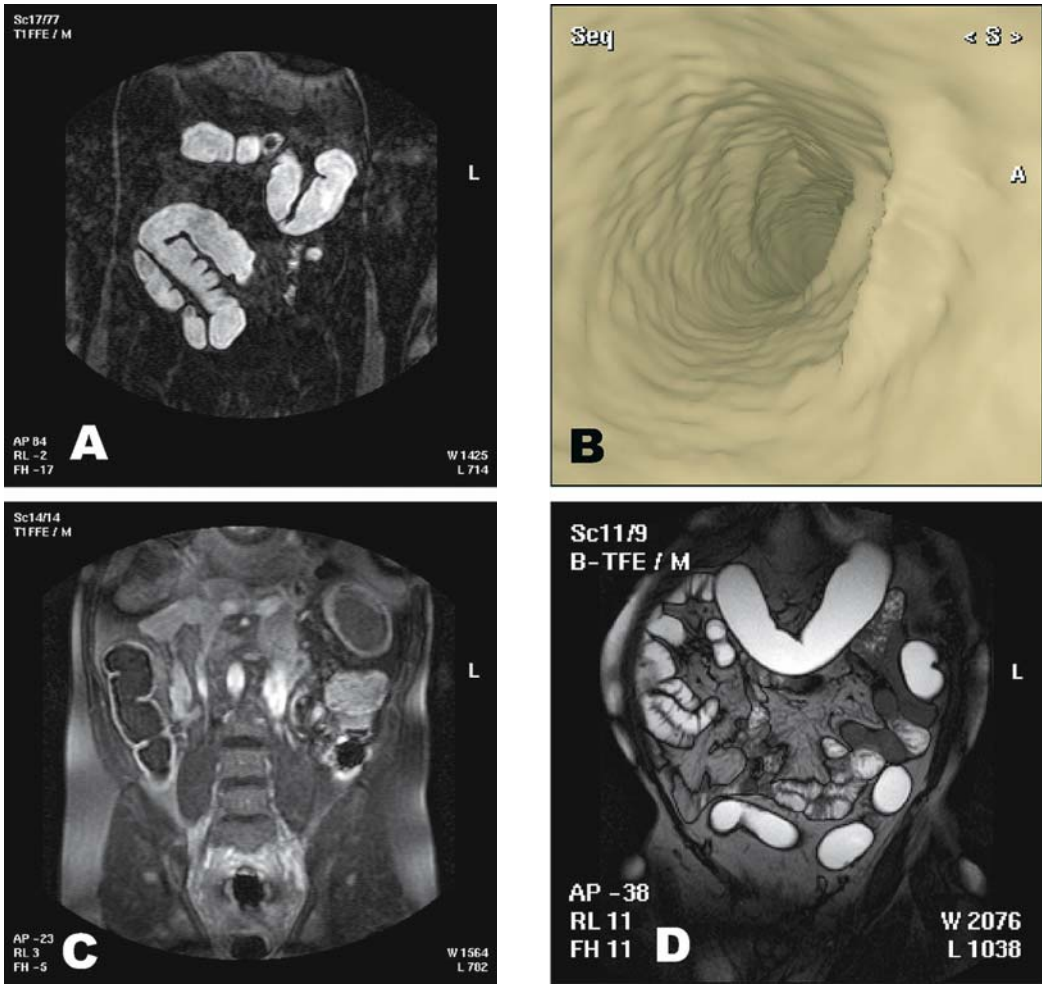

Figure 6. MR colonography. A, Bright lumen technique: 3D GRE sequence with water-gadolinium enema. B, Virtual colonoscopy of normal ascending colon. C, D, Combined bright and black lumen technique: C, contrast-enhanced 3D spoiled T1-weighted GRE image and, D, nonenhanced 3D spoiled and balanced GRE image.

Faecal tagging

MRC still requires bowel cleansing in a manner similar to conventional colonoscopy. As 75% of patients undergoing bowel preparation complain about symptoms ranging from "feeling unwell" to "inability to sleep", patient acceptance is affected negatively. To assure high patient acceptance of MRC, bowel cleansing needs to be eliminated. This can be accomplished with faecal tagging—a concept based on modulating the signal intensity of faecal material by adding contrast compounds to regular meals.

Fitting the two approaches to MRC (bright lumen and dark lumen); there are also two theoretical approaches to faecal tagging. Its principle was demonstrated on the basis of a bright rectal enema distending the colonic lumen containing brightly tagged stool in conjunction with bright lumen MRC. By adding a T1 shortening Gd based MR contrast agent to regular meals before the MR examination, harmonisation of signal properties between faecal material and the Gd based enema was achieved. The oral administration of a paramagnetic MR contrast agent (Gd-DOTA) has been shown to be safe. The combination of faecal tagging with a paramagnetic contrast agent and colonic filling results in a homogenous signal distribution throughout the colon. In these examinations virtual MRC permits an unobstructed view through the colon because the tagged stool is virtually indistinguishable from the administered enema. Although encouraging results concerning acceptance and image interpretation were obtained, the clinical implementation of bright lumen faecal tagging was hindered by the high cost of the Gd based paramagnetic contrast agent.

A second strategy for faecal tagging is based on rendering the colonic lumen dark. For faecal tagging, a highly concentrated, barium sulphate containing contrast agent (Micropaque; Guerbet, Sulzbach, Germany; 1 g barium sulphate/ml) is administered in a volume of 200 ml with each of four main meals beginning 36 hours before MRC. Patients are instructed to avoid the intake of all fibre rich foodstuff and nourishments with high concentration of manganese such as chocolate or fruits during this period, as manganese leads to increased signal intensity in T1w sequences. "Barium based" faecal tagging is combined with dark lumen MRC: the colon is distended with a rectally applied water enema and paramagnetic contrast is administered intravenously to render the colonic wall and adherent colorectal mass lesions bright.

Barium sulphate is a well known diagnostic contrast agent, still in common use as an oral agent for oesophageal, gastric, and small bowel radiography. Compared with Gd based contrast compounds, it is far less costly and characterised by an even better safety profile. Anaphylactoid reactions or other adverse side effects are virtually unknown. The agent is not absorbed and mixes well with stool. Thus, barium includes all characteristics as an ideal oral tagging agent for MRC.

The barium based approach to faecal tagging has been successfully assessed. The signal reducing effects upon stool has been documented in volunteer studies. By ingesting barium before the MR examination, stool is rendered virtually indistinguishable from the administered water enema on heavily T1w 3D GRE image. The MR examination without the prior ingestion of barium reveals signal rich stool that cannot readily be differentiated from the brightly enhancing colonic wall.

Recently, the barium based faecal tagging concept has been successfully evaluated in a pilot patient study. Faecal tagged MRC detected all polyps larger than 8 mm in a population of 24 patients with known

or suspected colorectal tumours. The overall sensitivity of MRC amounted to 89.3% for the detection of colorectal masses, and specificity was 100%. Colorectal cancers and polyps were readily identified as such.

Although further work is required to confirm these excellent results, it seems that barium tagged MRC has vast potential to emerge as the examination strategy of choice for the early detection of polyps in asymtomatic subjects. The technique seems to combine the excellent diagnostic accuracy with the high patient acceptance based on a painless examination and no need for colonic cleansing.

Conclusions

In conclusion, CT and MR colonography are new techniques for imaging of the colon. In symptomatic patients, these new techniques show promising results for the detection of polyps equal to or larger than 1 cm in diameter. It must be remembered that in all research protocols, colonoscopy was considered to be the standard of reference, which implies that other imaging modalities with which colonoscopy is compared will always perform worse. In most studies, patients preferred CT colonography to conventional colonoscopy.

The bowel-cleansing regimen is considered to be cumbersome, so from the patient acceptance point of view, faecal tagging techniques are promising. Their value in polyp detection still needs to be determined in large studies. In medicine, there is a trend toward performing non-invasive or less invasive imaging techniques rather than older and more validated invasive techniques. (MR angiography or CT angiography *vs* digital subtraction angiography, MR cholangiopancreatography *vs* endoscopic retrograde cholangiopancreatography). The invasive techniques are used for problem solving and interventions. CT and MR colonography fit in this trend perfectly. Both techniques have shown promising initial results in symptomatic patients and are still in evolution. Before these techniques can be implemented in daily practice, they must show the same accuracy as colonoscopy and should be cost-effective in both high-risk and screening patients.

The radiation-dose issue in CT colonography must be discussed, and a consensus on the maximum acceptable dose for a screening patient must be reached. MR colonography has the advantage of being a zero-dose examination, but at this point, CT colonography is faster and provides images with higher resolution.

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images in clinical medicine

Recurrence of carcinoma of the lower lip treated by interferon and irradiation

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A seventy-year-old patient was referred to our hospital for a tumour on the lower lip, which had been growing for the last two years. On the first clinical examination, the tumour, measuring 3.5 cm in diameter, was visible to the naked eye. Histological examination of the biopsy sample confirmed verrucous carcinoma.

The patient had been treated for miocardiopathy and emphysema for several years. Though at rest, the patient was breathing heavily and suffered from oedemas and small ulcers on both shanks. It was thus evident that the patient was not eligible for surgery under general anaesthesia, but rather for irradiation therapy.

The irradiation was performed by an orthovolt machine (PANTAC) with a total dose of 40 Gy (10 x 4 Gy). The tumour regressed completely. Six months after the completed therapy, a minor lesion, which would not heal up, developed on the tumour site. Several subsequent fine-needle aspiration biopsy (FNAB) examinations did not detect any malignant cells in the lesion. The patient complained that the lesion was painful. Two years after the completed radiotherapy, a tumour with a diameter of 1 cm appeared on the lower lip on the same site as the primary which completely regressed after the therapy, but obviously recurred two years later. The patient, believing that the tumour would fade away by itself, refused surgical treatment under local anaesthesia.

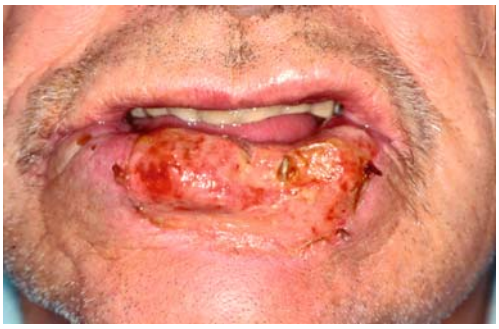

Figure 1. Recurrence of the tumour after radiotherapy.

In the following two years, the tumour was growing further and four years after the completed radiotherapy measured 3 x 2 cm (Figure 1). FNAB examination confirmed the recurrence of the squamous cell carcinoma. Due to poor physical condition of the patient, surgical treatment was most unlikely. The patient was therefore treated with the interferon injected directly into tumour. The tumour partially regressed after 5 injections and the therapy with interferon was then combined with irradiation. The patient was receiving 3 Mil IE per application and was submitted to hyperfractiona-

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ted radiotherapy (38 fractions, 2 x /day, 1.5 Gy/fraction). In two months' time, the tumour regressed. Nine months later the cosmetic effect was quite good (Figure 2). At the last follow-up control three years after the second therapy, the lower lip was NED.

As the patient's poor physical condition did not improve and the transfer from home to the hospital and back were getting more and more physically exhausting for him, he was not invited to follow-up controls any more. He died of myocardial infarction 4.5 years after the last therapy for the tumour, with NED on the lower lip.

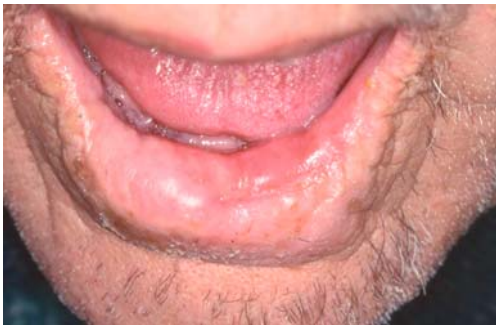

Figure 2. Nine months after combined treatment with irradiation and interferon.

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Subchronic exposure of rats to sublethal dose of microcystin-YR induces DNA damage in multiple organs

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Background. *Microcystins (MCs) are cyclic heptapeptides that are considered to be liver specific toxins. They are potent tumour promoters and recent studies indicate that they are also genotoxic. In this study we measured DNA damage in lymphocytes, liver, kidney (cortex and medulla), lung, spleen and brain cells of male Fisher F344 rats that were exposed to sublethal dose (every second day 10 μg/kg b.w.; i.p) of microcystin-YR (MCYR) for one month.*

Methods. *At the end of exposure the animals were sacrificed, the lymphocytes were isolated from blood taken from jugular vein, liver cells were obtained by perfusion with collagenase A and the cells from other organs were isolated by incubating small tissue pieces with collagenase A. The DNA damage in isolated cells was measured with the single cells gel electrophoresis (SCGE) also called the comet assay.*

Results. *A significant increase of the % tail DNA in MCYR-exposed animals compared to the nonexposed control ones was observed in brain (2.5 fold), liver (2.1 fold), kidney medulla (1.9 fold), kidney cortex (1.8 fold) and lung (1.7 fold) cells, while the DNA from lymphocytes and spleen cells was not affected.*

Conclusion. *This study demonstrated that subchronic exposure to sublethal doses of MCs can induce systemic genotoxicity in mammals, and it affects not only the liver but also other vital organs.*

Key words: DNA damage; comet assay; cyanobacteria; bacterial toxins; rats, inbred F344

Introduction

Microcystins (MCs) comprise a family of more than 60 structurally related hepatotoxins produced by cyanobacterial species.[1] Among them microcystin-LR (MC-LR) is the most toxic. The variable amino acids of the most common microcystin variants, MC-LR, RR and YR are leucine (L), arginine (R) and tyrosine (Y) (Figure 1). Toxic cyanobacteria found in eutrophic, freshwater, municipal and residential water supplies represent an increasing environmental hazard in many parts of the world.[2,3] Cyanobacterial blooms in surface water have been associated with

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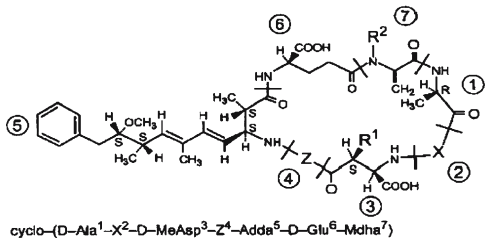

Figure 1. The structure of microcystins. The amino acids at the positions X and Z are variable. Microcystin-YR (X = tryptophyan, Z = arginin); microcystin-LR (X = leucin, Z = arginin).

poisoning and death of wildlife and domestic animals.[2] In humans MCs intoxication caused symptoms such as nausea/vomiting, weakness, skin irritation, and illnesses ranging from gastroenteritis and pneumonia to hepatoenteritis.[4] The most severe human intoxication happened in 1996 in Brazil, where 60 of 126 dialysis patients died of liver failure due to cyanobacterial contamination of the water used for dialysis.[5] Epidemiological studies have suggested that MCs are one of the risk factors for the high incidence of primary liver cancer in certain areas of China, where people have consumed pond-ditch water contaminated with cyanobacteria.[6]

Although MCs accumulate predominantly in the liver, they have also been detected in other organs.[7,8] Liver is the main target organ for MCs toxicity, because they are entering the cells through the multispecific transport system for bile acids[9,10] and the predilection for hepatic damage by MCs thus probably depends on the high concentration of these transporters in the hepatocyte membrane. However, several *in vitro* studies showed that MCs exert toxic effects in different non-hepatic cell lines. Microcystin-LR induced toxic effects in epidermoid carcinoma cells (KB)[11] and apoptosis in human endothelial and epithelial cells and in rat fibroblasts and promyelocytes.[12]

MCs are potent inhibitors of protein phosphatase 1 and 2A, leading to the increased protein phosphorylation, which is directly related to their cytotoxic and tumor-promoting activity.[13,14] Apart from the inhibition of protein phosphatases, the oxidative stress also plays a significant role in the pathogenesis of microcystin toxicity. MCs can induce intracellular reactive oxygen species (ROS) formation, cell injury and lipid peroxidation.[15-18] There is increasing evidence that MCs are also genotoxic. It has been reported that MCs induce DNA strand breaks in liver cells *in vivo*[19,20] and *in vitro.*[21,22] Several *in vitro* studies showed, that MCs induced DNA strand breaks also in different types of non-hepatic cells including baby hamster kidney cells, mouse embryo primary fibroblasts[23] and human peripheral lyphocytes.[24] In addition, they induced micronuclei formation and loss of heterozygosity in human lymphoblastoid TK6 cells,[25] and base substitution mutations at K-ras codon 12 in human RSa cells.[26]

The aim of our study was to explore if a subchronic exposure of rats to a sublethal dose of microcystine-YR (MCYR) induces DNA strand breaks in different organs. The DNA damage was measured by single cell gel electrophoresis (SCGE), also called the comet assay, which is a very sensitive method for detecting DNA double- and single-strand breaks, alkali labile sites, DNA-DNA and DNA-protein cross links, and single-strand breaks associated with the incomplete excision repair.[27] The *in vivo* comet assay is being increasingly used in genotoxicity testing because of its applicability to various tissues and its sensitivity to low levels of DNA damage.

Materials and methods

Animals

Male Fischer F 344 rats weighing 200 to 250 g were housed in standard plastic

cages with sawdust cover on the floor. They were maintained on a 12 h light-dark cycle (light on: 07.00–19.00 h) in a colony room controlled at 22–24 °C, with free access to rodent pellets and tap water. The animals were maintained following the guidelines in the Slovenian Law for Animal Health Protection and Instructions for Granting Permission for Animal Experimentation for Scientific Purposes.

Toxin and experimental design

MCYR was isolated from cyanobacterial bloom (*Microcystis aeruginosa*) from an artificial recreational pond (Koseze, Ljubljana, Slovenia) according to the method of Harada *et al.*,[28] as described previously.[3] The toxin was dissolved at a final concentration of 2.7 μg/ml in the vehicle solution of ethanol (0.8%) and methanol (0.2%) in physiological saline (0.9%).

The experimental rats (7 animals) were applied i.p. with 10 μg/kg b.w. MCYR in a volume of 3.7 ml/kg, every second day during the period of 30 days. The control group (4 animals) received 3.7 ml/kg i.p. vehicle (the mixture of ethanol and methanol dissolved in physiological saline). At the end of the experiment the animals were sacrificed using CO_2 anaesthesia. At sacrifice, blood, liver, kidneys (cortex and medulla were separated), lung, spleen and brain tissues were collected in order to proceed the comet assay as detailed below.

Cell isolation and preparation of single cell suspension

Blood was collected from jugular vein on heparin from anesthetized animals just before they were sacrificed. The lymphocytes were then isolated using Ficoll-Paque™ plus (Amersham Pharmacia Biotech AB, Sweden) and suspended in RPMI 1640 medium. The single cell suspensions of liver cells was prepared by liver perfusion with collagenase A as described.[29] The single cell suspensions from kidney (cortex and medulla were separated), lung (inferior lobe), spleen and brain (distal part) were prepared with a non-perfusion procedure using collagenase A. Briefly, partial tissue was cut from each isolated organ, washed twice with chilled PBS solution, gently cut in small pieces and incubated in the solution of 0,5 mg/ml collagenase A (Sigma) for 20 minutes. The cell suspension was then gently aspirated several times with the pipette and transferred into centrifuge tube with 2 ml Eagle's essential minimal medium (Sigma) containing 10% fetal bovine serum (FBS) to inactivate collagenase A. The cell suspension was then centrifuged for 10 minutes at 1000 rpm. The collagenase supernatant was removed and the precipitate was re-suspended in Eagle's essential minimal medium (Sigma) supplemented with 10% FBS. The viability of cells was assessed using trypan blue exclusion assay.[30]

Comet assay

The assay was performed as described by Singh *et al.*[31] 30 μl of single cell suspension (≈ 400,000 cells/ml) was mixed with 70 μl of 1% low melting point agarose and added to fully frosted slides that had been covered with a layer of 1% normal melting point agarose. The cells were then lysed (2.5 M NaOH, pH 10, 0.1 M EDTA, 0.01 M Tris and 1% Triton X-100 for 1 hr at 4 °C), rinsed with distilled water, placed in the electrophoresis solution (300 mM NaOH, 1mM EDTA, pH 13) for 20 minutes to allow DNA unwinding, and electrophoresed for 20 minutes at 25 V and 300 mA. Finally, the slides were neutralized with 0.4 M Tris buffer (pH 7.5), and the DNA stained with ethidium bromide (5 μg/ml). Two slides were prepared per tissue per animal and 50 randomly selected nuclei per slide were

captured under the fluorescence microscope (Olympus) and the images analyzed with image analysis software (VisCOMET, TillPhotonics, Germany). The % tail DNA was used to measure DNA damage.

Statistical Analysis

One-way analysis of variance (ANOVA, Kruskal-Wallis) was used to analyze the differences between treated and control animals. A Dunnet test was used to compare mean values of % tail DNA; $p<0.05$ was considered as statistically significant.

Results

In this study we recorded DNA damage in liver, kidney medulla and cortex, lung, brain and spleen cells and in lymphocytes of rats that were treated with sublethal dose of MCYR (10 μg/kg b.w.; i.p) every second day during the period of 30 days. The control rats received the vehicle (mixture of 0.8% etanol and 0.2% methanol dissolved in 0.9% physiological saline). The control animals appeared healthy and free from pathological signs, while animals that have received MCYR appeared less active and the fur was less shiny, suggesting a systemic toxic effect. After sacrifice and autopsy, no macroscopic evidence of degenerative processes was observed in any of the experimental animals. The cell viability after the isolation from organs was found to be more than 80% in all animals (data not shown).

A significant increase of DNA damage in MCYR treated animals compared to the control was detected in liver, kidney medulla and cortex, lung and brain, while no DNA damage was detected in spleen and lymphocytes (Figure 1 and Table 1). From the ratio between mean value of the % tail DNA of the cells from the treated animals and that of the control animals it can be seen that the highest level of DNA damage was induced in brain, followed by liver > kidney medulla > kidney cortex > lung (Table 1).

The data of the % tail DNA were further analyzed in terms of the distribution of single cells according to the extent of DNA damage in the whole population of analyzed cells from each organ (Figure 1). The cells isolated from vehicle treated control animals had relatively uniform low DNA damage; however, the mean values of the percent comet tail DNA were different for different organs. The cells isolated from liver, kidney medulla, kidney cortex, lung and brain of the treated animals showed a heterogeneous distribution ranging from cells with low to cells with high DNA damage. The majority of the cells had higher % tail DNA compared to the distribution of % tail DNA in cells isolated from the corresponding organ of the control animals.

Discussion

Acute hepatotoxic effects of MCs are well explored, while their effects on other organs have been neglected for a long time because the acute hepatotoxic effects caused by lethal intoxication are dominant and sufficient to cause the death of the animals before effects on other organs can be observed. However, at sublethal chronic intoxication it seems reasonable to expect that MCs could cause effects also in other organs. Recently Milutinović *et al*.[32] reported that the chronic intoxication of rats with sublethal doses of microcystins MCLR and MCYR induced kidney injury.

In the present study we investigated the *in vivo* genotoxicity of MCYR in some organs and tissues of rats by measuring the DNA damage with the comet assay. The organs examined were liver, which is the target organ and kidney, lung, brain, spleen and lymphocytes which are considered as non-

Table 1. The DNA damage in rat organs after 30 day exposure to sublethal dose (10 μg/kg b.w. i.p. every second day) of MCYR

Treatment	Organ	Number of animals	% tail DNA	IF[a]
Control	Liver	4	7.0 ± 1.44	
MCYR	Liver	7	14.8 ± 0.80*	2.1
Control	Kidney cortex	4	13.5 ± 1.86	
MCYR	Kidney cortex	7	24.4 ± 5.61*	1.8
Control	Kidney medulla	4	10.6 ± 1.36	
MCYR	Kidney medulla	7	20.6 ± 5.44*	1.9
Control	Lung	4	14.4 + 2.06	
MCYR	Lung	7	24.7 ± 5.77*	1.7
Control	Brain	4	10.0 ± 1.46	
MCYR	Brain	7	24.5 ± 6.30*	2.5
Control	Spleen	3	9.9 ± 0.49	
MCYR	Spleen	7	10.7 ± 3.67	1.1
Control	Lymphocytes	4	18.2 ± 2.34	
MCYR	Lymphocytes	7	20.8 ± 6.81	1.1

[a] induction factor: the ratio between the mean values of the % tail DNA of treated and control animals

* statistically significant differences between control and treted animals ($p<0.05$)

target organs. The results clearly showed that prolonged exposure of rats to sublethal dose of MCYR induced DNA damage not only in liver, but also in brain, kidney and lung cells. The observed DNA damage was most likely due to MCLY induced oxidative stress in affected organs. This assumption is based on: i) demonstration that the oxidative stress plays a significant role in the pathogenesis of chronic exposure to MCLR;[17] ii) reactive oxygen species (ROS) are known to induce DNA strand breaks, which can be readily detected with the comet assay and iii) MCLR induced DNA strand breaks in human hepatoma HepG2 cells were ROS mediated.[18]

The acute exposure of rats to MCLR resulted in a decrease of the endogenous antioxidant defence system together with an increase of lipid peroxidation in liver and in kidney.[33] This supports the assumption that the DNA damage of liver and kidney cells we observed in our study was mediated by oxidative stress. The extent of DNA damage in liver cells was higher than in kidney cells, which is in line with the above mentioned study of Moreno *et al.*,[33] who showed that antioxidant enzymes were significantly decreased in liver, while minor decrease was found in kidney, indicating different organ susceptibility to adverse effects of MCs.

An interesting finding of this study was the highest level of DNA damage in brain cells. The result corroborates recent results of Maidana *et al*.[34] who showed that intrahippocampal infusion of microcystin raw extract induced oxidative stress and DNA damage in cells isolated from hippocampus. The question is how MCs are transported through the body and absorbed by non hepatic tissue. Fisher *et al*.[35] reported that members of organic anion transporting polypeptide super family involved in MCs uptake (including the human OATP1A2 transporter) are expressed in liver and in endothelial cells of the blood-brain barrier. This explains brain as the target of MCs toxicity. The low antioxidant and DNA repair capacity of the brain could

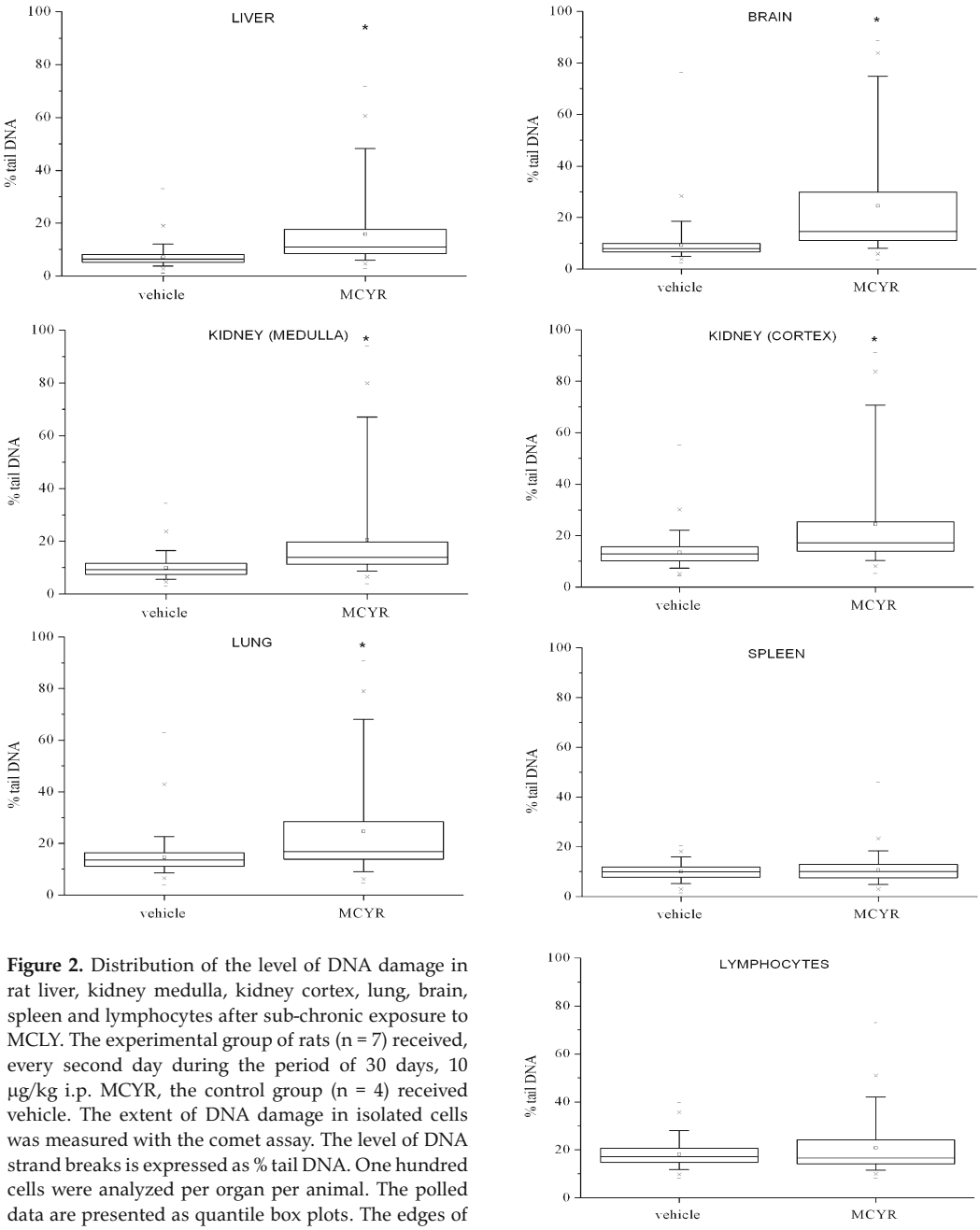

Figure 2. Distribution of the level of DNA damage in rat liver, kidney medulla, kidney cortex, lung, brain, spleen and lymphocytes after sub-chronic exposure to MCLY. The experimental group of rats (n = 7) received, every second day during the period of 30 days, 10 μg/kg i.p. MCYR, the control group (n = 4) received vehicle. The extent of DNA damage in isolated cells was measured with the comet assay. The level of DNA strand breaks is expressed as % tail DNA. One hundred cells were analyzed per organ per animal. The polled data are presented as quantile box plots. The edges of the box represent the 25th and 75th percentiles, the median is a solid line through the box, mean values are represented as square (□), and the error bars represent the 95% confidence intervals. * denotes a significant difference between MCLY-treated groups and control (Kruskal–Wallis test, $P < 0.05$).

be the explanation for the highest level of DNA damage in the brain.[36]

MCYR induced DNA damage also in lung, however, little is known about the effects of MCs on lung. The only report we are aware of is by Gupta *et al*.[37] who found that in mice after the acute exposure to MCLR, MCRR and MCYR induced pulmonary inflammation, congestion and haemorrhage. Interestingly no DNA damage was observed in the haematopoietic system; spleen and lymphocytes. An *in vitro* study has shown that MCs induce DNA damage in human lymphocytes,[24] however, no *in vivo* study of the effects of MCs on lymphocytes is available.

In conclusion, the subchronic administration of sublethal dose of MCYR induced DNA strand breaks that were observed in brain liver, kidney, and lung confirming the genotoxic potential of this toxin. However, the correlation of these findings with carcinogenicity of MCs needs to be further investigated.

Acknowledgments

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Testing of mechanisms of action of rituximab and clinical results in high-risk patients with aggressive CD20+ lymphoma

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Background. *Rituximab has been applied successfully in the treatment of indolent and aggressive CD20 positive B cell lymphomas, yet the exact in vivo mechanisms of its action have not been unambiguously explained. This study was therefore aimed to confirm the presumed major mechanisms of action of rituximab and concomitantly to assess the effectiveness of first-line chemoimmunotherapy in high-risk patients with aggressive CD20 lymphomas.*

Patients, materials and methods. *The activity of rituximab was tested in vitro on Raji and SU-DHL-4 cells using the cell proliferation assay and flow cytometry. In the clinical part of the study, 20 high-risk patients with aggressive CD 20 lymphomas were treated with R-CHOP.*

Results. *Only complement-mediated cytotoxicity was observed under the in vitro applied experimental conditions. Neither the direct apoptotic effect nor the antibody-dependent cell-mediated cytotoxicity was detected probably due to a too low concentration of rituximab and a too low ratio of cytotoxic lymphocytes to tumor cells. The treatment outcome in patients was excellent since complete remissions were achieved in 90% of poor-risk patients at the end of primary treatment and 80% of patients were disease-free at 18.5 months median observation period.*

Conclusions. *According to our results, the complement-dependent cytotoxicity is an important mechanism of rituximab action in vitro. To achieve direct apoptosis, higher concentrations than 20 μg/ml of rituximab should be used, while for an effective antibody-dependent cell-mediated cytotoxicity, the ratio of cytotoxic lymphocytes to tumor cells should be higher than 1:1. In the high- risk patients with aggressive CD20 lymphomas, the addition of rituximab to CHOP substantially improves the therapeutic results.*

Key words: lymphoma, B-cell – therapy; antigens, CD 20; antibodies, monoclonal

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Introduction

The CD20 antigen, a 35 kDa phosphoprotein, is restricted to the B cell lineage and is expressed by mature B cells and most malignant B cell lymphomas. While

the exact functions of CD20 are presently unknown, it is considered to be involved in many cellular signaling events, including proliferation, activation, differentiation, and apoptosis upon crosslinking. Its attributes, as its tetraspan binding in the cell membrane and the lack of internalization or downregulation upon antibody binding, make CD20 a suitable target for an effective antibody.[1, 2]

Rituximab, a chimeric (human-mouse) IgG κ monoclonal antibody that recognizes the CD20 antigen[3], is the most widely recognized and used monoclonal antibody in the B cell lymphoid malignancies. It has been applied successfully in the treatment of indolent CD20 positive B cell lymphomas and, more recently, also in the treatment of aggressive lymphomas in combination with standard chemotherapy. The indications for its use are now expanding to autoimmune diseases.[4]

The mechanisms of anti-tumor action of rituximab are diverse. The human IgG component of the antibody is able to bind human complement (CDC) and also interact with effector cells to kill cells by antibody-dependent cell-mediated cytotoxicity (ADCC). Some investigators have also shown direct effects of the antibody on human tumor cell lines expressing CD20. These effects include inhibition of proliferation, induction of apoptosis and increased sensitivity to chemotherapeutic agents, although the extent to which each of these mechanisms may contribute to the anti-tumor action of rituximab remains to be determined. Rituximab thus acts by additional mechanisms compared to conventional chemotherapeutic agents. The chimeric nature of the antibody results in minimal immunogenicity and allows repeated use. The antibody may be combined with conventional chemotherapy, with potential for increased efficacy and minimal added toxicity.[5]

Due to still unambiguously explained mechanisms of action, we aimed our study at additional *in vitro* testing of rituximab activities. There were predominately three questions we wanted to resolve – firstly, to confirm the *in vitro* anti-tumor activity of the antibody against established CD20 positive lymphoma cell lines, secondly, to evaluate the importance of the three major mechanisms of action (*i.e.* complement mediated cytotoxicity, antibody mediated cellular cytotoxicity and apoptosis) in *in vitro* conditions, and thirdly, to determine some of the pharmacokinetic data (the time needed for rituximab binding as well as the duration of rituximab-CD20 binding). Furthermore, a smaller clinical research was performed in order to determine the effectiveness of first-line chemoimmunotherapy with rituximab and CHOP (R-CHOP) in the high-risk patients with aggressive CD20 positive NonHodgkin's lymphoma (NHL).

Patients, materials and methods

Cell cultures

The CD20+ human B-cell lines - Raji (American Type Culture Collection - ATCC, Rockville, MD, USA) and SU-DHL-4 (Deutsche Sammlung von Mikroorganismen und Zellkulturen - DSMZ, Braunschweig, D) were grown in RPMI 1640, 25 mM HEPES (Gibco, Invitrogen, Grand Island, NY) supplemented with 10% of inactivated fetal calf serum - iFCS (Sigma, St. Louis, MO), penicillin (100 units/ml, Pliva, Zagreb, CRO), and gentamycin (50 μg/ml, Krka, Novo mesto, SLO).

Isolation of human monocytes from peripheral blood (hPBMC)

Human PBMC were isolated on Ficoll-Paque (Amersham Pharmacia Biotech AB, Uppsala, S).

Determination of mechanisms of action of rituximab - design of in vitro experiments

In the experiments, CD20+ human B-cell lines Raji and SU-DHL-4 were used. When the cells in the tissue culture reached the optimal density (70-80% of confluence), the growth medium was removed and replaced with the growth medium (RPMI) containing the following tested components:

- 2% of inactivated fetal calf serum - FCS,
- 2% of inactivated human serum - iHS,
- 20% intact human serum - HS,
- 2% FCS + fresh hPBMC (ratio of target cells and lymphocytes - 1:1),
- 2% FCS + 20 μg/ml of rituximab,
- 2% iHS + 20 μg/ml of rituximab,
- 20% HS + 20 μg/ml of rituximab,
- 2% FCS + fresh hPBMC (ratio of target cells and lymphocytes - 1:1) + 20 μg/ml of rituximab.

The samples were taken from the culture 4 hours, 24 hours and 48 hours after the beginning of treatment.

The saturation of the CD20 epitopes on lymphocytes with rituximab was determined at each point of the experiment.

Cell proliferation assay

Biological test used for the detection of cell proliferation was the CellTiter 96® A_{queous} Non-Radioactive Cell Proliferation Assay (Promega, Madison, WI, USA). This is a colorimetric method for determining the number of viable cells in chemosensitivity assays. The method is based on the detection of MTS (tetrazolium compound) bioreduction into a formazan product that is soluble in tissue culture medium. The absorbance of the formazan was measured at 490 nm. In the experiments, $2x10^4$ CD20+ human B-cells/well were cultured in the growth medium supplemented with 10% of serum (either FCS or iHS or HS) with or without rituximab. Survival in the control group (cell growth medium and FCS) was taken as 100%.

Flow cytometry

Staining for the presence of CD20 antigen. The CD20+ human B-cells ($1x10^6$) were spun down at 1000 rpm/min. The sediment was carefully resuspended in the residual fluid and 100 μl of culture medium was added (MeM with 2% inactivated FCS). The cells were stained with 10 μl of CD20 monoclonal antibodies conjugated with PE-Cy5 (BD Biosciences Pharmingen, San Diego, CA, USA) for 30 minutes at room temperature in the dark and then washed 3 times using MeM and resuspended in Facsflow solution (BD Biosciences, San Diego, CA, USA).

Apoptosis – Annexin test. For the detection of apoptosis, Annexin V test was used (BD Pharmingen, San Diego, CA, USA). The CD20+ human B-cells were resuspended in 100 μl of binding buffer and stained with 5 μl Annexin V-FITC reagent and 10 μl of propidium iodide (Molecular probes, Eugene, Oregon, USA) for 15 minutes at room temperature in the dark. After incubation, 400 μl of binding buffer was added to each tube. Measurements were performed within one hour.

Adjustment of the flow cytometer. Flow cytometer (FACSort, Becton Dickinson, San Jose, CA, USA) was adjusted for the optimal acquisition of lymphocytes. In the dot plot screen {FSC = (X) toward the SSC = (Y)}, the lymphocyte-like population was gated. In the histogram screen, PE-Cy peak was selected and transferred into the dot plot screen. The percentage of live, apoptotic and dead CD20+ human B-cells was calculated using the quadrant statistic tool.

Statistical analysis

The *in vitro* experiments were set up in triplicates and the results were expressed as means ± SD. The results were analyzed for statistical significance of difference between the groups using the unpaired two

tail Student's *t* test. The *p* level <0.05 was considered as statistically significant.

Patients

In the clinical part of the research, 20 patients with aggressive CD20 positive NHL were treated with R-CHOP at the Department of Medical Oncology of the Institute of Oncology Ljubljana, Slovenia, from October 2003 to February 2005. The research included 6 male patients with the median age of 66.5 years (range 44 to 74) and 14 female patients with the median age of 63.5 years (range 37 to 78). Seventeen patients were diagnosed with diffuse large B-cell lymphoma and 3 patients had follicular lymphoma grade 3. The R-CHOP treatment was first-line treatment for newly diagnosed lymphomas and all patients included in the study had advanced lymphomas (stages III and IV according to Ann Arbor staging).

Rituximab (kindly donated by Roche) was applied at standard doses (375 mg/m^2) intravenously on day 1, followed by CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicyn 50 mg/m^2 and vincristine 2 mg, unless adjusted to the patient's performance status or previous toxicity). Premedication with methylprednisolone, paracetamole and clemastine was given prior to every rituximab application. The cycles of chemo-immunotherapy were repeated every three weeks. The majority of patients received 8 cycles of such treatment, one patient died of complications after the first cycle, and in one patient, the treatment was terminated due to disease progression after the sixth cycle. Eleven patients received intrathecal chemotherapy in order to prevent the spreading of lymphoma into CNS, and in two patients, middle doses of methotrexate were added to R-CHOP due to concomitant CNS localization of lymphoma.

Treatment response was evaluated after the 4th and after the 8th cycle of treatment according to Cheson's criteria.[6]

Results

Cell growth inhibition by rituximab

In order to determine the *in vitro* effect of rituximab on CD20+ B lymphocytes, Raji and SU-DHL-4 cell lines were grown in the growth medium supplemented with rituximab and either 10% of inactivated FCS (FCS) or 10% of inactivated human serum (iHS) or 10% of intact human serum (HS). The viability of cells after 24h, 48h and 72h was determined using the cell proliferation assay.

The growth of both Raji and SU-DHL-4 cells was inhibited by rituximab in the presence of HS. In Raji cells, the inhibition was observed at all time points – at 24h, 48h and 72h. The difference was statistically significant at all time points when compared to the cell growth of cells cultured only with iHS or HS (*p* values were in the range of 0,045 to 0,003) (Figure 1A). When comparing with the growth of the cells cultured with rituximab and FCS or iHS, a statistically significant growth reduction of the cells cultured with rituximab in the presence of HS was obtained only after 72h. The *p* values were 0.026 (R+iHS/R+HS) and 0.003 (R+FCS/R+HS), respectively (Figure 1A).

In SU-DHL-4 cells, a statistically significant growth reduction was obtained for the cells cultivated with rituximab in the presence of HS compared to all other groups at 48h and 72h. The *p* values were in the range of 0.012 to 0.001. After 24h, the only statistically significant growth reduction was observed when we compared the growth of the cells cultured with rituximab in the presence of HS with the growth of the cells cultured only with iHS ($p = 0.013$) (Figure 1B).

Determination of mechanisms of rituximab action

In order to confirm the mechanisms by which rituximab induces killing of CD20+ B lymphocytes, Raji cells were incubated with rituximab for 4h, 24h, and 48h in the presence of HS (20%) or hPBMC (ratio 1:1) and the proportions of alive, apoptotic, or dead cells were determined by flow cytometry.

There was no difference in the proportions of alive, dead or apoptotic cells between the cells that were grown in the medium supplemented with FCS or iHS and the cells grown in the same medium, but with added rituximab (data not shown). However, the ratio of apoptotic cells was substantially increased in those cells that had been co-incubated with rituximab in the presence of 20% HS. Comparing these cells to the cells cultured only with HS, a significantly increased proportion of apoptotic cells was obtained after 24h and after 48h. The relating *p* values were 0.001 after 24h and 0.003 after 48h. Similar results were obtained when the ratios of apoptotic cells among the cells incubated with rituximab in the presence of 20% HS and among the cells cultured only with FCS were compared. The relating *p* values were 0.017 after 24h and 0.009 after 48h (Figure 2).

In our study, hPBMC (isolated from the same blood sample as human serum) did not affect significantly the number of apoptotic cells either when used alone or in combination with rituximab. There was also no statistically significant difference in the number of apoptotic cells when CD20+ B lymphocytes were co-incubated with rituximab and hPBMC in the presence of FCS or when co-incubated only with hPBMC in the presence of FCS. Significant difference was not observed even when the results obtained with rituximab and hPBMC were compared to other groups.

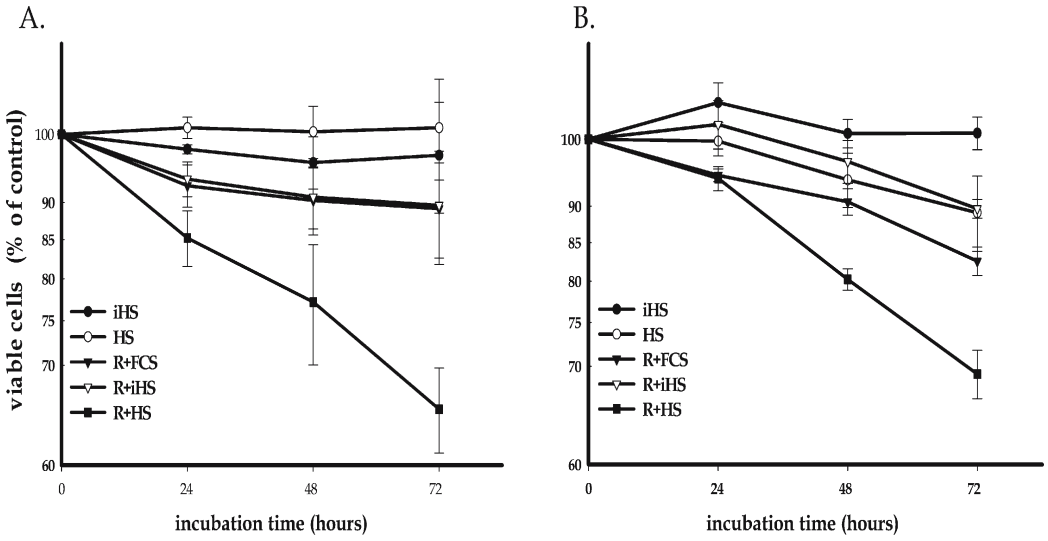

Figure 1. Growth of lymphoma CD20+ Raji (panel A.) and SU-DHL-4 cells (panel B.) in the presence of 20 μg/ml of rituximab. The plots represent the AM±SD of three independent experiments. The proportion of viable cells in experimental groups was calculated as % of the control (cells grown in medium supplemented with FCS).
iHS – cells grown in 10% of inactivated human serum, **HS** – cells grown in 10% of intact human serum, **R+FCS** - cells grown with rituximab in 10% of inactivated fetal calf serum, **R+iHS** - cells grown with rituximab in 10% of inactivated human serum, **R+HS** - cells grown with rituximab in 10% of intact human serum.

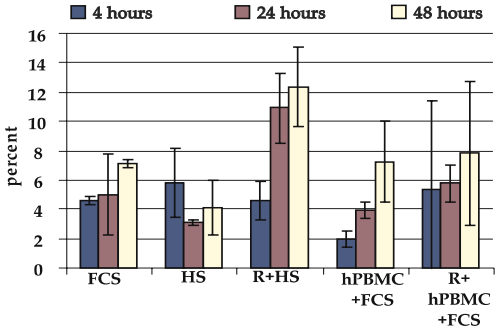

Figure 2. Proportion of apoptotic cells among Raji cells incubated with rituximab for 4h, 24h, and 48h in the presence of HS (20%) or hPBMC (ratio 1:1) determined by flow cytometry. The plots represent the AM±SD of three independent experiments. **FCS** - cells grown in 2% of inactivated fetal calf serum, **HS** – cells grown in 20% of intact human serum, **R+HS** - cells grown with rituximab in 20% of intact human serum, **hPBMC+FCS** – cells grown in 2% of FCS with fresh hPBMC, **R+hPBMC+FCS** – cells grown with rituximab in 2% of FCS and in the presence of fresh hPBMC.

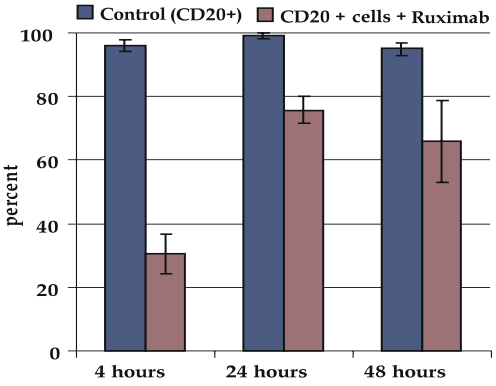

Figure 3. Saturation of CD20 receptors on Raji cells by rituximab after different periods of time. Raji cells ($1x10^6$) were co-incubated with 20 μg/ml of rituximab in the presence of FCS. As the control, the same number of Raji cells without rituximab was used. The plots represent the AM±SD of three independent experiments.

Saturation of CD20 receptors by rituximab

Binding of rituximab to cell receptors was followed by flow cytometric determination of free CD20 receptors after 4h, 24h and 48h when $1x10^6$ Raji cells were co-incubated with 20 μg/ml of rituximab in the presence of FCS. As the control, the same number of Raji cells without rituximab was used. Four hours following the addition of rituximab, only 30.7% of CD20 receptors remained free. However, after 24h and 48h the proportion of free CD20 receptors increased to 75.6% and 66.0%, respectively (Figure 3).

Clinical results

According to Ann Arbor staging system, 3 patients had stage III.A disease, 3 patients III.A.E, 1 patient III.B, 1 patient IV.A, 5 patients IV.A.E, and 7 patients IV.B.E disease. Extranodal localizations of lymphoma were found in as much as 15 patients (and in some patients they were multiple). Five patients had lymphomatous infiltration of the stomach/intestine, 4 had skeletal involvement, 2 CNS involvement, 4 patients lung and 2 patients pleural infiltration, 2 patients pancreatic and 1 renal infiltration, in 4 patients, there was soft tissue involvement (skin or muscles), and in 4 patients, infiltrates were detected in the ORL region (tonsils, maxillary sinus, salivary glands).

The international prognostic index was low intermediate (2) in 5 patients, high intermediate (3) in 8 patients, and high (4 or 5) in 7 patients. The serum LDH concentrations were also elevated in 15 patients, with the highest concentration reaching 29 μkat/l (*i.e.* approximately seven-times the upper normal limit).

During the treatment, some grade 3 or 4 toxicities developed in 15 patients and only the remaining 5 had practically no or only minor side effects. Among the most common side effects were neutropenia with or without fever (in 14 patients) and serious infection/septicemia (in 6 patients), all of which resulted in the necessity for drug dosage reductions in 7 patients.

Table 1. Treatment response to R-CHOP in patients with aggressive CD20 Non-Hodgkin's lymphomas.

Treatment response	After 4th cycle	After 8th cycle	After RT*
PR	8 (40%)	4 (20%)	
CR	10 (50%)	14 (70%)	18 (90%)
SD	2**		
PD		1***	

* - just the 4 patients with PR after the 8th cycle were irradiated
** - in 1 patient there was stable disease (IPI 4), another one died 2 days after the first cycle (IPI 3)
*** - PD after the 6th cycle (IPI 4)

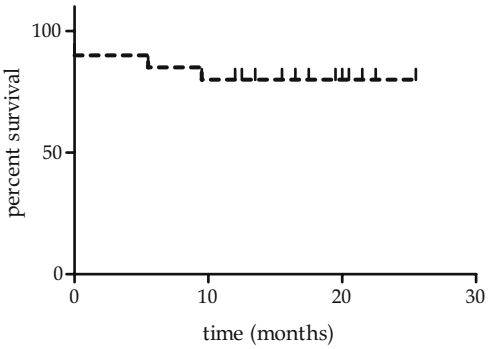

Figure 4. Disease free survival in 20 high-risk patients with aggressive CD 20 lymphoma after treatment with R-CHOP.

After the 4th cycle of treatment, partial response (PR) was observed in 8 patients, complete response (CR) in 10 patients, and stable disease (SD) in 1 patient. One patient died 2 days after the first cycle in septic shock most probably due to necrotizing pancreatitis. This patient had a lymphomatous infiltration of the pancreas confirmed prior to the introduction of treatment.

At the end of systemic treatment, 4 of 8 patients with prior partial remission achieved complete remission, while in the other 4, the final outcome was partial remission. These 4 patients continued their treatment with irradiation of the residual lymphoma masses and eventually achieved complete remission. The patient with stable disease following the 4th cycle progressed (PD) after another two cycles of treatment and was further on treated with another chemotherapy schedule. This patient died of progressive lymphoma 4 months after the last R-CHOP cycle (Table 1).

The complete response still lasts in 16 patients (80%) with the median observation period of 18.5 months (range 12 to 15.5 months) and the median response duration has not been reached yet (Figure 4). On the other hand, two patients progressed (both IPI 3), one 5.5 and the other 9.5 months after the end of treatment. These two patients were subsequently treated with different chemotherapy schedules and are still alive – one of them in the second remission and the other one still under treatment.

Discussion

Clinical application of rituximab in combination with chemotherapy has significantly improved the treatment outcome in the patients with indolent and aggressive non-Hodgkin's lymphoma (NHL).[4] Still, the exact *in vivo* mechanisms of action of rituximab are not fully understood, although antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis have been suggested.[7] This study, was aimed to confirm the presumed major mechanisms of action of rituximab and concomitantly to assess the effectiveness of first-line chemoimmunotherapy with R-CHOP in the high-risk patients with aggressive CD20 NHL.

The results of *in vitro* experiments on Raji and SU-DHL-4 cells provided evidence for a significant effect of rituximab on the cell growth starting more than 24 h after the exposure to the drug, but only when the cells were grown in the presence of intact HS. Culturing of these cells with rituximab and inactivated FCS or HS did not result in

a significant growth reduction alluding to the possibility that, in *in vitro* conditions, rituximab by itself was not sufficient to affect critically the tested cells. The observation was unexpected since certain previous studies validated this very mechanism of action of rituximab.[7-10] A gene expression analysis revealed that the binding of rituximab to CD20 receptors induces *in vitro* activation of genes known to be involved in the cell growth control and apoptosis. In the study of Jazirehi *et al.*, evidence was provided that rituximab treatment of B-cell lines Ramos and Daudi inhibits the constitutive NF-κB signaling pathway thereby down-regulating the Bcl-x_L expression. In this way, the antibody directly affects cells through CD20 receptors diminishing their proliferative activity and, even more, rituximab also sensitizes tumor cells to the cytotoxic activity of certain drugs.[10] Due to the observed discrepancy between the stated results and our results, we expanded the *in vitro* experimentation to flow cytometry. The effects of rituximab were thus followed by the determination of proportions of apoptotic, dead and alive cells among the differently treated cells. Surprisingly, also the results obtained from the flow cytometric analysis confirmed our previous observations. There was a statistically significant reduction in the number of live cells (for the groups HS/R+HS after 24h and 48h the *p* values were 0.005 and 0.044, respectively) and a statistically significant increase of apoptotic cells, but only among the cells treated with rituximab in the presence of intact HS (for the groups HS/R+HS after 24h and 48h the *p* values were 0,001 and 0,003, respectively). The anticipated increase in the number of apoptotic cells among cells treated with rituximab in the presence of iHS or FCS was not observed. Since the degree of apoptosis and growth conditions in the studies evaluating this mechanism varied from study to study[7], it is quite possible that the model used in our study was not sensitive enough to detect the changes as direct consequences of the monoclonal binding to CD20 receptors. Therefore, the next step in our investigation was the determination of the extent of rituximab binding and saturation of CD20 receptors on the target cells. Using 20 μg of rituximab per one ml of cell growth medium, the saturation of CD20 receptors was the highest 4 h after the beginning of treatment (almost 70%). In the next hours, the saturation rapidly decreased indicating that the initial concentration of rituximab was probably too low - which may actually be one of the reasons why direct apoptosis due to cross-linking of CD20 has not been observed. Additionally, in some studies of normal and malignant human B cells *in vitro*, B-cell depletion was observed predominately with rituximab in the presence of mononuclear cells, but not in the presence of a complement, suggesting the importance of cell-mediated mechanisms (ADCC).[11] In other studies, however, both the activation of ADCC and complement-mediated lysis have been demonstrated *in vitro* and *in vivo* after the treatment with rituximab.[12-14] Our *in vitro* testing failed to demonstrate any significant difference in the number of alive, apoptotic or dead cells between the cells co-incubated only with hPBMC or with hPBMC in combination with rituximab. Most probably, the reason for this is an inadequate ratio between hPBMC and CD20+ B-cells. This ratio was 1:1 in our study, meaning that the ratio of the cells capable of mediating the cytotoxic response, *i.e.* NK cells and monocytes, was at the best 1:1 or lower, making it unlikely that cytotoxicity had any significant impact on the proportion of dead cells.

When commenting the clinical data, the treatment results in the poor-risk patients with aggressive NHL were disappointing in the pre-rituximab era as reported by Shipp *et al* in 1993.[15] For example, complete remis-

sion was achieved in only 44% of patients with high IPI and in 55% of patients with high intermediate IPI as compared to 87% of patients with low IPI. In our research, predominately the patients with high intermediate (8 patients) and high IPI (7 patients) were included and not one single patient had low IPI. Therefore, the fact that as much as 90% of these patients finally achieved complete remission (14 patients after chemoimmunotherapy and 4 patients after additional radiotherapy) definitely speaks for superior activity of R-CHOP compared to chemotherapy alone in the high-risk patients (in spite of the small number of the patients included in our study).

Also the rate of disease free survival was much higher in our study (80% of the patients) compared to the data of Shipp *et al.*[15] who reported 58% and 59% 2-year relapse-free survival for high and high intermediate IPI groups, respectively, even though our median observation period was only 18.5 months.

Obviously the addition of rituximab to the treatment protocol for the poor-risk patients with aggressive NHL improved the previous treatment results achieved only with chemotherapy (± radiation treatment). This improvement could be the reflection of an increased sensitivity to chemotherapeutic agents induced by rituximab which is in accordance with the *in vitro* results of the two lately published studies.[10,11]

Conclusions

The results of our study indicate that the complement-dependent cytotoxicity (CDC) is an important mechanism of rituximab action *in vitro* since it seems to be triggered easily even if the absolute saturation of CD20 receptors is not reached. To achieve direct apoptosis, higher concentration of rituximab (>20 μg/ml) should be used while for an effective ADCC, the ratio of cytotoxic lymphocytes to tumor cells should be increased (to more than >1:1). From the clinician's point of view, the addition of rituximab to CHOP in the high-risk patients with aggressive CD20 NHL is obligatory if the goal of the treatment is to cure the patient. Accordingly, it is no exaggeration to state that rituximab changes the prognosis of poor-risk patients with aggressive CD20 NHL.

Acknowledgements

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Radiofrequency ablation of lung tumours – new perspective in treatment of lung neoplasms

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Background. *Percutaneous radiofrequency ablation (RFA) is a minimally invasive technique used to treat solid tumours. Because of its ability to produce large volume of coagulation necrosis in controlled fashion this technique has been progressively tested as a possible treatment of lung malignancies. Recent clinical studies have shown that RFA enables successful treatment of relatively small lung malignancies with high rate of complete response and acceptable morbidity and have suggested that the technique could represent a viable alternate or complementary method for patients with non-small cell lung cancer or lung metastases of favourable histotypes who are not candidates for surgical resection.*

Conclusions. *Initial intenational studies as well as the clinical experience of Institute of Radiology in Clinical Center Ljubljana, although limited, indicated that RFA is mostly well tolerated by patients and also, that it can result in complete necrosis of targeted lesion. Pneumothorax is most common procedure related complication, occurring in up to 40% of cases, with approx. half of them requiring drainage.*

Key words: lung neoplasms – surgery; catheter ablation

Introduction

Image-guided percutaneous radiofrequency ablation (RFA) is a minimally invasive technique for the treatment of solid tumours that has only been introduced recently into every day clinical practice. Now it is considered to be a feasible treatment option for patients with primary hepatocellular carcinoma or limited metastatic liver disease.[1,2] With the improvement of the technology RFA is now being evaluated for in other types of tumours, including lung neoplasms.

As being well known, the lung is the most common site of primary cancer worldwide and is also a common site for metastatic disease. Many of these patients and also the patients with otherwise resectable tumours are not operable due to associated conditions such as age, poor cardiovascular and/or respiratory function and/or other serious coexisting health conditions or because of the size and location of the tumour itself. For all these patients (e.g. patients with limited lung tumours not eligible for surgical resection) radiofrequency ablation seems to be a good treatment option.[3-8]

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RFA

In principle RFA is caused by high-frequency current from radiofrequency generator passed between the needle electrode placed in the tumour and a large electrode on patient's skin. Electrodes create an alternating electric field which induces marked agitation of iones resulting in frictional heating of the surrounding tissue, which results in irreversible damage.[3,5,6,9,10] Experimental studies in animals showed a well defined area of coagulation 72 hours after RFA, surrounded by a zone of hyperaemia that gradually resolves.

The technique found to be especially suitable for lung tumours since the air in surrounding alveoli acts as insulation, helping to concentrate the energy in the lesion. The disadvantage of the method is, however, that the technique is suitable only for patients with solitary or small number of lung lesions since each tumour or metastasis need to be treated individually.[3]

Detailed diagnostic workup, including chest CT, is essential to determine the exact number, site and position of target tumour(s). The treatment procedure is CT guided. During the procedure the needle electrode is positioned in the tumour, using the workflow of stereotactic biopsy of lung lesions.[3] It is important to select the entry site on the skin that allows the shortest and most vertical path for the needle, avoiding blood vessels, interlobar fissures and bullae. Image reconstructions and multiple planes help us to ensure the correct placement of the electrode needle within the tumour, which is a crucial point of the procedure. The ablation device has 9 flexible hooks, deployed from the trocar tip, some use cooled tip electrodes. The power output of the radiofrequency generator and duration of the ablation are programmed according to tumour volume and continuously monitored by a computer. At the end of procedure the track ablation is carried out to reduce the risk of seeding tumour cells.[3]

The important limitation for the procedure is the size of the tumour. Since we need to ablate all viable tumour tissue and an adequate tumour-free margin which is 1 cm, it is clear, that largest, a 5 cm ablation device can be used to treat tumours up to 3 cm in diameter and not more.[11] One cm margin is necessary to assure that all possible microscopic invasions around the periphery of a tumour have been eradicated.

Lung RFA is painful and requires adequate pain relief with conscious sedation or general anaesthesia, although the latter seems to be connected with greater risk of pneumothorax in the ventilated patient.[3,5,7,8,12]

International clinical experience

Initial studies as well as the clinical experience of Institute of Radiology in Clinical Center Ljubljana, although limited, indicated that RFA is mostly well tolerated by patients and also, that it can result in complete necrosis of targeted lesion. Pneumothorax is most common procedure related complication, occurring in up to 40% of cases, with approx. half of them requiring drainage.[3,5,6,9,10]

Recently, one of the largest trials of RFA for lung tumours was completed.[12] Patients were followed up to 27 months. Patients with primary lung cancer or lung metastases 3.5 cm or less in diameter, who were not candidates for surgery, were included into this multicenter, prospective study. One hundred and six patients with 186 malignant masses were enrolled. There were 33 patients with non-small cell lung cancer, 53 with colorectal lung metastases and 20 with other primary malignancy metastasis, none of them eligible for surgery. Patients underwent CT guided RFA treatment un-

der conscious sedation. There were no procedure-related deaths, but 27 cases of pneumothorax, requiring treatment and also 4 pleural effusions, 2 pneumonias and 1 atelectasis.

At CT evaluation after 3 months post procedure, complete ablation of the tumour was observed in 173 of 186 tumours, which set the primary effectiveness rate to 93%. Overall survival rate of the primary lung cancer patients was 69% at year 1 and 49% at year 2. However, many deaths were not cancer related and when excluded, the cancer specific survival rates were 91% at year 1 and 2. In patients with colorectal metastases the survival rates were 88% at year 1 and 72% at year 2, after exclusion of non-cancer related deaths.[12]

Clinical experience of Institute of Radiology in Clinical Center Ljubljana

We have treated 5 patients up-to date. In all cases the procedure was performed with intent to cure. All patients have had cito/histologically proven non-small cell lung cancer without metastatic disease. The disease was resectable in all cases but patients were inoperable due to cardiac and pulmonary disease (3 patients), extreme obesity (1 patient) and consent withdrawal (1 patient).

During pre-ablation work-up patients underwent a chest CT to determine target tumour(s) location and size and percutaneous or CT-guided fine needle biopsy to confirm the nature of the lesion. Abominal US or CT were used to search for distant metastases. All patients had solitary primary lung neoplasms without distant metastatic disease. In all cases the disease was unilateral and as such treated during single session. One patient had larger (3 x 5 cm) tumour with central necrosis while the rest were smaller, up to 3 cm in diameter, and solid.

Figure 1. Radiofrequency generator with multiple temperature displays and impedance and power monitoring.

In case of patients with history of diffuse lung disease or lung surgery lung spirometry is needed, since it is known that the tolerance is good in patients with a FEV1 of more that 1 litre but transitory respiratory insufficiency developed in about one third of patients with a FEV1 less than 1 litre.

We used general anaesthesia in 4 cases and conscious sedation in one. The first provides higher feasibility while with latter

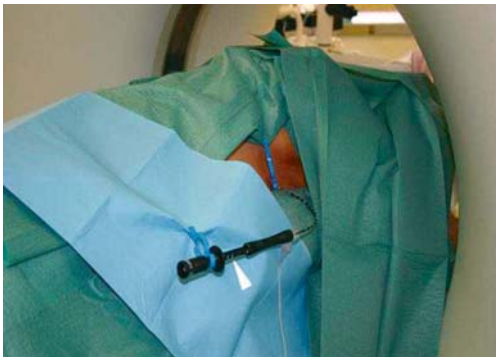

Figure 2. Radiofrequency ablation procedure in patient with NSLC of the left lung. The flexible part of expandable needle is outside the patient while the rigid part is already placed in patient's lung. On the handle of the electrode there are clearly seen the markings (arrow), which indicate the amount of electrode array deployment from the trocar.

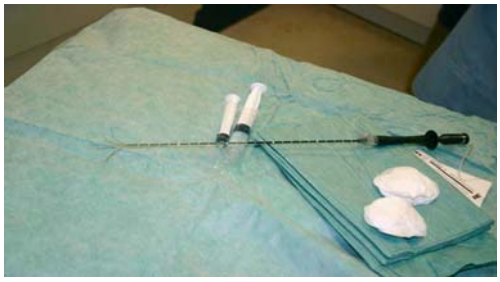

Figure 3. Radiofrequency ablation device. 15-gauge, 9-hook expandable electrode needle (StarBurst XL, RITA Medical Systems).

patient suffered from periprocedural pain and the treatment needed to be interrupted twice due to pain. Duration of the procedure was 1-3 hours, mean duration was 1.5 hour.

We used a 150 W generator (Figure 1) and 15-gauge ablation needles. The ablation procedure was CT-guided (Figure 2) and handled with 9-hook expandable electrode needle (StarBurst XL, RITA Medical Systems) which was flexible and stiff (Figure 3). They enabled direct temperature measurement throughout the tissue to prevent any electrode in multi-tined configuration from exceeding 110^0 C.

The radiofrequency generator had multiple temperature displays as well as impedance and power monitoring. The generator was programmed on the "average temperature" mode and the target temperature was set at 90^0. Ablation protocols, appropriate for lungs, were used, since lung parenchyma is different from e.g. liver in terms of energy deposition, electrical conductivity, heat diffusion and heat convection. The ablation procedure was terminated by coagulating the needle track to prevent tumour cell dissemination along the needle path.

After completion of the procedure a single expiratory scan is obtained throughout the thorax to detect pneumothorax and other possible complications (parenchymal changes, haemorrhage, pleural effusion). We put the patient into the needle

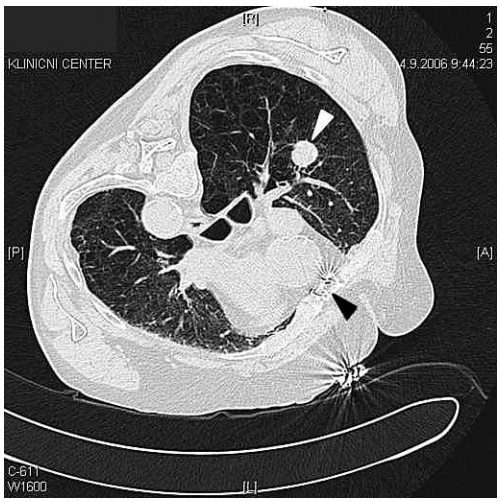

Figure 4a. Lung tumour treated with radiofrequency ablation. Pre-treatment CT shows the focal mass of about 2 cm in diameter in right upper lobe (white arrow). In the parenchyma there are numerous larger and smaller emphysematic bullae – this patient was not a surgical candidate due to severe emphysema, COPD and cardiac condition – note artefacts after sternotomy for CABG (black arrow) and a cardiac pacemaker.

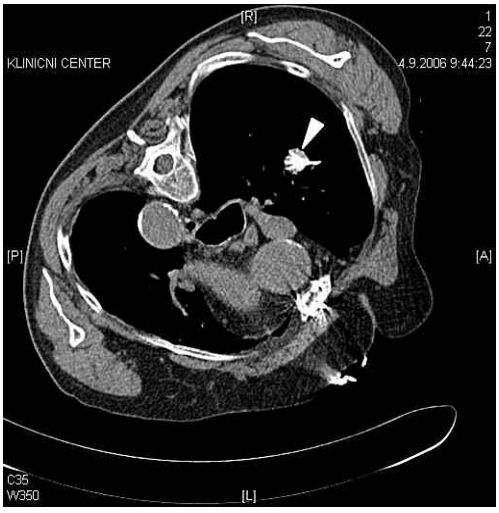

Figure 4b. Lung tumour treated with radiofrequency ablation. CT obtained after electrode placement confirm proper deployment (arrow).

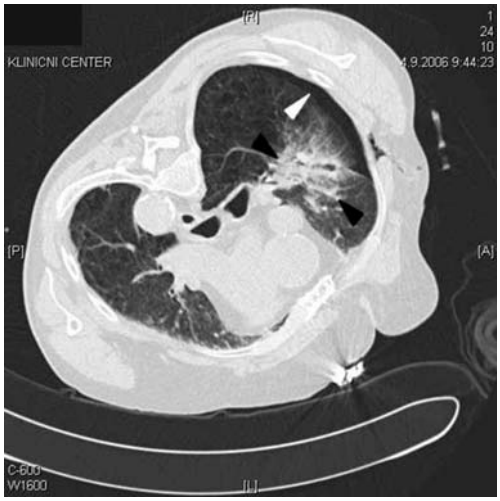

Figure 4c. Lung tumour treated with radiofrequency ablation. CT after completed ablation procedure shows ground glass density area (between black arrows) encompassing the native tumour as well as a safety margin of surrounding lung parenchyma. In addition, a small asyptomatic pneumothorax (white arrow) was detected at the end of procedure.

site dependent position which helps reduce air leak and post-procedural pneumothorax and possibly prevents transbronchial spread of induced alveolar haemorrhage.

There were no major procedure-related complication in our patients, in general the procedure was well tolerated. Pneumothorax requiring catheter drainage occurred in only one case. Productive cough with brown sputum lasting about one week was observed in one patient (Figures 4a, 4b, 4c).

All patients received antibioprophylaxis with broad spectrum antibiotic administered intravenously immediately before ablation. Antibiotics were given orally after 24 hors and prolonged over 7 days.

Follow up examinations are usually performed at month 1, 3 and 6 after the procedure and at 3-month or 6-month intervals thereafter. However the compliance of the patients was low. One of our patient had 6 month disease free interval while in second we observed tumour recurrence at month 9 follow up. The rest were lost to follow up.

Conclusions

RFA is a new, minimally invasive procedure that shows promise for the treatment of primary and secondary lung cancer. Results of recent clinical studies have shown that it can provide effective and reproducible tumour destruction with acceptable morbidity but no survival benefit associated with the use of RFA of lung malignancies has been demonstrated so far.

Owing to small number of treated cases and short follow-up period, no definite conclusion concerning the potential clinical role can currently be drawn. For this reason additional clinical trials are required to further evaluate the place of the method in the management of primary tumours and metastases in lung, either alone or with respect to additional chemotherapy or radiotherapy.

Nevertheless, with continued improvement in technology and increasing clinical experience RFA could represent a viable alternate or complementary treatment for patients with NSCLC or lung metastases who are not candidates for surgical resection.

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Paratesticular adenocarcinoma: unusual presentation of metastasis of pancreatic cancer

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Background. *Metastatic paratesticular adenocarcinoma from the pancreatic cancer is very rare. To our knowledge, there are less than 20 cases published in the literature.*

Case report. *We experienced a case of paratesticular adenocarcinoma from the primary pancreatic cancer. A 42-year-old man was presented with locoregionally advanced carcinoma of the tail of the pancreas with intraoperatively found liver metastases and with a tumour in the right hemi-scrotum. Ultrasound of the scrotum revealed a paratesticular tumour. A fine needle aspiration biopsy (FNAB) confirmed a poorly differentiated adenocarcinoma and it was in concordance with the diagnosis of the primary tumour. The patient started treatment with chemotherapy with gemcitabine. Unfortunately, he progressed one month later and the treatment was discontinued.*

Conclusions. *Outcome in the adenocarcinoma of the pancreas is dismal. The only possible treatment option for metastatic disease is systemic therapy but the results are disappointing, as in the present case.*

Key words: pancreatic neoplasms; neoplasms metastasis; testicular neoplasms - secondary

Introduction

Pancreatic cancer can be silent for a long time before it manifests with features related to local and distant spread. Paratesticular metastases of pancreatic cancer are unusual tumours. Generally, paratesticular tumours are rare. Primary malignant tumours and metastatic tumours account for 32.9% of all tumours and 6-8% of malignant tumours of paratesticular tissue, respectively. In 47.6% of the cases, the metastases and the primary tumours are found simultaneously. Uncommonly, in 9.5% they are the first sign of occult cancer. The most common primary sites of metastasis of the paratesticular tissue are prostate, kidney, gastrointestinal tract, lung and breast cancer.[1,2]. We report a case of simultaneous metastatic paratesticular adenocarcinoma originating in the tail of the pancreas.

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Case presentation and management

A 42-year-old man was presented to abdominal surgeon with recurrent vague upper abdominal discomfort lasting for few months and without significant weight loss. His past history was not remarkable. Abdominal and endoscopic ultrasound examinations

revealed a suspicious cystic and nonhomogeneous lesion in the tail of the pancreas. Chest X-ray was negative for metastasis. The abdominal CT scan confirmed a 2 cm cystic lesion in the tail of the pancreas. The serum tumour marker antigens Ca 19-9 and CEA were elevated, 78 U/ml and 2.6 ng/ml, respectively. Explorative laparatomy was done and locoregionally inoperable tumour of the pancreas with multiple liver metasteases was found. Histologically, moderately differentiated adenocarcinoma from the pancreas and the liver was confirmed.

Afterwards, the patient was presented to the medical oncologist and he complained of palpable tumour mass in the right hemi-scrotum. On examination a painless, hard and irregular 2x2 cm large swelling was identified. Ultrasound revealed a paratesticular tumour. A fine needle aspiration biopsy (FNAB) confirmed a poorly differentiated adenocarcinoma.

Tumour marker antigens Ca 19-9 and CEA were further elevated, 296 U/ml and 15.4 ng/ml, respectively. Based on these findings, the patient was diagnosed as having a metastatic paratesticular adenocarcinoma originating from pancreatic carcinoma with liver metasteses.

He started treatment with chemotherapy with gemcitabine. Unfortunately, he progressed one month later and the treatment was discontinued.

Discussion

Metastatic paratesticular adenocarcinoma from the pancreatic cancer is very rare. To our knowledge, there are less than 20 cases published in the literature. In most cases the primary tumour was located in the body or the tail of the pancreas what is in concordance with the present case.[3-6]

Results from the 154 consecutive autopsies of the patients with pancreatic adenocarcinoma revealed that carcinomas of the body and/or tail of the pancreas were more frequent characterized by transperitoneal and hematogenous dissemination than carcinomas of the head of the pancreas.[7] Kamisawa *et al* have sugested a mechanisem of unusual pattern of spread due to hepatofugal portosystemic shunting induced by splenic vein obstruction, retrograde lymphatic infiltration or even aggressive tumour characteristics.[8] In the present case, we postulate a hematogenous route of dissemination to the paratesticular tissue because of the presence of liver metastases without any metastatic lymph nodes.

Outcome in the adenocarcinoma of the pancreas is dismal with a five-year survival rate of 4%.[9] The only possible treatment option for metastatic disease is systemic therapy but the results are disappointing, as in the present case.

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Analytical investigation of properties of the iso-NTCP envelope

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Background. *A property of the integral dose-volume histogram (DVH) space is analytically investigated in this work. A curve called an α-iso-NTCP (normal tissue complication probability) envelope is constructed by connecting points belonging to step-like integral DVHs, each corresponding to homogeneous partial organ irradiation of a relative volume v_k to dose D_k such that the resulting NTCP has, in all cases, a particular value α. The two subspaces into which the envelope divides the DVH space are analytically explored in terms of the equivalent uniform doses (EUDs) corresponding to the different DVHs. It is theoretically proven that any DVH, other than the step-like DVH, passing through a point (D_k, v_k) from the α-iso-NTCP envelope, will result in an NTCP > α.*

Conclusions. *Thus, it is proven that any DVH that at least partially lies above the envelope results in an NTCP > α. For some of the DVHs lying under the envelope, e.g. those that are tangential to the envelope, it is also true that the resulting NTCP > α. However, it was numerically demonstrated elsewhere that there exist DVHs lying entirely in the lower subspace that result in an NTCP < α. Therefore, one can conclude that since there is a chance that a DVH lying under the α-iso-NTCP envelope will result in NTCP < α, it would be preferable in the treatment optimization process to seek solutions for DVHs lying entirely under an iso-NTCP envelope and avoid solutions that have DVHs above an iso-NTCP envelope.*

Key words: dose – response relationship, radiation; NTCP, iso-effect, DVH

Introduction

Recently we proposed that the DVH averaged from those resulting in a certain normal tissue complication probability (NTCP) can be used as a source of dose-volume constraints for inverse planning.[1,2] Constraint points were estimated for a number of organs using two NTCP models – the Lyman model[3] with the parameters of Burman *et al*.[4] and the critical volume population model[5] with the parameters of Stavrev *et al*.[6] We also reported an observed property of the integral dose-volume histogram (DVH) space.[1,2] In those reports we constructed a curve, which we called an

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α-iso-NTCP envelope, by connecting points belonging to step-like integral DVHs. Each of these DVHs corresponded to homogeneous partial organ irradiation of a relative volume v_k to dose D_k such that, for each DVH, the resulting NTCP had a particular value α.

We numerically demonstrated that any DVH passing through a point (D_k, v_k) from the α-iso-NTCP envelope, i.e., any DVH that tangents or crosses the envelope, will result in an $NTCP \geq \alpha$. It should be emphasized that the equality is valid only for the step-like DVH that corresponds to the homogeneous partial organ irradiation of v_k to D_k. In our present report, we prove, analytically, this property of the α-iso-NTCP envelope for the three most commonly used NTCP models – the Lyman model, the individual critical volume model and the population critical volume model.

Proof for the Lyman model

For our purposes, a normalized integral DVH is defined as a monotonically decreasing function characterized by the set of points D_i, v_i: i = 1, ..., N such that $v_1 = 1$, $v_{N+1} = 0$, $v_{i+1} < v_i$, $D_i < D_{i+1}$..

We begin this proof for the Lyman[3] NTCP model:

$$[1] \quad NTCP = \Phi\left(\frac{EUD - D_{50}}{mD_{50}}\right);\ \Phi(x) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{x}\exp\left(\frac{-t^2}{2}\right)dt = \frac{1}{2}\left[1 + erf\left(\frac{x}{\sqrt{2}}\right)\right],$$

where m and D_{50} are model parameters, and *EUD* is the equivalent uniform dose, which will be defined later. It is clear from Eq. [1] that NTCP is a monotonically increasing function of *EUD*. Thus, for two arbitrary *EUD*s, if $EUD_1 > EUD_2$, then it follows that $NTCP(EUD_1) > NTCP(EUD_2)$.

Consider an arbitrary integral DVH, with points (D_i, v_i : i = 1,...,N), that passes through the point (D_k, v_k) on the α-iso-NTCP envelope (see Figure 1). The EUD of this arbitrary DVH will be referred to as *EUD*. Now consider a step-like DVH that also passes through the same point. This step-like DVH has an NTCP of α. If we call the EUD of this DVH EUD_α, then we may write that $NTCP(EUD_\alpha) = \alpha$. According to our observation,[2] the NTCP of the arbitrary DVH that passes through a point on the α-iso-NTCP envelope will be greater than α:

$$[2a] \quad NTCP\left(EUD\right) > NTCP\left(EUD_\alpha\right) = \alpha\,.$$

Because of the monotonic nature of NTCP as a function of *EUD*, this statement is true, if and only if,

$$[2b] \quad EUD > EUD_\alpha\ .$$

Therefore, if we can show that $EUD > EUD_\alpha$, then Eq. [2a] is also true.

To calculate *EUD*, the integral DVHs must be converted into differential DVHs. In the case of homogeneous partial organ irradiation of volume v_k to a dose D_k, the integral and the differential DVHs are determined solely by the pair (v_k, D_k). For any other type of irradiation, the corresponding differential DVH is given by the following set of points: ($v_i - v_{i+1}$, D_i). One of the commonly accepted forms of *EUD* is the one given by the generalized mean dose (*GMD*):[7-9]

[3] $$EUD = GMD = \left(\sum_i (v_i - v_{i+1}) D_i^{1/n} \right)^n ,$$

where n is a volume parameter. For the case of partial organ irradiation of the volume v_k to dose D_k, Eq. [3] simplifies to:

[4] $$EUD_\alpha = \left(v_k D_k^{1/n} \right)^n = v_k^{\,n} D_k .$$

For the arbitrary DVH passing through point (D_k, v_k), the *EUD* may be written as:

[5] $$\begin{aligned} EUD &= \left(\sum_{i=1}^{N} (v_i - v_{i+1}) D_i^{1/n} \right)^n \\ &= \left(\sum_{i=1}^{k-1} (v_i - v_{i+1}) D_i^{1/n} + (v_k - v_{k+1}) D_k^{1/n} + \sum_{i=k+1}^{N} (v_i - v_{i+1}) D_i^{1/n} \right)^n . \end{aligned}$$

To prove Eq. [2b], we have to prove, from Eqs. [4] and [5], that the following inequality is valid:

[6] $$EUD_\alpha < EUD$$
$$\Rightarrow \left(v_k D_k^{1/n} \right)^n < \left(\sum_{i=1}^{k-1} (v_i - v_{i+1}) D_i^{1/n} + (v_k - v_{k+1}) D_k^{1/n} + \sum_{i=k+1}^{N} (v_i - v_{i+1}) D_i^{1/n} \right)^n .$$

Taking each side of Eq. [6] to the power of $1/\boldsymbol{n}$, we obtain:

[7] $$v_k D_k^{1/n} < \sum_{i=1}^{k-1} (v_i - v_{i+1}) D_i^{1/n} + (v_k - v_{k+1}) D_k^{1/n} + \sum_{i=k+1}^{N} (v_i - v_{i+1}) D_i^{1/n} ,$$

which can then be written as:

[8] $$v_{k+1} D_k^{1/n} < \sum_{i=1}^{k-1} (v_i - v_{i+1}) D_i^{1/n} + \sum_{i=k+1}^{N} (v_i - v_{i+1}) D_i^{1/n} .$$

We now proceed by proving that Eq. [8] is true.
First, consider the term $v_{k+1} D_k^{1/n}$ in Eq. [8]. It may be re-written as:

[9] $$\begin{aligned} v_{k+1} D_k^{1/n} &= (v_{k+1} - v_{k+2}) D_k^{1/n} + (v_{k+2} - v_{k+3}) D_k^{1/n} + \ldots + (v_N - v_{N+1}) D_k^{1/n} \\ &= \sum_{i=k+1}^{N} (v_i - v_{i+1}) D_k^{1/n} , \end{aligned}$$

where, by definition, $v_{N+1} = 0$.
We can expand the second sum in Eq. [8]:

[10] $$\sum_{i=k+1}^{N} (v_i - v_{i+1}) D_i^{1/n} = (v_{k+1} - v_{k+2}) D_{k+1}^{1/n} + (v_{k+2} - v_{k+3}) D_{k+2}^{1/n} + \ldots + (v_N - v_{N+1}) D_N^{1/n} .$$

According to our definition of the integral DVH, $D_i < D_{i+1}$ for all $i = 1 \ldots N$. Therefore, each term of the sum in Eq. [9] is less than the corresponding term in Eq. [10], and we can write:

[11] $$v_{k+1}D_k^{1/n} < \sum_{i=k+1}^{N}(v_i - v_{i+1})D_i^{1/n}\ .$$

Because of our definition of an integral DVH, $v_i > v_{i+1}$ for all $i = 1...N$, the first sum in Eq. [8] is greater than zero:

[12] $$\sum_{i=1}^{k-1}(v_i - v_{i+1})D_i^{1/n} > 0\,.$$

From Eqs. [11] and [12], the following is true:

[13] $$v_{k+1}D_k^{1/n} < \sum_{i=1}^{k-1}(v_i - v_{i+1})D_i^{1/n} + \sum_{i=k+1}^{N}(v_i - v_{i+1})D_i^{1/n}\,,$$

which is identical to Eq. [8]. Thus, we have proven Eq. [8], which is equivalent to Eq. [6], and thus, Eq. [2b]. Therefore, Eq. [2a] is also true, and we have thus mathematically proven the property of the envelope for the Lyman model.

Proof for the critical volume model

The basic property of the α-iso-NTCP envelope will also be proven for the critical volume (CV) NTCP model. The CV model exists in two forms – individual and population models. The individual CV model is given by:

[14] $$NTCP_{ind} = \Phi\left[\frac{\sqrt{N}(\overline{\mu}_d - \mu_{cr})}{\sigma_{\mu_d}}\right],$$

where N is the total number of functional subunits (FSUs) comprising the organ, $\overline{\mu}_d$ is the mean relative damaged volume, σ_{μ_d} is the variance in $\overline{\mu}_d$, and μ_{cr} is the relative critical volume of the organ.[5,10,11]

The population CV model, under the assumption that only the relative critical volume displays inter-patient variability, is given by:

[15] $$NTCP_{pop} = \Phi\left[\frac{-\ln(-\ln\overline{\mu}_d) + \ln(-\ln\overline{\mu}_{cr})}{-\sigma_{\mu_{cr}}/\overline{\mu}_{cr}\ln\overline{\mu}_{cr}}\right],$$

where $\overline{\mu}_{cr}$ is the population mean relative critical volume and $\sigma_{\mu_{cr}}$ is the variance in $\overline{\mu}_{cr}$.[5]

As can be seen in Eqs. [14] and [15], both the individual and the population CV models are monotonically increasing functions of the mean relative damaged volume $\overline{\mu}_d$. This quantity is given by the following sum:

[16] $$\overline{\mu}_d = \sum_i (v_i - v_{i+1})P_{FSU}(D_i),$$

where $P_{FSU}(D_i)$ is the probability that a functional subunit is damaged beyond repair. It, in turn, is given by:

[17] $$P_{FSU}(D_i) = \exp[-N_c\exp(-\alpha_c D_i)],$$

where N_c is the number of cells in an FSU and α_c is the cell radiosensitivity. The quantity $\exp(-\alpha_c D)$ is the probability that a cell survives an irradiation to dose D. Since α_c is a positive quantity, then $\exp(-\alpha_c D)$ is a decreasing function of dose. The term $N_c \exp(-\alpha_c D)$ is the mean number of cells that survive dose D and also decreases as D increases. Equation [17] is the probability that a functional subunit is damaged beyond repair, which is equivalent to the probability that all cells in the subunit are destroyed. Therefore, $\exp\left(-N_c e^{-\alpha_c D}\right)$, which is the probability of zero cell survivals, increases with decreasing mean number of cell survivals, $N_c \exp(-\alpha_c D)$, or increasing dose D.

We now compare the mean relative damaged volume caused by an arbitrary DVH that is tangential to or is crossing the α-iso-NTCP envelope at point (D_k, v_k) with the mean relative damaged volume caused by a step-like DVH given by (D_k, v_k). From Eq. [16], the mean relative damaged volume for the arbitrary DVH passing through the point (D_k, v_k) on the α-iso-NTCP envelope is:

$$\begin{aligned}\bar{\mu}_d &= \sum_{i=1}^{N}(v_i - v_{i+1})P_{FSU}(D_i) \\ &= \sum_{i=1}^{k-1}(v_i - v_{i+1})P_{FSU}(D_i) + (v_k - v_{k+1})P_{FSU}(D_k) + \sum_{i=k+1}^{N}(v_i - v_{i+1})P_{FSU}(D_i)\end{aligned} \quad [18]$$

The mean relative damaged volume caused by partial organ homogeneous irradiation of relative volume v_k to dose D_k will be denoted as $\bar{\mu}_{d,\alpha}$ and is given by:

$$\bar{\mu}_{d,\alpha} = v_k P_{FSU}(D_k). \quad [19]$$

We now compare $\bar{\mu}_d = \sum_{i=1}^{N}(v_i - v_{i+1})P_{FSU}(D_i)$ (Eq. [18]), containing point (D_k, v_k), with $\bar{\mu}_{d,\alpha} = v_k P_{FSU}(D_k)$ (Eq. [19]). Since $P_{FSU}(D)$ is an increasing function of dose, Eqs. [18] and [19] are similar to the *EUD* form of Eq. [3] from the Lyman model. By applying the same process as to the proof of Eq. [6] it can be shown that the following inequality is valid:

$$\bar{\mu}_d = \sum_{i=1}^{N}(v_i - v_{i+1})P_{FSU}(D_i) > \bar{\mu}_{d,\alpha} = v_k P_{FSU}(D_k). \quad [20]$$

Given that NTCP is an increasing function of the mean relative damaged volume, it follows that $NTCP(\bar{\mu}_d) > NTCP(\bar{\mu}_{d,\alpha}) = \alpha$ for DVHs having a common point with the α-iso-NTCP envelope.

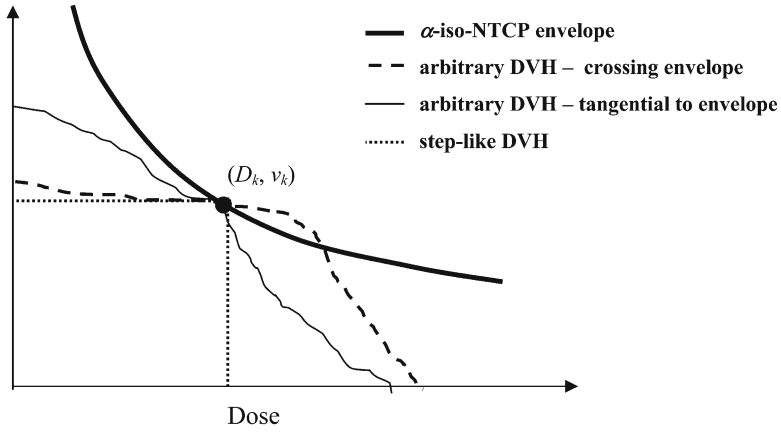

Figure 1. Illustration of an α-iso-NTCP envelope and two arbitrary DVH curves – one that crosses the envelope at the point (D_k, v_k) and one that is tangential to the envelope at the same point. Also shown is a step-like DVH passing through (D_k, v_k) that corresponds to homogeneous partial organ irradiation. The NTCP of the step-like DVH should be equal to α, while the NTCP for both arbitrary DVHs should be greater than α.

Discussion and conclusions

Because we have proven that the discussed property of the α-iso-NTCP envelope applies to three of the most commonly used NTCP models – the Lyman model, the critical volume individual model, and the critical volume population model – there is reason to believe that this property may be model-independent.

The α-iso-NTCP envelope divides the dose-volume space in two sub-spaces. For the sub-space above the envelope, we have analytically proven that all DVH curves with at least one point in this region result in an NTCP > α. For the sub-space under the α-iso-NTCP envelope, it was numerically demonstrated elsewhere[2] that there exist DVH curves that result in an NTCP < α. However, as it is shown above, there do exist other curves, e.g., those that are tangential to the envelope from below, which result in an NTCP > α. Nevertheless, since there is a chance that a DVH lying under the α-iso-NTCP envelope will result in an NTCP less than α, one can conclude that it would be preferable in the treatment optimization process to seek solutions for DVHs lying entirely under an iso-NTCP envelope and avoid those that lie even partially above the envelope.

The physical dose-volume constraint points that we calculated in a previous work[2] were found to be dependent on the NTCP model as well as the parameters used for their determination. The iso-NTCP envelope could be used to estimate the impact of a change of NTCP model and/or parameters on the calculated constraint points for a given organ, since the envelope curve is dependent on both of these quantities. Dawson *et al*.[12] observed that the iso-NTCP curve corresponding to their liver parameters for the Lyman[3] model was shifted considerably to the right in DVH space compared to the iso-NTCP curve corresponding to the Burman *et al*.[4] parameters for the same organ. To estimate how the source of dose-volume constraints (the average of DVHs with a certain NTCP) would change

with a change of NTCP parameter values, one could calculate the iso-NTCP envelope corresponding to these new parameters. The distance in DVH space between the old and new iso-NTCP curves is approximately the same as the distance between the old and new averaged DVHs. The position of the new dose-volume constraints could then be estimated by shifting them in DVH space by an amount equal to the distance between the two iso-NTCP curves. In this way, one can avoid having to perform an extensive recalculation of the dose-volume constraints.

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Implementing of the offline setup correction protocol in pelvic radiotherapy: safety margins and number of images

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Background. *Patient positioning errors in pelvic radiotherapy at Department of Oncology and Radiotherapy in Osijek are explored in order to establish the offline setup correction protocol and determine the safety margins.*

Material and methods. *Film portal imaging is used during the whole treatment in order to find patient positioning errors. Eleven patients are included in the study and 420 images are analyzed. Setup errors are found by measuring distances between the center of the field and bony landmarks. Systematic and random errors are analyzed.*

Results. *Safety margins that should be employed at our department are 11 mm, 13 mm and 14 mm in mediolateral, craniocaudal and anteroposterior direction, respectively. Time trend is found only in an aged, obese patient with a hip problem. No action level offline setup protocol was employed by taking and averaging first four images in mediolateral and craniocaudal and 5 images in anteroposterior direction.*

Conclusions. *Since time trend is found only in a patient who was hard to position because of his age, obesity and the hip problem, we decided that such patients are to be positioned without a bellyboard and in supine position. Time trends are not found in all of the other patients so we employed the offline setup error protocol by averaging setup errors from the first few consecutive images. Safety margins that will ensure 90 % probability of depositing at least 95 % of the prescribed dose in the target are calculated. Safety margins and number of images that should be taken showed that the most inaccurate positioning was in the anteroposterior direction.*

Key words: pelvic neoplasms – radiotherapy; radiotherapy dosage - methods

Introduction

The pelvic radiotherapy is often indicated for patients with cervical, uterine and rectum carcinomas. One of the problems during the radiotherapy is that total doses of 40-50 Gy to the whole pelvis can give rise to early or late complications of the

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small bowel.[1-3] This is important especially because a long term survival is very often expected among those patients. The useful methods to reduce the irradiated small bowel volume are: three-field box technique, individualized normal tissue blocks, physically moved healthy tissues from the treatment field, bladder distention and prone position of the patient.[1,3,4]

The use of open tabletop devices or the bellyboard, where patients are in the prone position, has been described previously.[2-6] Positioning of patients with gynecologic tumours for radiotherapy has proven to be relatively inaccurate.[7] Misspositioning of the patient can give rise to complications or influence the results of the treatment.[8] With now commonly available electronic portal imaging devices (EPID) it is possible to correct systematic and random field placement errors on a daily basis.[7,9] The systematic error (SE) is defined as the mean displacement of the treatment isocenter from the planning isocenter,[10] and the random error (RE) as a deviation of the each individual position from the mean position of the patient. The systematic error is the main factor when considering the margin size to account for setup uncertainties.[10-12] When correcting the patient position, only the systematic component of the setup error must be corrected.[8,11,12]

The purpose of this study was to investigate the accuracy of daily patient positioning in our department in the bellyboard pelvis radiotherapy. Since our department is not equipped with EPID, we chose to implement strategy called no action level (NAL) protocol for reducing patient setup errors.[13] It means that position of the patient will be measured during the first *N* treatment fractions, and an unconditional correction of the setup position will be done once at the $(N + 1)^{th}$ fraction. In this paper we investigated how many images (N) are needed to be performed, before deciding that the error is systematic and that repositioning of the patient should be done. Too low number of images taken means that random errors (a mistake in positioning of the patient, a wrong field size, a wrong distance between the film and the patient, wrong readings of parameters on the film, wrong calculation of deviations, moving the patient during the treatment or some other reason) can cause an action and too high number of images would prolong the treatment time unnecessarily.

Materials and methods

Six patients with cancer of corporis uteri, four patients with cancer of cervicis uteri and one patient with rectal carcinoma were included in this study. The median age of the 11 patients was 64 years (47-76 years). All patients were treated using the three-field box technique at the linear accelerator Siemens Mevatron MD2. Patients are simulated at the conventional simulator SIMVIEW 3000. Shielding was done with conformal Cerrobend blocks made individually for each patient. Seven patients received the total dose of 50 Gy in 25 daily fractions, two patients received 40 Gy in 20 daily fractions followed by brachytherapy, and the patient with rectal carcinoma received the total dose of 45 Gy in 25 daily fractions of 1.8 Gy + boost 3 x 1.8 Gy. One patient was predicted to receive 50 Gy in 25 daily fractions, but she died after the 21^{st} fraction.

All patients were simulated in the prone position using our custom-made bellyboard. We constructed two identical bellyboards (one for the simulator, and the other for the linear accelerator) with a thickness of 8 cm, overall size 56 cm x 104 cm and opening 28.5 cm x 30.5 cm. Bellyboards do not have small caudal aperture for the pubic bone and they are used in the combination with the leg support.

To reduce the volume of the small bowel within the treatment fields, patients were set in the way that the caudal border of the bellyboard opening is at the lower end of the sacroiliac joints. It means that the symphysis is out of the bellyboard opening for at least 5 cm. The isocentar position was visualized using laser equipment and marked on patients' skin by markers. To enable the reproducible position of the patient, the opening of the bellyboard was marked by two lines on the skin.

During the simulation procedure two sets of simulation films were obtained. One film was taken for the anteroposterior field and the other for one of the lateral fields.

During the treatment session, for the verification of positioning of the patient, we were using the Kodak EC-L film system. The setup errors in patient positioning are defined by the deviations from the measured distance between the centre of the field and visible bony anatomical landmarks[8,10] along the craniocaudal (CC), anteroposterior (AP), and lateral (ML) axis. Displacements of the ML and CC direction were measured from the anteroposterior field, and AP direction from the lateral field. The ML displacement was defined as a distance from the isocentar to the pelvic rim; the CC as a distance to the obturator point and the AP as a distance to the symphysis (Figure 1). We tried to measure the CC setup error also from the lateral field, but the results showed big uncertainty so we decided to omit those measurements. All deviations in the caudal direction, to the left and dorsum were marked as positive, and the deviations in the cranial direction, to the right and anterior were marked as negative.

The image acquisition was completed in 80.4 %. In total, 420 images were acquired for the analysis.

At the beginning of the analysis the safety margins for the setup inaccuracy were 15 mm in all directions.

At first, we examined the presence of time trends in any direction. The time trend is defined as drift of the field displacement in a one, systematic way during the treatment. If the time trend exists, the correction of the systematic error may not be accurate.[11] Time trends were investigated using a linear regression approach and the existence of time trends was considered if the slope was greater than 4 mm during the treatment. This limit was used to avoid

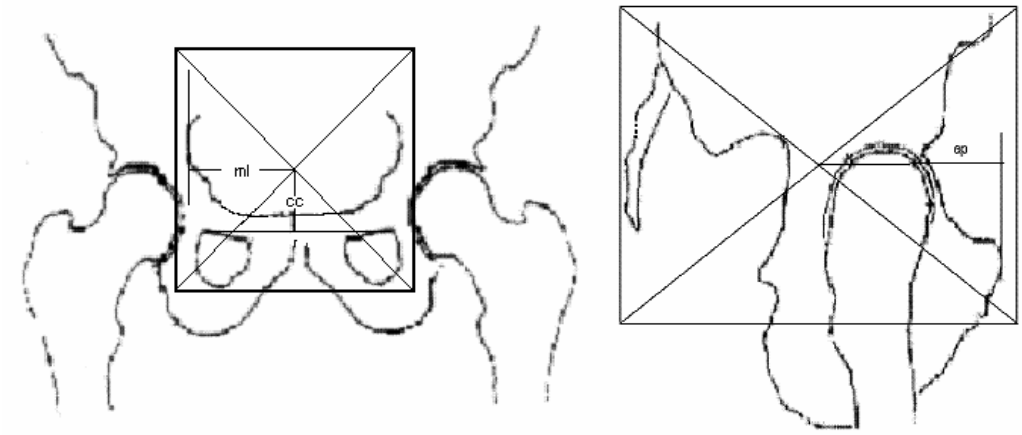

Figure 1. Determination of ML, CC and AP displacements, according to the pelvic anatomic structures, on anteroposterior and lateral projections.

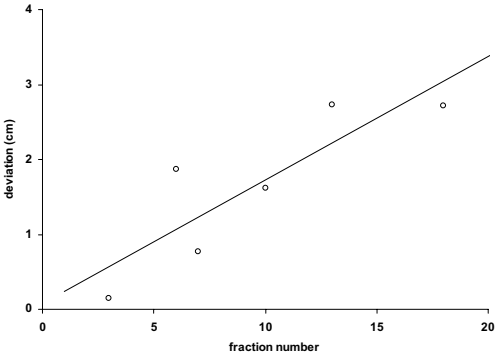

Figure 2. Presence of the time trend in the AP direction in one patient. Those data were excluded from the study.

too many patients to be excluded from the study.

The systematic error (SE) is defined as the mean displacement of the treatment isocentar from the planning isocentar, and the random error (RE) as a deviation of each individual measurement from the mean value.

The systematic error is the main factor when considering the margin size for setup uncertainties.[10-12] The systematic error for the entire group (SEeg) was defined as the arithmetic mean of all patients' systematic errors. The random deviation of the patients' SE from SEeg was estimated by 1 SD (SDse). The random deviation of all individual RE around the mean patients' RE was also estimated by 1 SD (SDre). Thus, systematic and random setup errors were calculated for the entire group of patients and the safety margin size was formed according to the sizes of those deviations.

The margin size is the one that ensures the 90% probability of depositing at least 95% dose in the target.[12,14] These values are a sensible compromise between the risk of underdosing the target volume and of excessive overdosing the surrounding healthy tissue[14]. The calculation of the safety margins, H, is done by using the following expression.[12]

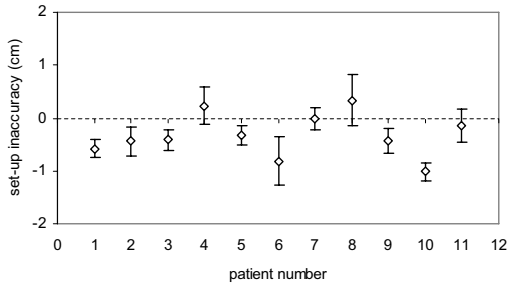

Figure 3. Mean translations and their SD for each patient in the craniocaudal direction.

$$H = 2.5\ SDse + 0.7\ SDre.$$

Because these margins do not include rotational errors, they should be used as the lower limit for safe radiotherapy.[12]

We chose to implement strategy called no action level (NAL) protocol[13] for reducing patient setup errors. It means that the position of the patient will be measured during the first N treatment fractions, and an unconditional correction of the setup position will be done once at the $(N + 1)^{th}$ fraction. We investigated when to do the correction of systematic positioning error by evaluating setup errors during the whole treatment session.

Results

At the beginning, we checked for the presence of time trends for all patients and directions. Data were fitted as linear, and the slope of the curve is tested to be less than 4 mm during the whole treatment. For the ML and CC directions there was no evidence of time trends. In the AP direction, a time trend existed in an aged, obese patient with a hip problem (Figure 2).

Since that patient was very difficult to position, we excluded his AP data from our analysis.

Figures 3, 4 and 5 show the mean translations and their SDs for each patient in all three directions.

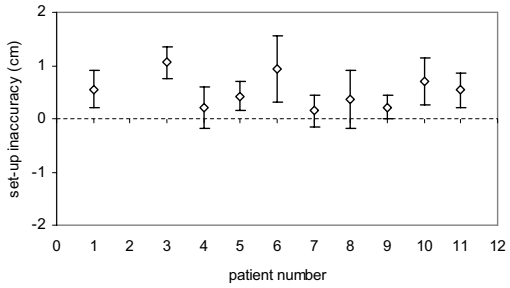

Figure 4. Mean translations and their SD for each patient in the anteroposterior direction.

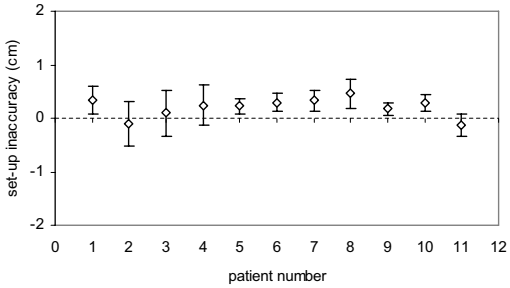

Figure 5. Mean translations and their SD for each patient in the lateral direction.

The ranges of errors along the lateral, craniocaudal and anteroposterior are shown in the Table 1 together with ranges of the systematic and random components of the errors. The systematic and random errors represented by 1 SD are also shown in the Table 1 together with the safety margins (SMs) calculated as explained before.

The calculated SMs are the lower limits for the treatment planning and we will use rounded values in upper directions. Besides, we neglected the existence of the time trends less than 4 mm in all directions, so this value was added to the SM sizes. Finally SMs are 11 mm, 13 mm and 14 mm in ML, CC and AP directions respectively.

To avoid random errors to cause repositioning of the patient, we investigated how many images (fractions) should be averaged to determine whether the error is random or systematic. In a direction, the sum of all patients' REs around SE is zero. We determined the fraction number (N) where the random error averaged over 1^{th}, 2^{nd}...N^{th} fraction is a good approximation of the zero value. For the j^{th} patient the array $n_{i,j}$ was formed by averaging all deviations of preceded fractions for a fraction i. Since REs are equally dispersed around the zero value, all patients' arrays will fast converge to the zero value. A characteristic curve for a patient is shown in Figure 6.

At a fraction i = N, the array value can be approximated as it reached the zero value. It means that one can decide how many fractions (N) should be averaged for a good approximation of the zero value. In this way, for the j^{th} patient, we approximated the systematic error at the end of the treatment

Table 1. The range of the setup errors, and systematic and random components of the setup errors, standard deviations of systematic errors (SDse), standard deviations of random errors (SDre) and calculated safety margins (SM) of 11 patients included in the study

Deviation-direction	Lateral	Craniocaudal	Anteroposterior
Setup error-range (mm)	-14.7 to +18	-30.3 to +15.4	-19.2 to +30.5
Systematic error (mm)	-1.1 to +8.9	-11.7 to +2.4	-1.7 to +12.1
Random error (mm)	-9.1 to 16.9	-31.1 to 18.2	-22.1 to 17.6
SDse (mm)	1.9	2.6	2.5
SDre (mm)	2.7	3.3	4.1
SM (mm)	6.6	8.8	9.2

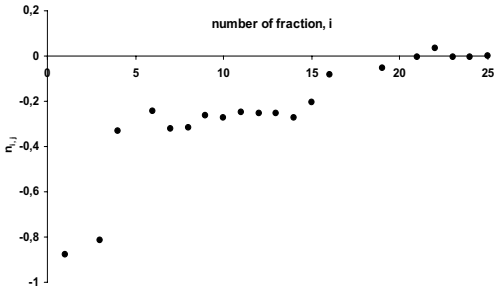

Figure 6. Array of averaged REs around SE in AP direction for a patient. After all the REs are averaged, the array ends at zero value.

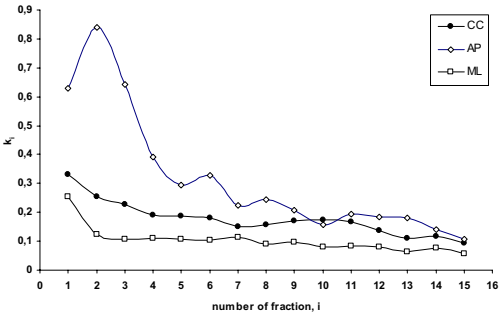

Figure 7. Averaged random deviations in CC, AP and ML directions for all of the patients during the treatment. It can be seen that random deviations are close to zero after a certain number of fractions in all of the directions and after that the slope of the curve is very mild.

(SE_j), with systematic and random error at the chosen fraction. In order to be able to make this decision for a number of patients (M), all absolute values of $n_{i,j}$ are averaged for all of the patients. Thus, we formed the new array $k_i = \frac{1}{M}\sum_j^M |n_{i,j}|$ of average absolute REs at a fraction i for all fractions. Again, the array converges to the zero value and one can decide how many fractions should be averaged for a good approximation of the zero value. In this way a number of fractions, i = N, for a group of patients is found, which can be averaged to represent a good approximation of the systematic error at the end of the treatment. The calculation is done in all of the directions. Arrays of k_i values are shown in Figure 7.

According to the Figure 7, numbers of images that must be taken for a patient were 3 in the ML, 4 in the CC and 5 in the AP direction. Since deviations in ML and CC directions are measured from the same image we decided to average four images in the ML direction as well.

Discussion

Accuracy data of daily patient positioning at our department are shown in Figures 3, 4 and 5. The setup errors of individual measurements ranged up to 18 mm, 30.3 mm, 30.5 mm in ML, CC and AP directions, respectively. Out of systematic and random setup errors the safety margins were calculated. They were 11 mm in the ML, 13 mm in the CC and 14 mm in the AP direction. To find out how many images must be taken to decide that the setup error is systematic, the average REs of all patients during the treatment were compared. It is possible to decide when this error is close enough to zero for a group of the patients, so at that fraction, the error can be considered systematic (Figure 7). Numbers of images that must be taken are 4 in ML and CC directions and 5 in the AP direction. The group of the patients included in the study is assumed to be representative for treatments done at our department.

Only one patient showed time trend in one direction to be greater than 4 mm through the treatment (Figure 2) and those data were excluded from the study. That patient was elderly, obese and had a hip problem. We decided that the patients difficult to position by bellyboard would be planed in the supine position.

The problem that occurred during this study is non-existence of "pubic aperture"

in our bellyboard device. This makes the position of the patient uncomfortable and they tend to move. Our measurements showed that there are no preferable directions. For future treatments the "pubic aperture" is improvised in our bellyboard.

Systematic and random errors reported are comparable to the results published in the referenced studies of gynecological patients.[3,15] The safety margins extracted from this study are smaller than the margins employed before and they are on the upper side of the range of other reported results.[14,15] It is important to note that the most of the published results are from advanced institutions and may not indicate variations applicable to an average, busy department.[14]

Although at the beginning all of the SM sizes were equally sized, the study showed that patients are moving mostly in the AP direction, so in that direction the calculated SM was the largest. This can be explained by the specific prone position of a patient and use of a bellyboard device as it was reported before.[14, 15] In order to apply the NAL protocol, a number of fractions for reposition value determination was found. Again, more images must be taken in AP than in CC and ML direction in order to find SE. The use of the NAL protocol means that every patient will be repositioned once during the treatment and we will explore future setup errors in order to compare them to the results of this study.

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report

Basic Clinical Radiobiology Course Ljubljana (Slovenia), 21.-25. May 2006 View from a local participant

As the course took place in Slovenia, I should first of all tell a couple of words about my country and its capital Ljubljana. Slovenia is a small country with only two million people, but it has all that one needs to enjoy life: the sea, mountains, some beautiful lakes and Karst landscapes with a lot of natural caves. Add to this some very good wines and food delights – but you should really find out first hand. Ljubljana is a city of cultural and rich historical heritage. It is similar to other Central European cities. Some compare it to Vienna or Prague, but its particular charm lies in the smallness of this town, with the total population of only around 300.000 people.

The course started on Sunday, the 21st of May with the introduction to radiobiology. In the afternoon, after the coffee break, the participants could attend the tutorials of "basic" or "advanced knowledge" of radiobiology. I suppose people who work in radiotherapy must be modest, since most participants chose the "basic knowledge" group. Even if the group was supposed to be "basic", the discussions were not. During the first day, as well as during the following days, we discussed some very interesting topics like re-radiation, modifiers of late complications, α/β ratio in prostate cancer and whether or not to give the same treatment for the whole course of radiotherapy. We also touched upon the eventual connection between IMRT and secondary tumors. The second day started with a lecture about radiobiology of normal tissues and continued with an explanation of the role of checkpoints in the cells. The next lecture emphasized the importance of proper documenting. The day continued with a presentation of the linear quadratic model, followed by a lecture about hyperfractionation. During the third day, the issues of oxygenation in radiotherapy, of mathematical models and of combination of radiotherapy with chemotherapy were discussed. The following day when the participants were confronted with the problems of using such models in practice, all the enthusiasm about models faded away. It became obvious that, unfortunately, models do not always work well in practice. The next topic on the agenda was biological image-guided radiotherapy, and in the afternoon, the combination of new biological therapies with radiotherapy was presented.

Tuesday was the so called "social day". The participants first took a trip to the beautiful lake of Bled, and in the evening, they were invited to dinner. The atmosphere was excellent, just right to meet other people and make new acquaintances. The participants had a great time – but how could it have been otherwise with such great lecturers and participants. They came from all around the world, from exactly eighteen countries. During the evening two new members of the "radiobiology" team were presented to us, the new lecturer Dr. Susan Short and the new organizer Mrs. Viviane Van Egten.

One of the standard features of such events is the poor quality of the coffee served during the breaks. Surprisingly, during this course, the coffee was really good and one of the lecturers even said that this was the best coffee he had ever had at any course. However, this course will not be remembered because of the coffee, but rather for excellent lectures and teachers. Thanks to them, the course was really good. The participants had the chance to learn a lot and were challenged to use this knowledge in everyday practice. Special thanks go to the course director Professor Van der Kogel for the excellent scientific program. And to all of you, hope to see you next time in Ljubljana.

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Radiol Oncol 2007; 41(1): 1-12.

Računalniško tomografska in magnetno resonančna kolonografija

Vegar-Zubović S, Sefić-Pašić I, Lincender L, Vrcic D, Klancevic M, Delic U

Izhodišča. V razviten svetu je rak debelega črevesa drugi najpogostejši vzrok smrti pri onkoloških bolnikih. Pogosto se razvije iz žleznih kolorektalnih polipov, ki jih najdemo pri 30-50% Američanov, starejših od 50 let. Zato je zgodnje odkrivanje črevesnih polipov in njihova odstranitev učinkovita prevencija črevesnega raka. Do sedaj pa nismo poznali metode odkrivanja črevesnih polipov, ki bi imela visoko senzitivnost in specifičnost, ki bi bila hkrati poceni ter ne bi obremenjevala bolnika. Endoskopska kolonoskopija omogoča natančno ugotavljanje zelo majhnih sprememb in je skoraj popolnoma nadomestila fluoroskopijo. V novejšem času za ugotavljanje kolorektalnih polipov vedno v večji meri uporabljamo slikovne preiskave z magnetno resonanco (MRI) in računalniško tomografijo (CT.

Zaključki. CT in MR kolonografija sta novi slikovni tehniki pri preiskavi črevesa. Zaradi obetavnih rezultatov pri ugotavljanju polipov, ki so enaki ali večji kot 1 cm, jih v vedno večji meri uporabljamo pri simptomatskih bolnikih.

Radiol Oncol 2007; 41(1): 15-22.

Podaljšana izpostavljenost podgan neletalnim odmerkom mikrocistina-LR povzroči poškodbe DNA v različnih organih

Filipič M, Žegura B, Sedmak B, Horvat-Žnidaršič I, Milutinovič A, Šuput D

Izhodišča. Mikrocistini (MC) so obročasti hepatapeptidi, za katere velja, da so specifični jetrni strupi. So učinkoviti promoterji tumorjev, novejše raziskave pa kažejo, da so tudi genotoksični. V tej raziskavi smo merili poškodovanost DNA limfocitov, jetrnih, ledvičnih (skorje in sredice), pljučnih, vraničnih in možganskih celic samcev podgan Fisher F344, ki so bili en mesec izpostavljene neletalnim odmerkom mikrocistina-YR (MCYR) (vsak drugi dan 10 μg/kg t.m.; i.p).

Metode. Po končani izpostavljenosti smo živali žrtvovali. Limfocite smo izolirali iz krvi, odvzete iz podjezične vene, jetrne celice smo izolirali s perfuzijo s kolagenazo A, celice ostalih organov pa smo izolirali z inkubiranjem drobnih koščkov tkiv s kolagenaso A. Poškodovanost DNA izoliranih celic smo merili z elektroforezo posamezne celice, ki jo imenujemo tudi test komet.

Rezultati. Pri živalih, ki so bile izpostavljene MCYR, smo ob primerjavi s kontrolnimi živalmi ugotovili značilno povečanje % DNA v repih kometov celic možganov (2,5 krat), jeter (2,1 krat), sredice ledvic (1,9 krat), ledvične skorje (1,8 krat) in pljuč (1,7 krat). DNA limfocitov in celic vranice ni bila poškodovana.

Zaključki. Raziskava je pokazala, da podaljšana izpostavljenost neletalnim odmerkom mikrocistinov pri sesalcih lahko povzroči sistemski genotoksični odziv, ki prizadene ne le jetra, ampak tudi druge organe.

Radiol Oncol 2007; 41(1): 23-32.

Ugotavljanje mehanizmov delovanja rituksimaba in klinični rezultati pri visoko rizičnih bolnikih z agresivnimi CD20+ limfomi

Jezeršek Novaković B, Kotnik V, Južnič Šetina T, Vovk M, Novaković S

Izhodišča. Rituksimab se je izkazal kot učinkovito zdravilo pri zdravljenju bolnikov z indolentnimi in agresivnimi CD20 pozitivnimi B celičnimi limfomi, vendar natančnih mehanizmov njegovega delovanja *in vivo* še ne poznamo v celoti. To raziskavo smo zato usmerili v potrjevanje domnevnih glavnih mehanizmov delovanja rituksimaba in hkrati želeli oceniti učinkovitost prvega zdravljenja visoko rizičnih bolnikov z agresivnimi CD20 limfomi s kemoimunoterapijo.

Bolniki, materiali in metode. Delovanje rituksimaba smo preučevali *in vitro* na Raji in SU-DHL-4 celicah s testom pomnoževanja celic in s pretočno citometrijo. V kliničnem delu raziskave smo 20 visoko rizičnih bolnikov z agresivnimi CD20 limfomi zdravili s kemoimunoterapijo R-CHOP.

Rezultati. V *in vitro* pogojih smo ugotavljali le s komplementom posredovano citotoksično delovanje rituksimaba. Pri tem pa nismo dokazali niti direktnega apoptotičnega delovanja niti s protitelesi posredovane celične citotoksičnosti verjetno zaradi prenizke koncentracije rituksimaba oziroma neustreznega razmerja med citotoksičnimi limfociti in tumorskimi celicami. Klinični rezultati zdravljenja z R-CHOP so bili odlični, saj smo popolno remisijo ob koncu primarnega zdravljenja dosegli pri 90% visoko rizičnih bolnikov. Poleg tega se pri 80% bolnikov bolezen v medianem času opazovanja 18,5 mesecev ni ponovila.

Zaključki. Glede na naša opažanja je s komplementom posredovana citotoksičnost pomemben mehanizem delovanja rituksimaba *in vitro*. Za direktno sprožitev apoptoze so potrebne višje koncentracije rituksimaba od 20 μg/ml, medtem ko je za učinkovito od protiteles odvisno celično citotoksičnost potrebno razmerje med citotoksičnimi limfociti in tumorskimi celicami, ki je večje od 1:1. Pri bolnikih z visoko rizičnimi agresivnimi CD20 limfomi dodatek rituksimaba k CHOP kemoterapiji pomembno izboljša učinek zdravljenja.

Radiol Oncol 2007; 41(1): 33-8.

Radiofrekvenčna ablacija pljučnih tumorjev – nova oblika zdravljenja pljučnih novotvorb

Kocijančič K, Kocijančič I

Izhodišča. Perkutana radiofrekvenčna ablacija (RFA) je minimalno invazivna tehnika zdravljenja solidnih tumorjev. Preizkušati so jo začeli tudi kot možen postopek zdravljenja pljučnega raka in zasevkov, ker lahko z njo v kontroliranih pogojih dosežemo obsežnejša področja koagulacijske nekroze. Na ta način lahko uspešno zdravimo sorazmerno majhne zločeste spremembe v pljučih. RFA je sprejemljiva zamenjava ali dodatna metoda zdravljenja za bolnike z nedrobnoceličnim pljučnim rakom ali s pljučnimi zasevki drugih rakov, ki jih iz različnih vzrokov ne moremo operirati.

Zaključki. Dosedanje mednarodne klinične raziskave pa tudi začetne izkušnje Inštituta za radiologijo v Kliničnem centru Ljubljana so pokazale, da zdravljenje z RFA bolniki sorazmerno dobro prenašajo in da lahko s to metodo zdravljenja dosežemo popolno nekrozo tkiva v tarčnem volumnu. Najpogostejši zaplet je pneumotoraks (do 40%), pri polovici bolnikov s tem zapletom pa je potrebna torakalna drenaža.

Radiol Oncol 2007; 41(1): 39-40.

Paratestikularni žlezni rak – neobičajna oblika zasevka raka trebušne slinavke

Ocvirk J, Šeruga B

Izhodišča. Metastatski paratestikularni žlezni rak trebušne slinavke je zelo redka oblika bolezni. Po nam dostopnih podatkih je v literaturi do sedaj opisanih manj kot 20 primerov.

Prikaz bolnika. Predstavljamo bolnika z zasevkom primarnega raka repa trebušne slinavke v paratestikularnem tkivu. Pri 42-letnem bolniku z lokalno napredovalim rakom v repu trebušne slinavke smo intraoperativno odkrili jetrne zasevke, sočasno pa tudi tumor v desni polovici mošnje, ki je ultrazvočno pripadal paratestikularnemu tkivu. S tankoigelno aspiracijsko biopsijo (TAB) je bila potrjena citološka diagnoza slabo diferenciiranega žleznega raka, ki je bila skladna z diagnozo primarnega raka v repu trebušne slinavke. Bolnika smo pričeli zdraviti s kemoterapijo z gemcitabinom. Kljub temu smo že po enem mesecu ugotovili napredovanje bolezni in smo sistemsko zdravljenje prekinili.

Zaključki. Pričakovani potek bolezni pri bolnikih z žleznim rakom trebušne slinavke je zelo neugoden. Edino možno zdravljenje pri razširjeni obliki bolezni je sistemska terapija, vendar rezultati zdravljenja niso ohrabrujoči, kot kaže tudi opisani primer bolnika.

Radiol Oncol 2007; 41(1): 41-7.

Analitična raziskava lastnosti izo-NTCP ovojnice

Stavrev P, Schinkel C, Stavreva N, Markov K, Fallone BG

Izhodišča. V članku smo raziskali lastnost prostora integralnega dozno-volumskega histograma (DVH). Krivuljo enake verjetnosti poškodbe zdravega tkiva [α-izo-NTCP (*normal tissue complication probability)*] smo oblikovali s povezovanjem točk, ki pripadajo intervalom v_k stopničastega integralnega DVH s pripadajočo dozo D_k in posledičnim NTCP z vrednostjo α. Podprostora, na katera krivulja razdeli DVH prostor, smo raziskali v smislu ekvivalentnih uniformnih doz (EUD), ki pripadajo različnim DVH-jem.

Zaključki. Teoretično je dokazano, da ima vsak DVH, ki je različen od stopničastega DVH in ki gre skozi točko (D_k, v_k) α-izo-NTCP ovojnice, NTCP > α. Iz česar sledi, da vsakemu DVH, ki vsaj delno leži nad ovojnico, pripada NTCP > α. Nekaterim DVH, ki ležijo pod ovojnico, npr. se je dotikajo, prav tako pripada NTCP > α. Vendar je bilo numerično dokazano, da ima DVH, ki v celoti leži v spodnjem podprostoru, NTCP < α. Glede na slednje bi bilo v postopku optimizacije zdravljenja zaželeno iskati rešitve z DVH povsem pod izo-NTCP ovojnico in se izogibati tistim, ki ležijo nad njo.

Radiol Oncol 2007; 41(1): 48-55.

Uvedba protokola za izvedbo *ofline* popravkov pri nastavitvah: varnostne meje in število slik

Kasabašić M, Faj D, Belaj N, Faj Z, Tomaš I

Izhodišča. Na Oddelku za onkologijo in radioterapijo Univerzitetne bolnice v Osjeku smo proučili, kakšne so napake pri nastavitvi pacientov ob radioterapiji v območju medenice. Izsledke smo uporabili za izdelavo protokola korekcij nastavitev in za določitev varnostnih robov.

Bolniki in metode. Natančnosti nastavitve smo preverjali z gamagrafijo. V študijo smo vključili 11 bolnikov, obdelali pa smo 420 slik. Napake pri nastavitvi smo določali z meritvijo razdalj med centrom polja in značilnimi kostnimi točkami. Analizirali smo sistemske in naključne napake.

Rezultati. Varnostni robovi, ki bi jih na našem oddelku morali upoštevati, so 11 mm v mediolateralni smeri, 13 mm v kraniokaudalni in 14 mm v anterioposteriorni smeri. V *offline* korekcijskem protokolu smo upoštevali povprečje prvih štirih gamagrafij za popravke v medio-lateralni in kranio-kavdalni smeri ter povprečje petih slik za popravke v anterio-posteriorni smeri.

Zaključki. Natančnost nastavitve se med frakcijami ni bistveno spreminjala, razen pri enem bolniku. Tega bolnika je bilo posebno težko nastavljati zaradi njegovih let, debelosti in težav s kolkom. Odločili smo se, da bomo takšne paciente odslej nastavljali brez podlag za trebuh *(bellyboardov),* na hrbet. Pri vseh ostalih bolnikih se natančnost nastavitve med frakcijami ni bistveno spreminjala. Za te smo uvedli *offline* nastavitveni protokol, pri katerem smo upoštevali povprečne napake pri prvih nekaj nastavitvah. Izračunali smo varnostne meje, za katere velja, da tarčni volumen z 90 % gotovostjo obsega vsaj 95 % predpisane doze. Varnostni robovi in variacije nastavitev kažejo, da je najnenatančnejše nastavljanje v anterioposteriorni smeri.

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

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Brachytherapy

May 10-12, 2007
The GEC-ESTRO brachytherapy meeting will take place in Montpellier, France.
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Oncology

May 12-14, 2007
The "10th International Wolfsberg Meeting on Molecular Biology/Oncology" (in association with ESTRO) will take place in Wolfsberg, Germany.
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Rectal cancer

May 21-23, 2007
The ESTRO teaching course "Evidence and Research in Rectal Cancer" will take place in Rome, Italy.
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Radiotherapy

May 27-31, 2007
The ESTRO teaching course "Imaging for Target Volume Determination in Radiotherapy" will take place in Izmir, Turkey.
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Radiobiology

June 3-7, 2007
The ESTRO teaching course "Basic Clinical Radiobiology (extra edition)" will take place in Beijing, China.
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Oncology

June 12-15, 2007
The EORTC annual course "Clinical Trials Statistics for Non Statisticians" will take place in Brussels, Belgium.
Contact Mr. Danielle Zimmermann; EORTC Education Office, Avenue E. Mounier, 83, bte 11, B-1200 Brussels, Belgium; or call +32 2 774 16 02; or fax +32 2 772 61 33; or e-mail Danielle.zimmermann@eortc.be; or see http://www.eortc.be

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Oncology

June 20-30, 2007
The 5th Central European Oncology Congress will take place in Opatia, Croatia.
Contact Dr. Mirko Šamija; Central European Oncology Congress Secretariat, University Hospital for Tumors; Ilica 197, 10000 Zagreb, Croatia; or call +385 1 3783 520; or fax +385 1 3775 536; or e-mail mirko.samija@kzt.hr; or see http://www.penta-zagreb.hr/CEOFC2007

Brachyradiotherapy

June 24-26, 2007
The ESTRO teaching course "Brachyradiotherapy for Prostate Cancer" will take place in Prague, Czech Republic.
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

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Oncology

July 5-8, 2007
The "ESMO Conference Lugano" will take place in Lugano, Switzerland.
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/activities/ecluconference/

Radiotherapy

July 1-5, 2007
The ESTRO teaching course "IMRT and Other Conformal Techniques in Practice" will take place in Vienna, Austria.
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Radiation oncology

July 1-6, 2007
The ESTRO teaching course "Evidence Based Radiation Oncology: Methodological Basis & Clinical Application (extra edition)" will take place in Krakow, Poland.
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Toxicology

July 15-19, 2007
The "11th International Congress of Toxicology" will be offered in Montreal, Canada.
Contact Congress Secretariat, e-mail: ict2007@nrc-cnrc.gc.ca; or see http://www.ict2007.org

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Radiotherapy

August 22-25, 2007
The ESTRO teaching course "3D Planning and Imaging (special edition)" will take place in St Petersburg, Russia.
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

Gynaecology

August 30 – September 1, 2007
The ESTRO teaching course "3D Image-based Brachytherapy in Gynaecological Malignancies" will take place in Copenhagen, Denmark.
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Lung cancer

September 2-6, 2007
The "12th World Conference on Lung Cancer" will be offered in Seoul, Korea.
Contact Conference Secretariat; e-mail WCLC2007@ncc.re.kr; or see http://www.iaslc.orgIumages/12worldconfannounce.pdf

Oncology

September 7, 2007
The EORTC annual course "One-Day Introduction to EORTC Trials" will take place in Brussels, Belgium.
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Radiotherapy

September 8-13, 2007
The "9th Biennial ESTRO Meeting on physics and Radiation Technology for Clinical Radiotherapy will take place in Barcelona, Spain.
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Oncology

September 23-27, 2007
The "14th European Cancer Conference ECCO 15/ESTRO 26" will take place in Barcelona, Spain.
Contact Conference Secretariat, ECCO 14, The European Cancer Conference, European Cancer Societies (FECS), Avenue E. Mounier, 83, B-1200 Brussels, Belgium; or call +32 2 775 02 01; or fax +32 2 775 02 00; or e-mail ECCO14@fecs.be; or see http://www.fecs.be

Radiotherapy

September 30 – October 4, 2007
The ESTRO teaching course "Radiotherapy with Protons and Ions" will take place in Heidelberg, Germany.
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

Radiobiology

October 14-18, 2007
The ESTRO teaching course "Basic Clinical radiobiology" will take place in Giardini Naxos, Italy.
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Radiotherapy

October21-25, 2007
The ESTRO teaching course "Physics for Clinical radiotherapy" will take place in Limassol, Cyprus.
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Radiation oncology

November 11-16, 2007
The ESTRO teaching course "Evidence Based Radiation Oncology: Methodological Basis & Clinical Application" will take place in Athens, Greece.
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Prostate cancer

November 15-17, 2007
The ESTRO multidisciplinary prostate cancer meeting will be offered.
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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

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://en.ce-lung2008.org/

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.
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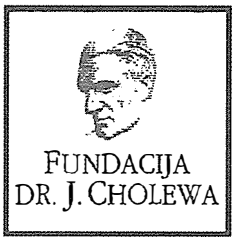

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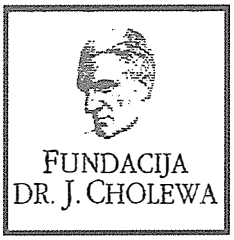

Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the first quarter of 2007

The Dr. J. Cholewa Foundation for Cancer Research and Education plans to stay active in promoting all the forms of cancer education in general population, among medical and nursing students and among all the others in 2007. It will particularly focus its activities and attention to cancer research and education in Slovenia. The requests and proposals for research grants and scholarships will thus be dealt with great attention and responsibility, with the Foundation members with clinical and research experience in cancer and by members with important experience in finance being instrumental in this activity.

As noted previously, the support for cancer research and education in various forms, financial and otherwise, remains the top priority of the Dr. J. Cholewa Foundation. A number research and study grants have been bestowed and allocated by the Foundation in 2006 and this will remain its core activity in 2007. The Foundation is continuing to pay special attention to the support of the publication of the results from cancer research in Slovenia in respectable international scientific journal worldwide.

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 is in line with the philosophy of the Foundation, emphasizing the spread of information and knowledge among many professionals in clinical and laboratory cancer research in Slovenia, but it also gives special attention to many interested individuals in lay public and others in Slovenia and elsewhere.

The Dr. J. Cholewa Foundation for Cancer Research and Education once again respectfully acknowledges the contribution of its members with clinical and research experience in cancer and its members with important experience in finance. Without their efforts the Foundation would lack many of its qualities.

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

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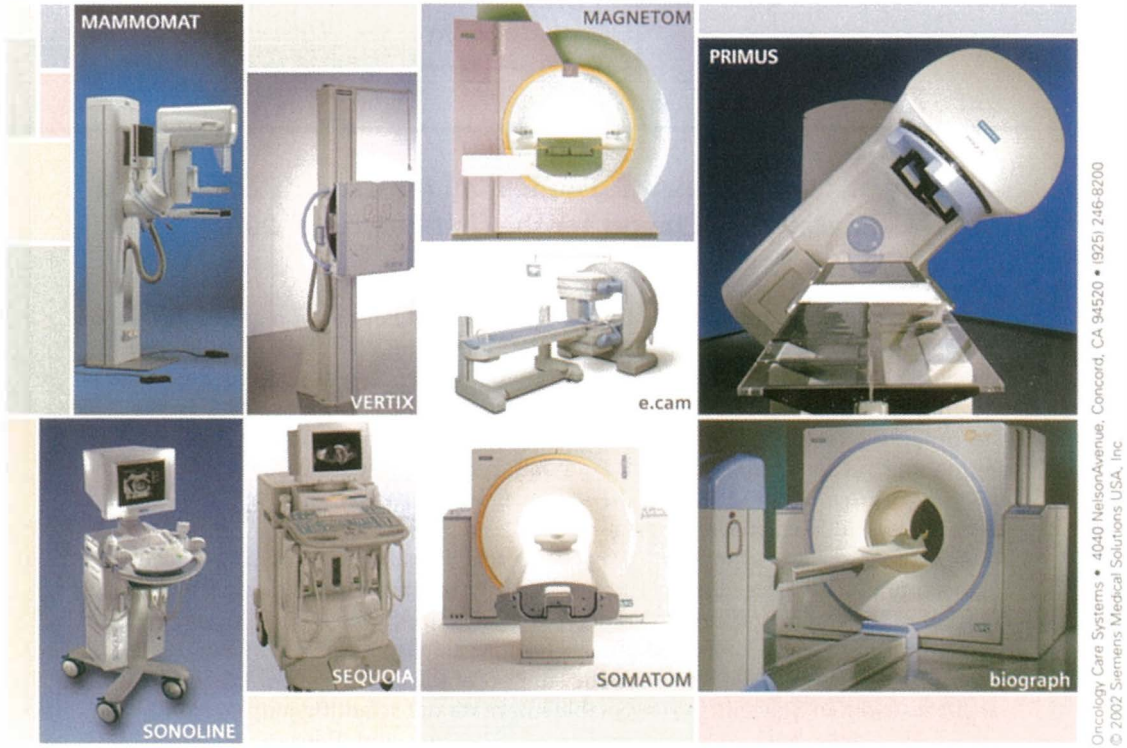

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Dodatne informacije so vam na voljo pri: Merck, d.o.o., Dunajska cesta 119, 1000 Ljubljana, tel.: 01 560 3810, faks: 01 560 3831, el. pošta: info@merck.si

[1] ploščatocelični rak glave in vratu
[2] v primerjavi z radioterapijo
[3] Bonner et al. Radiotherapy plus Cetuximab for Squamous Cell Carcinoma of the Head and Neck. N Engl J Med 2006; 354(6): 567 78

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Temodal 20 mg; 100 mg, 250 mg. Sestava zdravila Vsaka kapsula zdravila Temodal vsebuje 20 mg, 100 mg ali 250 mg temozolamida.**Terapevtske indikacije** Temodal kapsule so indicirane za zdravljenje bolnikov z: - za zdravljenje novo diagnosticiranega glioblastoma multiforme, sočasno z radioterapijo in kasneje kot monoterapija, - malignim gliomom, na primer multiformnim glioblastomom ali anaplastičnim astrocitomom, ki se po standardnem zdravljenju ponovi ali napreduje. **Odmerjanje in način uporabe** Temodal smejo predpisati le zdravniki, ki imajo izkušnje z zdravljenjem možganskih tumorjev. **Odrasli bolniki z novo diagnosticiranim glioblastomom multiforme** Temodal se uporablja v kombinaciji z žariščno radioterapijo (faza sočasne terapije), temu pa sledi do 6 ciklov monoterapije z temozolomidom.**Faza sočasne terapije** Zdravilo Temodal naj bolnik jemlje peroralno v odmerku 75 mg/m² na dan 42 dni, sočasno z žariščno radioterapijo (60 Gy, danih v 30 delnih odmerkih). Odmerka ne boste zmanjševali, vendar se boste vsak teden odločili o morebitni odložitvi jemanja temozolomida ali njegovi ukinitvi na podlagi kriterijev hematološke in nehematološke toksičnosti. Zdravilo Temodal lahko bolnik jemlje ves čas 42-dnevnega obdobja sočasne terapije do 49 dni, če so izpolnjeni vsi od naslednjih pogojev: absolutno število nevtrofilcev $\geq$ 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 alopecije, slabosti in bruhanja). Med zdravljenjem morate pri bolniku enkrat na teden pregledati celotno krvno sliko. **Faza monoterapije** Štiri tedne po zaključku faze sočasnega zdravljenja z zdravilom Temodal in radioterapijo naj bolnik jemlje zdravilo Temodal do 6 ciklov monoterapije. V 1. ciklu (monoterapija) je odmerek zdravila 150 mg/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 stopnje $\leq$ 2 (z izjemo alopecije, slabosti in bruhanja), absolutno število nevtrofilcev (ASN) $\geq$ 1,5 x 10^9/l in število trombocitov $\geq$ 100 x 10^9/l. Če odmerka niste povečali v 2. ciklusu, ga v naslednjih ciklusih ne smete povečevati. Ko pa odmerek enkrat povečate, naj ostane na ravni 200 mg/m² na dan v prvih 5 dneh vsakega naslednjega ciklusa, razen če nastopi toksičnost. Med zdravljenjem morate pregledati celotno krvno sliko na 22. dan (21 dni po prvem odmerku zdravila Temodal). **Ponavljajoči se ali napredujoči maligni gliom: Odrasli bolniki** Posamezen ciklus zdravljenja traja 28 dni. Bolniki, ki še niso bili zdravljeni s kemoterapijo, naj jemljejo Temodal peroralno v odmerku 200 mg/m² enkrat na dan prvih 5 dni, temu pa naj sledi 23-dnevni premor (skupaj 28 dni). Pri bolnikih, ki so že bili zdravljeni s kemoterapijo, je začetni odmerek 150 mg/m² enkrat na dan, v drugem ciklusu pa se poveča na 200 mg/m² enkrat na dan 5 dni, če ni bilo hematoloških toksičnih učinkov. **Pediatrični bolniki** 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, potem 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 povečanjem 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 bolnikih z blagimi ali zmernimi motnjami v delovanju jeter je farmakokinetika temozolomida podobna kot pri tistih z normalnim delovanjem jeter. Podatki o uporabi zdravila Temodal pri bolnikih s hudimi motnjami v delovanju jeter (razred III po Child-u) ali motnjami v delovanju ledvic niso na voljo. Na podlagi farmakokinetičnih lastnosti temozolomida obstaja majhna verjetnost, da bo pri bolnikih s hudimi motnjami v delovanju jeter ali ledvic potrebno zmanjšanje odmerka zdravila. Kljub temu je potrebna previdnost pri uporabi zdravila Temodal pri teh bolnikih. **Starejši bolniki** Analiza farmakokinetike je pokazala, da starost ne vpliva na očistek temozolomida. Kljub temu je potrebna posebna previdnost pri uporabi zdravila Temodal pri starejših bolnikih. **Način uporabe** Temodal mora bolnik jemati na tešče. Temodal kapsule mora bolnik pogoltniti cele s kozarcem vode in jih ne sme odpirati ali žvečiti. Predpisani odmerek mora vzeti v obliki najmanjšega možnega števila kapsul. Pred jemanjem zdravila Temodal ali po njem lahko bolnik vzame antiemetik. Če po zaužitju odmerka bruha, ne sme še isti dan vzeti drugega odmerka. **Kontraindikacije** Temodal je kontraindiciran pri bolnikih, ki imajo v anamnezi preobčutljivostne reakcije na sestavine zdravila ali na dakarbazin (DTIC). Temodal je kontraindiciran tudi pri bolnikih s hudo mielosupresijo. Temodal je kontraindiciran pri ženskah, ki so noseče ali dojijo. **Posebna opozorila in previdnostni ukrepi** Pilotno preskušanje podaljšane 42-dnevne sheme zdravljenja je pokazalo, da imajo bolniki, ki so sočasno prejemali zdravilo Temodal in radioterapijo, še posebej veliko tveganje za nastanek pljučnice zaradi okužbe s *Pneumocystis carinii* (PCP). Profilaksa proti tovrstni pljučnici je torej potrebna pri vseh bolnikih, ki sočasno prejemajo zdravilo Temodal in radioterapijo v okviru 42-dnevne sheme zdravljenja (do največ 49 dni), ne glede na število limfocitov. Če nastopi limfopenija, mora bolnik nadaljevati s profilakso, dokler se limfopenija ne povrne na stopnjo $\leq$ 1. **Antiemetična terapija:** Z jemanjem zdravila Temodal sta zelo pogosto povezana slabost in bruhanje. **Laboratorijske vrednosti** Pred jemanjem zdravila morata biti izpolnjena naslednja pogoja za laboratorijske izvide: ANC mora biti $\geq$ 1,5 x 10^9/l in število trombocitov $\geq$ 100 x 10^9/l. Na 22. dan (21 dni po prvem odmerku) ali v roku 48 ur od navedenega dne, morate pregledati celotno krvno sliko in jo nato spremljati vsak teden, dokler ni ANC nad 1,5 x 10^9/l in število trombocitov nad 100 x 10^9/l. Če med katerimkoli ciklusom ANC pade na $\leq$ 1,0 x 10^9/l ali število trombocitov na $\leq$ 50 x 10^9/l, morate odmerek zdravila v naslednjem ciklusu zmanjšati za eno odmerno 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 genotoksično, zato morate moškim, ki se zdravijo z temozolomidom svetovati, da naj ne zaplodijo otroka še šest mesecev po zdravljenju. **Interakcije** Sočasna uporaba zdravila Temodal in ranitidina ni povzročila spremembe obsega absorpcije temozolomida ali monometiltriazenoimidazol karboksamida (MTIC). Jemanje zdravila Temodal s hrano je povzročilo 33 % zmanjšanje Cmax in 9 % zmanjšanje površino pod krivuljo (AUC). Ker ne moremo izključiti možnosti, da bi bila sprememba Cmax lahko klinično pomembna, naj bolniki jemljejo zdravilo Temodal brez hrane. Analiza populacijske farmakokinetike v preskušanjih druge faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka temozolomida. Sočasno jemanje z valprojsko kislino je bilo povezano z majhnim, a statistično značilnim zmanjšanjem očistka temozolomida. Uporaba zdravila Temodal v kombinaciji z drugimi mielosupresivnimi učinkovinami lahko poveča verjetnost mielosupresije. **Nosečnost** Študij na nosečih ženskah ni bilo. Predklinične študije na podganah in kuncih z odmerkom 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 nosečnosti nujna, morate bolnico opozoriti na možne nevarnosti zdravila za plod. Ženskam v rodni dobi svetujte, naj med zdravljenjem z zdravilom Temodal preprečijo zanositev. **Dojenje** Ni znano, ali se temozolomid izloča v materino mleko, zato ženske, ki dojijo, ne smejo jemati zdravila Temodal. **Neželeni učinki V** kliničnih preskušanjih so bili najpogostnejši neželeni učinki, povezani z zdravljenjem, prebavne motnje, natančneje slabost (43 %) in bruhanje (36 %). Oba učinka sta bila ponavadi 1. ali 2. stopnje (od 0 do 5 epizod bruhanja v 24 urah) in sta prenehala sama ali pa ju je bilo mogoče hitro obvladati s standardnim antiemetičnim zdravljenjem. Incidenca hude slabosti in bruhanja je bila 4 %. **Laboratorijski izvidi:** Trombocitopenija in nevtropenija 3. in. 4. stopnje sta se pojavili pri 19 % in 17 % bolnikov, zdravljenih zaradi malignega glioma. Zaradi njiju je bila potrebna hospitalizacija in/ali prekinitev zdravljenja z zdravilom Temodal pri 8 % in. 4 % bolnikov. Mielosupresija je bila predvidljiva (ponavadi se je pojavila v prvih nekaj ciklusih in je bila najizrazitejša med 21. in 28. dnem), okrevanje pa je bilo hitro, ponavadi v 1 do 2 tednih. Opazili niso nobenih dokazov kumulativne mielosupresije. Trombocitopenija lahko poveča tveganje za pojav krvavitev, nevtropenija ali levkopenija pa tveganje za okužbe.**Imetnik dovoljenja za promet** SP Europe 73, rue de Stalle B-1180, Bruselj, Belgija. **Način in režim izdaje** Zdravilo se izdaja samo na recept, uporablja pa se pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Datum priprave informacije** januar 2006 Podrobnejše informacije o zdravilu Temodal dobite na sedežu podjetja.

Priprava informacije Schering-Plough, november 2006.

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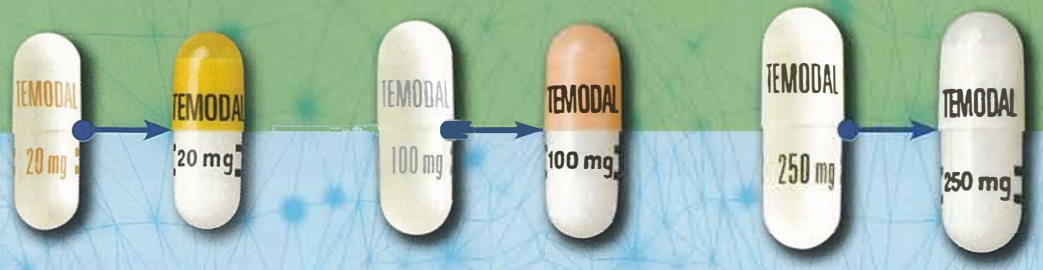

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Reference:
1- Tarceva (erlotinib) summary of product characteristics, F.Hoffmann-La Roche LTD., 2005.

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Vehikel je brezbarvna raztopina. **Terapevtske indikacije:** ***Rak dojke:*** TAXOTERE (docetaksel) je v kombinaciji z doksorubicinom in ciklofosfamidom indiciran za adjuvantno zdravljenje bolnic z operabilnim rakom dojke s pozitivnimi bezgavkami. TAXOTERE (docetaksel) v kombinaciji z doksorubicinom je indiciran za zdravljenje bolnic z lokalno napredovalim ali metastatskim rakom dojke, ki zaradi te bolezni še niso prejemale citotoksične terapije. TAXOTERE (docetaksel) v monoterapiji je indiciran za zdravljenje bolnic z lokalno napredovalim ali metastatskim rakom dojke, pri katerih predhodna citotoksična terapija ni bila uspešna. Predhodna kemoterapija bi morala vključevati antraciklin ali alkilirajočo učinkovino. TAXOTERE (docetaksel) je indiciran v kombinaciji s trastuzumabom za zdravljenje bolnic z metastatskim rakom dojke, katerih tumorji imajo čezmerno izražen HER2 in ki predhodno niso bile zdravljene s kemoterapijo za metastatsko bolezen. TAXOTERE (docetaksel) v kombinaciji s kapecitabinom je indiciran za zdravljenje bolnic z lokalno napredovalim ali metastatskim rakom dojke po neuspehu citotoksične kemoterapije. Predhodna kemoterapija bi morala vključevati antraciklin. ***Nedrobnocelični pljučni rak:*** TAXOTERE (docetaksel) je indiciran za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim rakom, pri katerih predhodna kemoterapija ni bila uspešna. TAXOTERE (docetaksel) v kombinaciji s cisplatinom je indiciran za zdravljenje neresektabilnega, lokalno napredovalega ali metastatskega nedrobnoceličnega pljučnega raka pri bolnikih, ki zaradi te bolezni še niso dobivali kemoterapije. ***Rak prostate:*** TAXOTERE (docetaksel) je v kombinaciji s prednizonom ali prednizolonom indiciran za zdravljenje bolnikov z metastatskim hormonsko neodzivnim rakom prostate. ***Adenokarcinom želodca:*** TAXOTERE (docetaksel) je v kombinaciji s cisplatinom in 5-fluorouracilom indiciran za zdravljenje bolnikov z metastatskim adenokarcinomom želodca, vključno z adenokarcinomom na gastroezofagealnem prehodu, ki predhodno še niso bili zdravljeni s kemoterapijo za metastatsko bolezen. ***Rak glave in vratu:*** *Taxo*tere (docetaksel) je v kombinaciji s cisplatinom in 5-fluorouracilom indiciran za indukcijsko zdravljenje bolnikov z inoperabilnim lokalno napredovalim skvamoznoceličnim karcinomom glave in vratu. **Odmerjanje in način uporabe:** ***Priporočeno odmerjanje:*** Pri zdravljenju raka dojke, nedrobnoceličnega pljučnega raka, raka želodca in raka glave in vratu lahko kot premedikacijo dajemo peroralne korlikosteroide, kot je deksametazon 16 mg na dan v trajanju treh dni, in sicer 1 dan pred aplikacijo docetaksela, razen v primeru kontraindikacij. Profilaktični G-CSF se lahko uporabi za ublažitev tveganja hematološke toksičnosti. Pri zdravljenju raka prostate, v primeru sočasne uporabe prednizona ali prednizolona, je priporočena premedikacija peroralni deksametazon 8 mg, 12 ur, 3 ure in 1 uro pred infuzijo docetaksela. Docetaksel apliciramo v enourni infuziji vsake tri tedne. ***Rak dojke:*** Pri dopolnilnem zdravljenju operabilnega raka dojke s pozitivnimi bezgavkami je priporočeni odmerek docetaksela 75 mg/m², apliciran eno uro po doksorubicinu 50 mg/m² in ciklofosfamidu 500 mg/m² vsake tri tedne v 6 ciklih. Za zdravljenje bolnic z lokalno napredovalim ali metastatskim rakom dojke je priporočeni odmerek docetaksela v monoterapiji 100 mg/m². Kot zdravljenje prvega izbora se docetaksel 75 mg/m² daje v kombinaciji z doksorubicinom (50 mg/m²). Za kombinacijo s trastuzumabom je priporočeni odmerek docetaksela 100 mg/m² vsake tri tedne, s tedensko aplikacijo trastuzumaba. Za odmerjanje in dajanje trastuzumaba prosimo, glejte povzetek glavnih značilnosti zdravila. V kombinaciji s kapecitabinom je priporočeni odmerek docetaksela 75 mg/m² na tri tedne, kombiniran s kapecitabinom 1.250 mg/m² dvakrat na dan (v 30 minutah po obroku) 2 tedna, čemur sledi 1-tedenski premor. Za izračun odmerka kapecitabina glede na telesno površino glejte povzetek glavnih značilnosti kapecitabina. ***Nedrobnocelični pljučni rak:*** Pri bolnikih z nedrobnoceličnim pljučnim rakom, ki še niso bili zdravljeni s kemoterapijo, je priporočena shema odmerjanja docetaksel v odmerku 75 mg/m², ki mu takoj sledi cisplatin v odmerku 75 mg/m², apliciran 30–60 minut. Za zdravljenje po neuspehu predhodne, na platini osnovane kemoterapije, je priporočeni odmerek 75 mg/m² v monoterapiji. ***Rak prostate:*** Priporočeno odmerjanje docetaksela je 75 mg/m². Prednizon ali prednizolon v odmerku 5 mg dvakrat dnevno dajemo nepretrgoma. ***Adenokarcinom želodca:*** Priporočeni odmerek docetaksela je 75 mg/m² v 1-urni infuziji, ki mu sledi cisplatin 75 mg/m² v 1- do 3-urni infuziji (oboje samo 1. dan); temu sledi 5-fluorouracil 750 mg/m² na dan v 24-urni stalni infuziji 5 dni, z začetkom ob koncu infuzije cisplatina. Terapija se ponavlja na tri tedne. Pred aplikacijo cisplatina moraju bolniki dobiti premedikacijo z antiemetiki in ustrezno hidracijo. Za zmanjšanje tveganja za hematološke toksične učinke je treba profilaktično uporabiti G-CSF. ***Rak glave in vratu:*** Za indukcijsko zdravljenje inoperabilnega lokalno napredovalega skvamoznoceličnega karcinoma glave in vratu, je priporočeni odmerek zdravila TAXOTERE 75 mg/m² v obliki enourne infuzije, ki ji sledi cisplatin 75 mg/m², infundiran 1 uro dolgo prvega dne, temu pa sledi 5-fluorouracil v obliki neprekinjene infuzije v odmerku 750 mg/m² na dan pet dni. Ta terapevtska shema se uporablja vsake 3 tedne za 4 cikle. Po kemoterapiji morajo bolniki prejeti radioterapijo. Bolniki morajo prejeti premedikacijo z antiemetiki in ustrezno hidracijo (pred prejemom cisplatina in po njem). Za zmanjšanje nevarnosti hematološke toksičnosti se lahko uporablja profilaktik G-CSF. Za spremembe odmerkov cisplatina in 5-fluorouracila glejte izdelovalčev povzetek glavnih značilnosti zdravila. **Prilagajanje odmerka med zdravljenjem:** ***Splošno:*** Docetaksel je treba aplicirati, ko je število nevtrofilcev ≥ 1.500 celic/mm³. Pri bolnikih, ki so med zdravljenjem z docetakselom doživeli febrilno nevtropenijo, zmanjšanje števila nevtrofilcev na < 500 celic/mm³ za več kot en teden, hude ali kumulativne kožne reakcije ali hudo periferno nevropatijo, je treba odmerek docetaksela zmanjšati s 100 mg/m² na 75 mg/m² oz. s 75 na 60 mg/m². Če bolnik tudi pri odmerku 60 mg/m² še doživlja te reakcije, je treba zdravljenje prekiniti. Za ostale informacije, prosimo, preberite celoten povzetek glavnih značilnosti zdravila. ***Posebne skupine bolnikov:*** *Bolniki z okvaro jeter:* Glede na farmakokinetične podatke o monoterapiji z docetakselom v odmerku 100 mg/m² je priporočljiv odmerek docetaksela za bolnike, ki imajo transaminazi (ALT, AST ali obe) zvišani nad 1,5-kratno zgornjo mejo normalnega območja (ULN) in alkalno fosfatazo nad 2,5-kratno ULN, 75 mg/m². Pri bolnikih, ki imajo serumski bilirubin > ULN in/ali ALT in AST > 3,5-kratno ULN ter hkrati alkalno fosfatazo > 6-kratno ULN, ni mogoče priporočiti zmanjšanja odmerka; pri teh bolnikih se docetaksela ne sme uporabljati, če ni strogo indiciran. *Otroci in mladostniki:* Izkušnje pri otrocih in mladostnikih so omejene. *Starostniki:* Za uporabo pri starostnikih glede na analizo farmakokinetike na populaciji ni posebnih navodil. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Docetaksela se ne sme uporabljati pri bolnikih z izhodiščnim številom nevtrofilcev < 1.500 celic/mm³. Docetaksela ne smejo dobivati nosečnice in doječe ženske. Docetaksela se ne sme uporabljati pri bolnikih s hudo okvaro jeter. Če se v kombinaciji z docetakselom uporabljajo še druga zdravila, veljajo tudi kontraindikacije zanje. **Posebna opozorila in previdnostni ukrepi:** Pri zdravljenju raka dojke in nedrobnocelične pljučnega raka lahko 3-dnevna premedikacija s peroralnim kortikosteroidom, npr. deksametazonom 16 mg na dan, ki se začne 1 dan pred aplikacijo docetaksela, zmanjša pogostnost in izrazitost zastajanja tekočine ter izrazitost preobčutljivostnih reakcij, če ni kontraindicirana. Pri zdravljenju raka prostate je premedikacija peroralni deksametazon 8 mg, 12 ur, 3 ure in 1 uro pred infuzijo docetaksela. ***Hematologija:*** Najpogostejši neželeni učinek docetaksela je nevtropenija. Vsem bolnikom, ki prejemajo docetaksel, je treba pogosto pregledovati celotno krvno sliko. ***Preobčutljivostne reakcije:*** Bolnike je treba skrbno opazovati glede preobčutljivostnih reakcij, zlasti med prvim in drugim infundiranjem. Preobčutljivostne reakcije se lahko pojavijo v nekaj minutah po začetku infundiranja docetaksela. ***Kožne reakcije:*** Na udih (dlaneh in podplatih) so opažali lokalen kožni eritem z edemi in poznejšo deskvamacijo. ***Zastajanje tekočine:*** Bolnike s hudim zastajanjem tekočine, npr. s plevralnim izlivom, perikardialnim izlivom ali ascitesom, je treba skrbno nadzorovati. ***Živčevje:*** Če se pojavijo hudi periferni nevrotoksični učinki, je treba odmerek zmanjšati. **Kardiotoksičnost:** Pri bolnicah, ki so prejemale TAXOTERE v kombinaciji s trastuzumabom so opazovali srčno popuščanje, še posebno, če je zdravljenje sledilo kemoterapiji z antraciklinom. ***Drugo:*** Med zdravljenjem in vsaj še tri mesece po njegovem koncu je treba uporabljati kontracepcijsko zaščito. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študije *in vitro* so pokazale, da lahko presnovo docetaksela spremeni sočasna uporaba zdravil, ki inducirajo ali inhibirajo citokrom P450-3A ali se z njim presnavljajo (in ga tako lahko kompetitivno inhibirajo). **Nosečnost in dojenje:** Ženskam v rodni dobi, ki dobivajo docetaksel, je treba odsvetovati nosečnost; če zanosijo, morajo o tem takoj obvestiti lečečega zdravnika. Zaradi možnih neželenih učinkov na dojenčke je treba dojenje med zdravljenjem z docetakselom prekiniti. **Neželeni učinki:** Napogosteje opisani neželeni učinki na sam TAXOTERE so: nevtropenija, anemija, alopecija, navzea, bruhanje, stomatitis, driska in astenija. Zelo pogosti neželeni učinki glede na različne režime dajanja so: *TAXOTERE 100 mg/m² v monoterapiji:* okužbe, nevtropenija, anemija, lebrilna nevtropenija, preobčutljivost, anoreksija, periferna senzorična nevtropatija, periferna motorična nevtropatija, dizgevzija, dispneja, stomatitis, driska, navzea, bruhanje, alopecija, kožna reakcija, spremembe nohtov, mialgija, zastajanje tekočine, astenija, bolečine. *TAXOTERE 75 mg/m² monoterapiji:* okužbe, nevtropenija, anemija, trombocitopenija, anoreksija, periferna senzorična nevropatija, navzea, stomatitis, bruhanje, driska, alopecija, kožna reakcija, astenija, zastajanje tekočine, bolečine. *TAXOTERE 75 mg/m² v kombinaciji z doksorubicinom:* okužba, nevtropenija, anemija, febrilna nevtropenija, trombocitopenija, periferna senzorična nevropatija, navzea, stomatitis, driska, bruhanje, zaprtje, alopecija, spremembe nohtov, kožna reakcija, astenija, zastajanje tekočine, bolečine. *TAXOTERE 75 mg/m² v kombinaciji s cisplatinom*: okužba, nevtropenija, anemija, trombocitopenija, preobčutljivost, anoreksija, periferna senzorična nevropatija, periferna motorična nevropatija, navzea, bruhanje, driska, stomatitis, alopecija, spremembe nohtov, kožna reakcija, mialgija, astenija, zastajanje tekočine, zvišana telesna temperatura. *TAXOTERE 100 mg/m² v kombinaciji s trastuzumabom*: nevtropenija, febrilna nevtropenija ali nevtropenična sepsa, anoreksija, nespečnost, parestezije, glavobol, dizgevzija, hipestezija, močnejše solzenje, konjunktivitis, limfedem, epistaksa, faringo-laringealna bolečina, nazofaringitis, dispneja, kašelj, rinoreja, navzea, driska, bruhanje, zaprtje, stomatitis, dispepsija, bolečine v trebuhu, alopecija, eritem, izpuščaj, spremembe nohtov, mialgija, artralgija, bolečine v udih, bolečine v kosteh, bolečine v hrbtu, astenija, periferni edemi, pireksija, utrujenost, vnetje sluznice, bolečine, gripi podobna bolezen, bolečine v prsih, mrzlica, povečanje telesne mase. *TAXOTERE 75 mg/m² v kombinaciji s kapecitabinom*: nevtropenija, anemija, roka/noga sindrom, alopecija, spremembe nohtov, stomatitis, driska, navzea, bruhanje, zaprtje, bolečine v trebuhu, dispepsija, dizgevzija, parestezije, anoreksija, zmanjšan apetit, močnejše solzenje, mialgija, artralgija, faringo-laringealna bolečina, astenija, pireksija, utrujenost/šibkost, periferni edemi. *TAXOTERE 75 mg/m² v kombinaciji s prednizonom ali prednizolonom*: okužba, nevtropenija, anemija, anoreksija, periferna senzorična nevropatija, dizgevzija, navzea, driska, stomatitis/faringitis, bruhanje, alopecija, spremembe nohtov, utrujenost, zastajanje tekočine. *TAXOTERE 75 mg/m² v kombinaciji z doksorubicinom in ciklofosfamidom:* okužba, nevtropenična okužba, anemija, nevtropenija, trombocitopenija, febrilna nevtropenija, preobčutljivost, anoreksija, dizgevzija, periferna senzorična nevropatija, vazodilatacija, navzea, stomatitis, bruhanje, driska, zaprtje, alopecija, toksični učinki na koži, spremembe nohtov, mialgija, artralgija, amenoreja, astenija, zvišana telesna temperatura, periferni edemi, povečanje ali zmanjšanje telesne mase. *TAXOTERE 75 mg/m² v kombinaciji s cisplatinom in 5-fluorouracilom za adenokarcinom želodca*: nevtropenična okužba, okužba, anemija, nevtropenija, trombocitopenija, febrilna nevtropenija, preobčutljivost, anoreksija, periferna senzorična nevropatija, driska, navzea, stomatitis, bruhanje, alopecija, letargija, zvišana telesna temperatura, zastajanje tekočine. *TAXOTERE 75 mg/m² v kombinaciji s cisplatinom in 5-fluorouracilom* (za rak glave in vratu): infekcija, nevtropenična infekcija, nevtropenija, anemija, trombocitopenija, anoreksija, dizgevzija/parozmija, periferna senzorična nevropatija, letargija, navzea, stomatitis, diareja, bruhanje, alopecija, pireksija, retenca tekočine, edem. Za ostale neželene učinke prosimo glejte celoten povzetek glavnih značilnosti zdravila. **Način izdajanja zdravila:** Izdaja zdravila je le na recept. **Ime in naslov imetnika dovoljenja za promet z zdravilom:** Aventis Pharma S. A., 20 avenue Raymond Aron, 92165 Antony Cedex, Francija. **Zadnji pregled besedila:** 12.01.2007

SI.DOC.07.02.01

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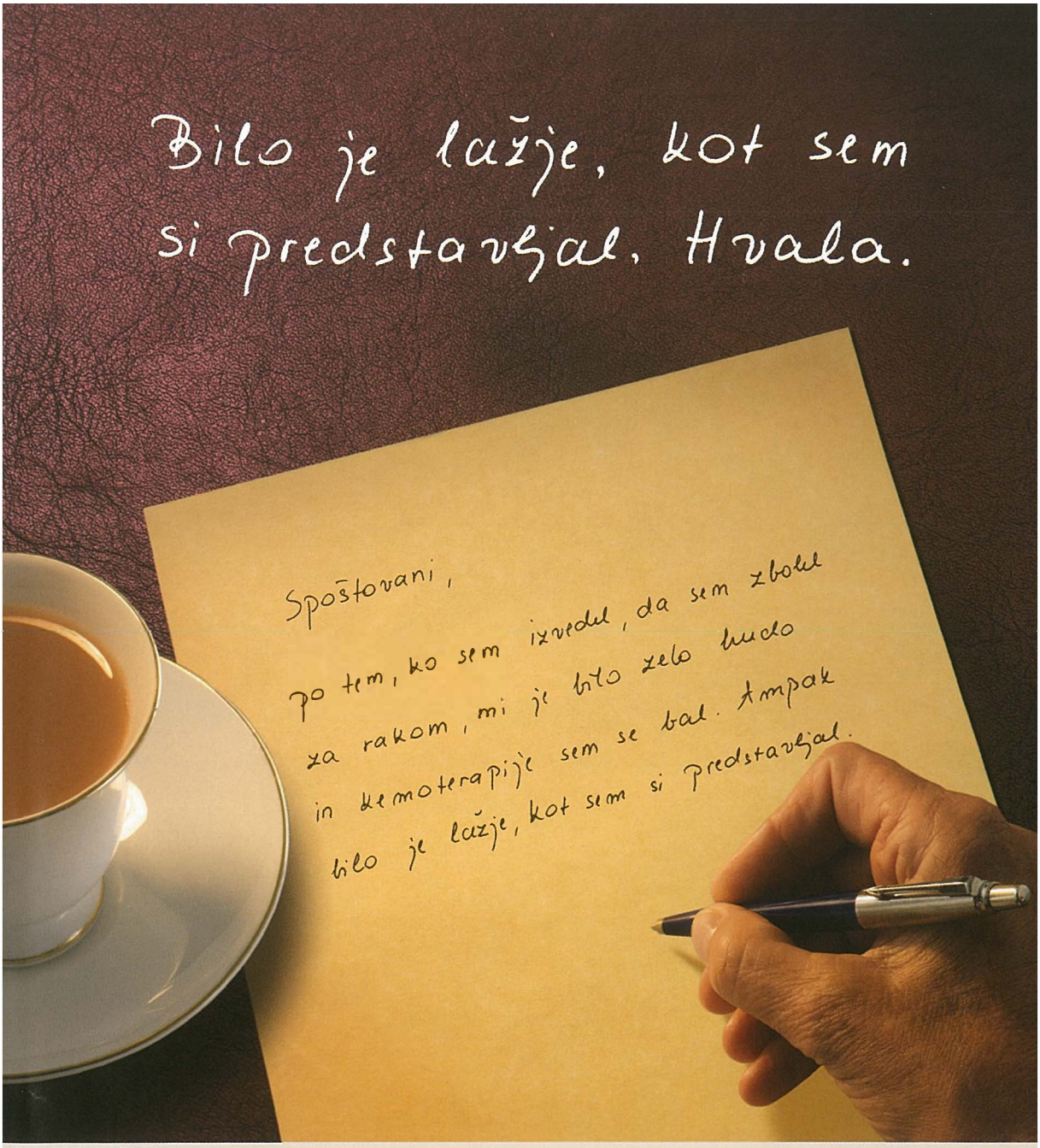
Zaupam v življenje

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih.
Podrobnejše informacije so na voljo pri: sanofi-aventis d.o.o.
Dunajska cesta 119, 1000 Ljubljana, tel.: 01 560 48 00, fax: 01 560 48 46

sanofi aventis

Ker je zdravje neprecenljivo



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Zaupam v življenj

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tava HYCAMTIN 4 mg prašek za koncentrat za raztopino za infundiranje. Vsaka viala vsebuje 4 mg topotekana (v obliki ida) **Indikacije** Samostojno zdravljenje s topotekanom je indicirano pri bolnicah z rakom jajčnika z metastazami, če pija prve izbire in tudi naslednje terapije niso uspele; bolnikih z relapsom drobnocelične pljučnega raka, pri katerih ovno zdravljenje s terapijo prve izbire ni primerno. Topotekan v kombinaciji s cisplatinom je indiciran pri bolnicah s ovitvijo karcinoma maternične vrata po zdravljenju z obsevanjem in bolnicah s stadijem IVB karcinoma maternične u. **Odmerjanje in način uporabe** *Karcinom jajčnika in drobnocelični pljučni karcinom; Začetni odmerek* Priporočeni erek topotekana je 1,5 mg/m² telesne površine na dan, z intravensko infuzijo, ki traja po 30 minut dnevno, v ciklih po poredih dni in s tritedenskimi presledki med začetki vsakega cikla zdravljenja. Če ga bolniki dobro prenašajo, smemo ravljenjem nadaljevati, dokler je bolezen v progresiji. *Nadaljevalni odmerki* Pred naslednjo uporabo topotekana mora tevilo nevtrofilcev ≥ x 10⁹/l, število trombocitov 100 x 10⁹/l, vrednost hemoglobina pa 9 g/dl (po transfuziji, če je le-ta ebna).Bolnike s hudo nevtropenijo (število nevtrofilcev < 0,5 x 10⁹/l), ki traja 7 ali več dni, ali hudo nevtropenijo z ano telesno temperaturo ali okužbo, ali tiste, ki jim je bilo treba zdravljenje preložiti zaradi nevtropenije, zdravimo tako, porabimo manjši odmerek, tj. 1,25 mg/m² na dan (ali ga po potrebi še dodatno zmanjšamo do 1,0 mg/m² na dan) ali mo v naslednjih ciklih profilaktično G-CSF za ohranjanje enake jakosti odmerka. Začnemo na 6. dan cikla (naslednjl po prenehanju vnašanja topotekana). Če se nevtropenija z vnašanjem G-CSF ustrezno ne popravi, je odmerke treba jšati. Podobno je treba zmanjšati odmerke, če pade število trombocitov pod 25 x 10⁹/l. Med kliničnimi preskušanji so tekan prenehali uporabljati, če je bil odmerek že zmanjšan na 1,0 mg/m² in bi ga bilo treba zaradi neželenih učinkov očatno zmanjšati. *Karcinom maternične vrata; Začetni odmerek* Priporočeni odmerek topotekana je 0,75 mg/m²/dan. ica ga 1., 2. in 3. dan prejme v obliki 30-minutne intravenske infuzije enkrat na dan. 1. dan po prejemu odmerka tekana bolnica prejme še intravensko infuzijo cisplatina v odmerku 50 mg/m²/dan. Takšna shema zdravljenja se po- ja vsakih 21 dni, 6 ciklov all dokler je bolezen v progresiji. *Naslednji odmerki* Bolnica topotekana ne sme prejeti, če ilo nevtrofilcev ni večje ali enako 1,5 x 10⁹/l, število trombocitov večje ali enako 100 x 10⁹/l in vrednost hemoglobina a ali enaka 9 g/dl (po transfuziji, če je le-ta potrebna). Pri bolnicah s febrilno nevtropenijo (število nevtrofilcev manjše x 10⁹/l in telesna temperatura 38 °C ali večja) je pri naslednjih ciklih priporočljivo odmerek topotekana zmanjšati 0 % na 0,60 mg/m²/dan.V primeru febrilne nevtropenije je alternativa zmanjšanju odmerka lahko dajanje G-CSF po edinjem ciklu (pred zmanjšanjem odmerka). Z njim se začne 4. dan cikla (vsaj 24 ur po koncu dajanja topotekana).Če ebrilna nevtropenija pojavi kljub uporabi G-CSF, je pri naslednjih ciklih priporočljivo odmerek topotekana zmanjšati za aljnjih 20 % na 0,45 mg/m²/dan. Pri bolnicah pri katerih se število trombocitov zmanjša pod 10 x 10⁹/l je pri naslednjih h priporočljivo odmerek topotekana zmanjšati za 20 % na 0,60 mg/m²/dan. *Odmerjanje pri bolnikih z ledvično okvaro* dravljenje bolnikov z očistkom kreatinina < 20 ml/min ne moremo priporočiti ustreznih odmerkov, saj imamo premalo šenj. Omejena količina podatkov, ki je na voljo, kaže, da je treba pri zdravljenju bolnikov z zmerno ledvično okvaro od- ek zmanjšati. **Kontraindikacije** Topotekan je kontraindiciran pri bolnikih, ki imajo v anamnezi hudo preobčutljivostno cijo na topotekan ali katero koli pomožno snov; bolnicah, ki so noseče ali dojijo; bolnikih, ki imajo hudo depresijo kost- a mozga že pred začetkom prvega cikla, kar je razvidno iz izhodiščnega števila nevtrofilcev < 1,5 x 10⁹/l in/all števila bocitov 100 x 10⁹/l. **Posebna opozorila in previdnostni ukrepi** Hematološka toksičnost je odvisna od odmerka, je treba bolnikom redno nadzorovati celotno krvno sliko, vključno s trombociti. Kot pri uporabi drugih citotoksičnih vil so tudi pri uporabi topotekana poročali o pojavu mielosupresije. O pojavu hude mielosupresije in posledične sepse so čali pri 5 % bolnikov, ki so se zdravili s topotekanom. Huda sepsa se lahko konča smrtno. Uporaba samega topotekana potekana v kombinaciji s cisplatinom je pogosto povezana s pojavom klinično pomembne trombocitopenije. To je treba tevati, npr. pri bolnikih, pri katerih obstaja večje tveganje za pojav krvavitve tumorja. Kot je bilo pričakovati, se bolniki v slabšem telesnem stanju (PS>1) slabše odzivajo na zdravilo in pri njih tudi pogosteje opažamo zaplete, kot so zvišana tele- sna temperatura, okužbe in sepsa. Pomembno je, da se bolnikovo telesno stanje ob začetku zdravljenja natančno oceni in zagotovi, da se ne poslabša na 3. Z uporabo topotekana za zdravljenje bolnikov s hudimi motnjami delovanja ledvic (očistek kreatinina < 20 ml/min) ali s hudo okvaro jetrne funkcije, ki je posledica ciroze (serumski bilirubin ≥ 10 mg/dl), nimamo izkušenj. Pri teh skupinah bolnikov zdravljenje s topotekanom ni priporočljivo. Le manjše število bolnikov z jetrno okvaro (vrednost serumskega bilirubina med 1,5 in 10 mg/dl) je prejelo odmerek 1,5 mg/m² po5 dni na vsake tri tedne. Pri tem so opazili manjši očistek topotekana. Vseeno za sedaj nimamo na voljo zadostne količine podatkov, da bi priporočili odmerek za to skupino bolnikov. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Topotekan ne zavira encimov človeškega citokroma P450. V populacijski študiji niso zasledili, da bi sočasno dajanje granisetrona, ondansetrona, morfina ali kortikosteroidov pomembneje vplivalo na farmakokinetiko celokupnega topotekana (aktivne in neaktivne ob- like). Pri sočasni uporabi topotekana z drugimi kemoterapevtiki je zaradi boljšega prenašanja potrebno zmanjšati odmerek vsakega zdravila. Pri sočasni uporabi s platinovimi spojinami pride do izrazite interakcije, ki je odvisna od zaporedja dajanja zdravil, in sicer od tega ali damo pripravek s platino na 1. ali 5. dan dajanja topotekana. Če dajemo cisplatin ali karboplatin na 1. dan dajanja topotekana, je potrebno zaradi boljšega prenašanja zmanjšati odmerek teh zdravil v primerjavi z odmerki, ki jih lahko dajemo, kadar damo platinove spojine na 5. dan uporabe topotekana. **Nosečnost in dojenje** Topotekan je med nosečnostjo kontraindiciran. Predklinične raziskave so pokazale, da uporaba topotekana povzroča smrt in deformacije zarodka oziroma ploda. Ženskam je potrebno svetovati, da med zdravljenjem s topotekanom ne smejo zanositi, v primeru zanositve pa naj o tem takoj obvestijo zdravnika. Topotekan je med dojenjem kontraindiciran. **Neželeni učinki** Zelo pogosti: nevtropenija s sočasno povišano telesno temperaturo, nevtropenija, trombocitopenija, anemija, levkopenija, anorek- sija, mukozitis, navzea, bruhanje, dlareja, zaprtje, abdominalna bolečina, alopecija, zvišana telesna temperatura, astenija, utrujenost. Pogosti: preobčutljivostna reakcija, vključno z izpuščajem, hiperbilirubinemija, pruritus, občutek slabosti. **Vrsta ovojnine in vsebina** HYCAMTIN 4 mg je na voljo v škatlah z 1 viala. **Način uporabe** Topotekan se sme uporabljati le v ustanovah, ki so specializirane za uporabo citotoksičnih kemoterapevtikov. Uporaba zdravila naj vedno poteka pod nadzo- rom zdravnika z izkušnjami na področju kemoterapije.

Datum priprave Informacije: Februar 2007

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

Literatura: 1 Long H J 3rd et al. J Clin Oncol 2005; 23 (21): 4626--4633

Dodatne informacije so vam na voljo pri: GSK d.o.o., Ljubljana, Knezov štradon 90, 1001 Ljubljana

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pri bolnicah po menopavzi z zgodnjim hormonsko odvisnim invazivnim rakom dojke

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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
Arimidexje 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

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Dodatne informacije in literatura so na voljo pri:
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Podružnica v Sloveniji
Verovškova 55, Ljubljana

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

AstraZeneca
ONKOLOGIJA

POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Fentanil Lek 25, 50 in 100 mikrogram/h transdermalni obliži **SESTAVA:** 1 transdermalni obliž vsebuje 2,5 mg, 5,0 mg ali 10,0 mg fentanila. **TERAPEVTSKE INDIKACIJE:** Kronične bolečine, pri katerih je potrebno zdravljenje z opioidnimi analgetiki. **ODMERJANJE IN NAČIN UPORABE:** Odmerek zdravila prilagodite posameznim bolnikom in po vsaki uporabi ovrednotite njegov učinek. *Izbira začetnega odmerka.* višina odmerka naj temelji na predhodni uporabi opioidov. Pri bolnikih, ki nimajo izkušenj z opioidi in ki opioidov predhodno niso jemali, začetni odmerek ne sme presegati 25 µg/h. Predhodnega zdravljenja z analgetiki ne smete prekiniti prej kot v 12 urah po namestitvi prvega transdermalnega obliža. *Določitev velikosti odmerka in vzdrževalnega odmerka.* Transdermalne obliže menjajte v 72-urnih presledkih. Odmerek titrirajte, dokler ne dosežete analgetičnega učinka. Če je analgetični učinek ob koncu začetnega obdobja uporabe neustrezen, lahko odmerek povečujete v tridnevnih presledkih do želenega učinka. *Prehod na drugo zdravljenje ali prenehanje zdravljenja.* Če želite preiti na zdravljenje z drugim opioidom, odstranite transdermalni obliž Fentanil Lek in titrirajte odmerek novega analgetika glede na bolnikovo poročanje o bolečini, dokler ne dosežete ustreznega analgetičnega učinka. Pri nekaterih bolnikih se lahko pojavijo odtegnitveni simptomi. *Uporaba pri otrocih.* Zaradi jakosti odmerkov tega zdravila se uporaba pri otrocih ne priporoča. *Uporaba pri starejših.* pri starejših bolnikih je treba biti pozoren na znake prevelikega odmerjanja in odmerek po potrebi zmanjšati. *Uporaba pri bolnikih z okvaro ledvic ali jeter.* pri teh bolnikih je treba biti pozoren na znake prevelikega odmerjanja in odmerek po potrebi zmanjšati. *Uporaba pri bolnikih s povišano telesno temperaturo.* med epizodami povišane telesne temperature bo morda potrebno prilagajanje odmerka. **KONTRAINDIKACIJE:** Znana preobčutljivost za fentanil, katerokoli pomožno snov ali lepilo transdermalnega obliža. Hudo okvarjeno delovanje osrednjega živčevja. Sočasna uporaba zaviralcev MAO ali uporaba v 14 dneh po prenehanju zdravljenja z zaviralci MAO. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Zaradi razpolovnega časa fentanila morate bolnika po pojavu resnega neželenega učinka nadzorovati še 24 ur po odstranitvi transdermalnega obliža. Uporabljene in neuporabljene transdermalne obliže hranite nedosegljive otrokom. Obliž ne smete razdeliti, razrezati ali na kakršenkoli na in poškodovati. Fentanil lahko povzroči znatno respiratorno depresijo. Fentanil Lek je treba previdno dajati: bolnikom s kronično pljučno boleznijo, povišanim intrakranialnim tlakom, možganskim tumorjem, boleznimi srca, jeter in ledvic, tistim z zvišano telesno temperaturo, pri starejših bolnikih, bolnikih z miastenijo gravis. *Odvisnost od zdravila:* Kot posledica ponavljajoče se uporabe se lahko razvijeta toleranca za učinkovino ter psihološka in/ali fizi na odvisnost od nje. *Drugi.* lahko se pojavijo neepileptične (mio)klonične reakcije. **MEDSEBOJNO DELOVANJE Z DRUGIM ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:**. Opioidi, sedativi, hipnotiki, splošni anestetiki, fenotiazini, anksiolitiki, sredstva za sproščanje mišic, sedativni antihistaminiki in alkoholne pijače, ritonavir, ketokonazol, itrakonazol in nekateri makrolidni antibiotiki, petidin in zaviralci monoaminske oksidaze (npr. tranilcipromin), pentazocin, buprenorfin. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Zdravilo ima močan učinek na sposobnost za vožnjo in upravljanje strojev. Bolniki naj se o tem, ali smejo voziti in upravljati stroje, posvetujejo z zdravnikom. **NEŽELENI UČINKI:** Najresnejši neželeni učinek fentanila je respiratorna depresija. Zelo pogosti (> 1/10): zaspanost, glavobol, navzeja, bruhanje, zaprtje, potenje, pruritus. Pogosti (> 1/100, < 1/10): sedacija, zmedenost, depresija, tesnoba, živčnost, halucinacije, zmanjšan apetit, kserostomija, dispepsija, kožne reakcije na mestu uporabe. Občasni (> 1/1000, < 1/100): evforija, amnezija, nespečnost, razdražljivost, tremor, parestezija, motnje govora, bradikardija, tahikardija, hipotenzija, hipertenzija, dispneja, hipoventilacija, hemoptiza, pulmonalna kongestija in faringitis, driska, izpuščaj, eritem, zadrževanje urina. *Preobčutljivostne reakcije* anafilaktične reakcije, laringospazem. *Drugi neželeni učinki.* pri dolgotrajni uporabi se lahko razvijeta toleranca in psihična ali fiziološka odvisnost. Pri nekaterih bolnikih, ki z drugega opioidnega analgetika preidejo na transdermalne obliže Fentanil Lek, se lahko pojavijo reakcije, značilne za prekinitev zdravljenja z opioidi. **NAČIN IZDAJE ZDRAVILA**: Na zdravniški recept. **OPREMA:** Škatlice s 5 transdermalnimi obliži po 25, 50 in 100 mikrogramov/h. **IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM:** Lek farmacevtska družba d.d., Verovškova 57, Ljubljana, Slovenija. **INFORMACIJA PRIPRAVLJENA:** oktober 2006

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UKRC 2007 - Advances in Technology

UKRC 2007 should prove to be one of the most stimulating congresses to date in terms of the scientific coverage of new and developing fields within medical imaging. Key sessions will build on the latest technology being presented within the technical exhibition, providing a unique multi-disciplinary forum to exchange ideas about the latest developments in technology which will impact on radiology and clinical applications.

Monday sees a revisit to a very popular session from 2006 on image perception, featuring an international cast from Europe and the USA, a key update on radiation protection and x-ray equipment performance issues, including Dr. Walter Huda from the USA presenting a new paradigm for CT dosimetry. This first day also involves a look at new emerging imaging techniques such as PET/MR systems and what promises to be a very poignant debate, hosted by Prof. Mike Smith and Dr. Giles Maskell, on whether advances in technology will render the radiologists and radiographer redundant.

Tuesday morning has a session on the latest advances in cartilage imaging and two sessions on developments in MR imaging, incorporating presentations on blood pool agents by Dr. Giles Roditi, molecular MRI by Dr. Arne Hengerer from Erlangen and MR elasticity imaging by Dr. Ralph Sinkus from Paris. The afternoon covers quantitative imaging applications in medicine and a key session on CT with Prof. Mathias Prokop from Utrecht addressing the future role of multi slice CT, dual source CT described by Prof. Thomas Flohr from Erlangen, and 256 slice CT systems from Toshiba.

The pace fails to slow down for the final day on Wednesday, so it's best not to have too late a night at Tiger-Tiger on the Tuesday night! The scientific sessions involve a look at interactive imaging applications for surgery, including interventional MR, stereotaxy in neurosurgery and surgical robotics along with a constantly topical look at the changing face of cardiac CT. The afternoon sees a CT teaching course for radiographers, clinicians, and scientists with everything you need to know about physics, technology, image quality and patient dose.

The advances in technology sessions provide a unique opportunity to view and appreciate developing areas of radiology from a truly multi-disciplinary standpoint. Where else could you meet colleagues of all disciplines and enjoy stimulating presentations from clinicians, scientists and radiographers; not to mention surgeons and cardiologists? Be there in Manchester or be disappointed!

Best wishes,
Mr Andrew Jones
Vice President, UKRC Advances in Technology
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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).

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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.

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

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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.

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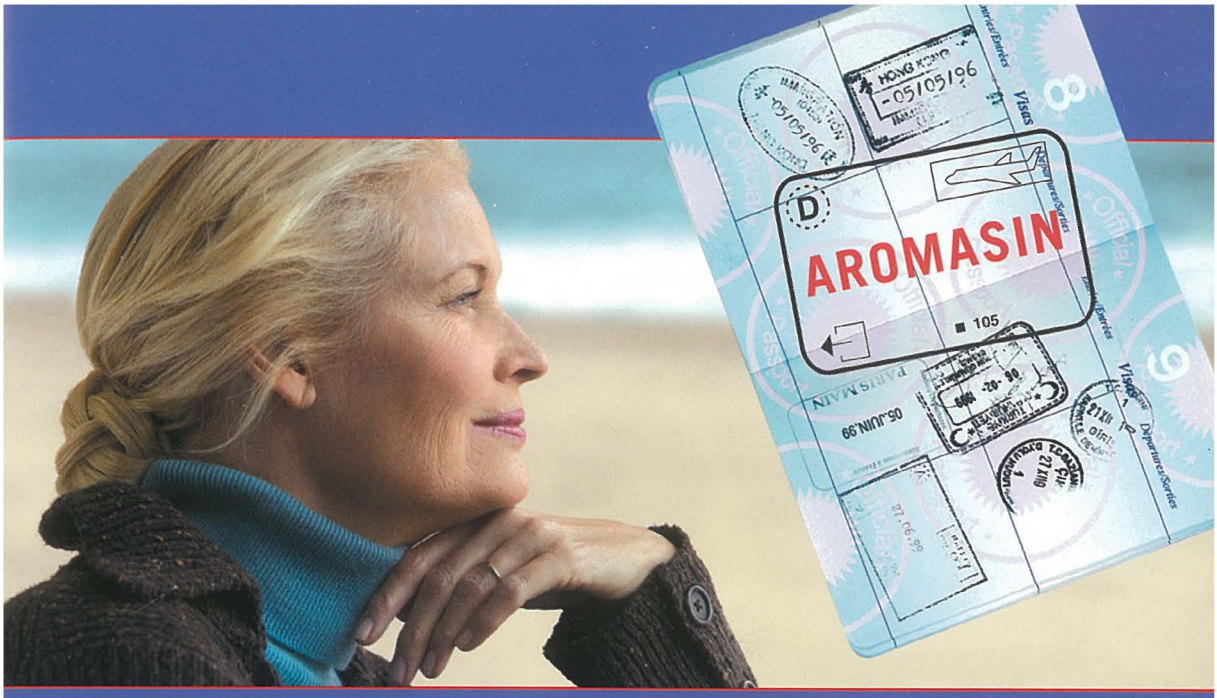

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BISTVENE INFORMACIJE IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA
AROMASIN® 25 mg obložene tablete
Sestava in oblika zdravila: obložena tableta vsebuje 25 mg eksemestana. **Indikacije:** adjuvantno zdravljenje žensk po menopavzi, ki imajo invazivnega zgodnjega raka dojke s pozitivnimi estrogenskimi receptorji in so se uvodoma vsaj 2 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.

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

Pfizer

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