RADIOLOGY AND ONCOLOGY

September 2005
Vol. 39 No. 3
Ljubljana

ISSN 1318-2099

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

September 2005
Vol. 39 No. 3
Pages 171-235
ISSN 1318-2099
UDC 616-006
CODEN: RONCEM

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

Publisher
Association of Radiology and Oncology

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

Reader for English
Vida Kološa

Key words
Eva Klemenčič

Secretaries
Mira Klemenčič

Design
Monika Fink-Serša

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

Published quarterly in 700 copies

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

Subscription fee for institutions EUR 100 (20.000 SIT), individuals EUR 50 (5000 SIT)

The publication of this journal is subsidized by the Ministry of Education, Science and Sport of the Republic of Slovenia.

Indexed and abstracted by:
BIOMEDICINA SLOVENICA
CHEMICAL ABSTRACTS
EMBASE / Excerpta Medica
Sci Base
Scopus

This journal is printed on acid- free paper

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

ISSN 1581-3207

RADIOLOGY AND ONCOLOGY

Ljubljana, Slovenia
September 2005
Vol. 39 No. 3

ISSN 1318-2099
UDC 616-006
CODEN: RONCEM

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Endosonography in the diagnosis of recurrent anal fistulas

Iwona Sudoł-Szopinska[1], Wiesław Jakubowski[1], Malgorzata Kolodziejczak[2], Tomasz Szopinski[3], Anna K. Panorska[4]

[1]Department of Diagnostic Imaging, Medical University Warsaw and Central Institute for Labour Protection – National Research Institute, Warsaw, Poland; [2]Subdepartment of Proctology, Srodmiejski Hospital, Warsaw, Poland; [3]Department of Urology, Central Railway Hospital, Warsaw-Miedzylesie 4, Department of Mathematics and Statistics, University of Nevada, Reno, USA,

Background. *The aim of this work was to compare non-contrast endosonography (NCE) and contrast-enhanced endosonography (CEE) in the diagnostics of recurrent anal fistulas.*

Methods. *In the years 1999-2002 we diagnosed 148 patients with anal fistulas. Fifty-one out of this group had recurrent anal fistulas, remaining had primary disease. For anal endosonography a Bruel&Kjaer scanner with 7.0 MHz transducer was used and 3% solution of hydrogen peroxide was used for CEE. In each case, NCE was followed by CEE, and results of both methods were compared.*

Results. *The difference of percentages of correct diagnoses between NCE and CEE carried out 35.29% in a group of patients with recurrent anal fistulas (95% confidence interval 50.5% - 20.09%); while the difference in a group of patients with primary anal fistulas was only 4.55% (95% confidence interval 11.09% - 2.00%).*

Conclusions. *CEE significantly improves the efficiency of endosonography in diagnosing recurrent anal fistulas, whereas in primary fistulas the value of NCE and CEE is comparable.*

Key words: rectal fistula-diagnosis; endosonography; recurrence

Introduction

The accuracy of anal endosonography (AES) in diagnosing the type of anal fistula, according to different authors, is from 25% to 100% and in cases of recurrent fistulas is the lowest.[1-4] In spite of underlined difficulties resulting first of all from impossibilities of the differentiation of fistula with scar, this problem has still not been examined exactly. This study presents the own results of standard, non –contrast endosonography (NCE) and contrast-enhanced endosonography (CEE) in diagnosing the recurrent anal fistulas, and compares them with the ones obtained in the group of primary fistulas.

Received 1 September 2005
Accepted 15 September 2005

Address to correspondence: Assist. Prof. Iwona Sudoł-Szopinska, MD, PhD, Zaklad Diagnostyki Obrazowej, Wojewodzki Szpital Brodnowski , ul Kondratowicza 8, 03-285 Warsaw; Fax +(48)22 326 5991; E-mail: iwsud@ciop.pl

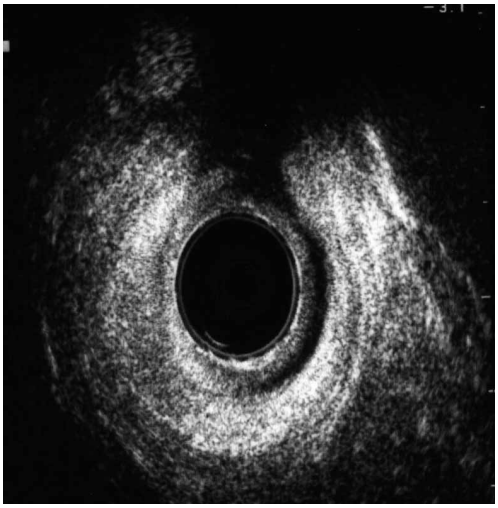

Figure 1a. Recurrent anterior transsphincteric fistula in a woman following obstetric anal sphincter trauma: complex fistula in NCE located in mid/low anal canal.

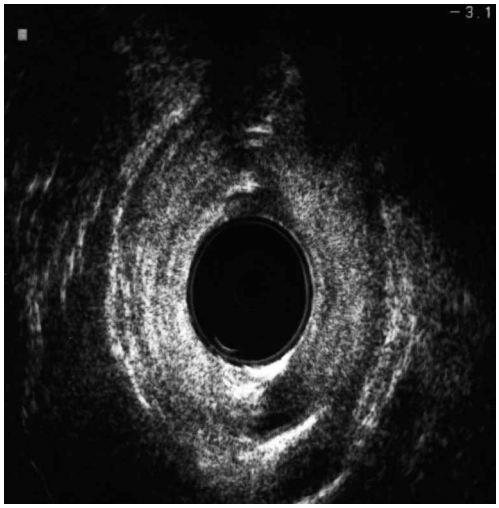

Figure 1b. Recurrent anterior transsphincteric fistula in a woman following obstetric anal sphincter trauma: simple fistula in CEE, located in the distal part of the scar tissues.

Methods

In years 1999-2002 AES was performed at 148 patients (86 male and 62 female, aged between 15 to 73 years, average 46.3 years) with the clinical diagnosis of anal fistulas. In 51 from among 148 persons fistula had a recurrent character. AES was performed by one experienced radiologist, and patients were operated by surgeons from different centres, from which one drove a compact cooperation. In order to compare NCE with CEE only fistulas which on a day of executing research had a permeable external outlet were diagnosed.

For AES a Bruel&Kjaer scanner 3535 with a mechanical transducer of frequency 7.0 MHz with the plastic cone or water balloon was used.[2] No preparation was necessary prior to AES. Patients were examined in the left-lateral position with knees pulled up to abdomen. The study was performed in two-steps. The initial type of anal fistula using Park's classification was defined,[5] together with differentiation between simple and complex fistula, and the location of the internal opening of this fistula was defined. It was followed by CEE, given through the external opening, and with the use of silicone catheter (Nelaton 10-fr), 1-2 ml of contrast which was 3% solution of hydrogen peroxide.[3,6,7] Again one estimated the type of fistula, including the presence of extensions, and location of internal opening. And then results obtained in both, NCE and CEE, were compared. For testing statistical differences between proportions of correct diagnoses in NCE and CEE methods for comparisons of dependent proportion were used.[1] Results of NCE and CEE were compared with surgery. The interval between AES and the operation did not exceed 8 days (1-8 days, average 2.8 days).

Results

In a group of 51 persons with recurrent anal fistulas one ascertained: 37 transsphincteric fistulas, 10 intersphincteric, 3 suprasphincteric, and 1 extrasphincteric (Table 1). Initially in NCE 40.8% of fistulas were simple, and 59.2% had extensions. After a contrast injection CEE showed that 82.4% of fistulas

Table 1. Comparison of non–contrast endosonography (NCE) and contrast-enhanced endosonography (CEE) in differentiation simple from complex fistulas in 51 patients with recurrent anal fistulas

Type and number	NCE		CEE		Surgery	
	simple	complex	simple	complex	simple	complex
transsphincters 37	14	23	32	5	30	7
intersphincteric 10	5	5	8	2	8	2
suprasphincteric 3	1	0	1	2	1	2
extrasphincteric 1	0	1	1	0	1	0

were simple, and only 17.6% were complex. From among all of complicated fistulas shown in NCE, in CEE one did not confirm the presence of extensions in 68, 9% of fistulas; changes described as extensions represented scars after the treatment of fistula (Figures 1a, 1b).

Surgery confirmed most of diagnoses of CEE and showed 78.4% of simple fistulas and 21.6% complex ones.

A statistical analysis was performed in order to qualify whether CEE is significantly more exact in differentiation simple from complex recurrent anal fistulas than NCE. In NCE correct diagnoses were obtained in 56.86%, whereas in CEE 92.16%. The difference of percentages of correct diagnoses between NCE and CEE carried out 35.29% and a 95% confidence interval for this difference was from 50.5% to 20.09%. A significant difference was showed between NCE and CEE in differentiating of simple and complex recurrent fistulas ($p<0.0006$), which proved that CEE is significantly more exact in differentiating simple from complex recurrent anal fistulas. The divergence between CEE and surgery is ascertained only in two transsphincteric fistulas. The injection of contrast extensions were not confirmed, in spite of the fact that the former ones were visible in NCE and became confirmed during the surgery. However, the general efficiency of CEE was significantly greater than that of NCE which proved to be not reliable of differentiating scars with the active fistula. The percentage of falsely positive diagnoses of complex fistulas in NCE carried out 36.7% (18 from 49 fistulas found in NCE), in CEE falsely positive results did not ascertain.

To confirm the diagnostic value of the use of contrast in the investigation of recurrent fistulas, the above results were compared with the endosonographic image of primary fistulas (Table 2). To compare this analysis more accurately, only the types of primary fistulas which were found in a group of recurrent fistulas (i.e. transsphincteric, intersphincteric, suprasphincteric, and extrasphincteric) were included. In NCE 89.9% of simple, and 10.1% of complex fistulas were found. After the contrast administration 97.1% appeared simple and 2.99% had extensions. By the surgery 97% were found simple, and 3% complex, similarly as in CEE.

Identical as for recurrent fistulas a statistical analysis was done for the primary fistulas.

Table 2. Comparison of non–contrast endosonography (NCE) and contrast-enhanced endosonography (CEE) in differentiation simple from complex fistulas in 66 patients with primary anal fistulas

Type and number	NCE		CEE		Surgery	
	simple	complex	simple	complex	simple	complex
transsphincteric 36	31	5	34	2	34	2
intersphincteric 13	12	1	13	0	13	0
suprasphincteric 7	10	0	8	0	7	0
extrasphincteric 10	9	1	10	0	10	0

In NCE 93.94% of correct diagnoses were obtained and in CEE 98.48%. The difference between percentage of correct diagnoses in NCE and CEE was 4.55% and 95% confidence interval was from 11.09% to 2.00%. A statistical difference between NCE and CEE in differentiating simple from complex primary fistulas was found at the level of significance p=0.09. The test was not characteristic on 5% but only on 10% level. Therefore it is ascertained that CEE only slightly improves the diagnostic accuracy of endosonography for the primary anal fistulas.

Discussion

Cheong *et al*[3] underlines that CEE is especially precious in diagnosing recurrent and complex anal fistulas. Our statistical analysis confirmed that for recurrent anal fistulas CEE is significantly more accurate than NCE ($p<0.0006$). In NCE 36.7% of falsely positive diagnoses of complex fistulas were found, in CEE such results were not observed. The efficient treatment of fistula depends on the eradication of all extensions. However, limitations of AES in patients with a history of surgery of anal fistula or abscess, resulting from difficulties in differentiating scars with the active fistula, and especially with its extensions, were well known.[3,4,8] Although Law *et al*[9] describes that the scar has lower and more homogeneous echogenicity than the fistula and smooth outlines as well; the most often image of these two is identical. Additionally narrow, irregular lumen of the recurrent fistula and its extensions has often no content liquid or air, which have a characteristic image.[6] Consequently not recognized and not removed extensions are the main reasons of the recurrence of fistula, and a wrong estimated type of fistula can lead to damages of anal sphincters.[3,4,8]

In spite of underlined difficulties with endosonographic diagnostics of recurrent fistulas, one did not examine the scale of this problem. This study confirmed a large number of false diagnoses of complex fistulas in NCE. A comparative analysis with primary fistulas showed that in a group of primary fistulas it had a place only in 7.2% of fistulas. In NCE scars following previous surgery were interpreted as extensions, and so the accuracy in such differentiation was only 56.86%. The introduction of contrast raised to 92.16%. Also Cheong *et al*[3] and Kruskal *et al*[6] emphasized that only CEE can be accurate. Using CEE Kruskal *et al* accurately differentiated scars with fistulas in 20 from 30 patients (67%), including 39 patients with a doubtfully initial, without contrast, image. Our results showed that in only in two cases (4%) extensions of transsphincteric fistulas were not recognized in CEE. One ran in the direction of the top of ischio-rectal fossa, the second crossed the levator ani muscle. The former was probably blocked by thick secretion, and the latter would become visible when AES was supplemented by the use of a water balloon. In this case, however, too hastily initial NCE became interpreted as scar and one did not extend the investigation of ampulla of the rectum. It seems that such an approach should be done in case of high fistulas, especially the recurrent ones. The other thing is that, in spite of the proved significantly higher accuracy of CEE, one should also taken into account the result of NCE. Results obtained in a group of primary fistulas (66 patients) diametrically differed from those of the recurrent ones.

The number of complex fistulas was not large, both in NCE and in CEE, and the percentage of falsely diagnosed complex fistulas in NCE was only 7.24%. As in a case of recurrent fistulas, the scars after the treatment of fistula were responsible for correct diagnoses; so, in the primary fistulas the only reason was the inability to differentiate extensions from the heterogeneous echotexture of perirectal tissues. A statistical analysis showed

that NCE has comparable values to CEE. However, although it seems that it is more important not to miss the extension that gives a false diagnosis of extension (regarding the risk of surgical complications: recurrence, damage of sphincters), one must remember that too aggressive approach during the operation, in order to find indicated in NCE extensions, can also lead to complications - creating of iatrogenic fistula.

Conclusions

1. Standard, NCE is not reliable method in differentiation scars with active recurrent fistula and application of contrast significantly improves efficacy of AES.

2. In the case of primary anal fistulas, NCE and CEE have comparable efficiency.

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Radiol Oncol 2005; 39(3): 177-80.

Diagnostics and operative treatment of retrorectal cysts – description of five cases

Małgorzata Kołodziejczak[1], Maciej Grochowicz[1], Iwona Sudoł-Szopińska[2], Anna Kosim[1], Robert Stefański[1]

[1]*Proctology, Sub-Department of General Surgery, City Traumatic Hospital, Warsaw, Poland*
[2]*Central Institute for Labour Protection – National Research Institute, Warsaw and Department of Imaging Diagnostics, Second Faculty, Medical School, Warsaw, Poland*

Background. *Retrorectal cysts (RC) are unusual lesions. Publications on RC are very rare and describe a few cases at most.*
Methods. *Authors describe five patients with RC. The diagnostics of RC was based on the medical history of the patients and the basic diagnostic investigation was trans rectal ultrasonography. An operation to remove the cysts from perineal access was the treatment administered in these cases.*
Results. *In three cases the histopathological examination showed cystis epidermalis. In another case a cyst epithelialized with ciliated epithelium was found. In the last case bone tissue, fatty tissue and fibrous tissue were depicted, all in the state of chronic inflammation.*
Conclusions. *Per rectum digital exam is the basic examination decisive in making the diagnosis. TRUS should be employed as the diagnostic investigation in order to estimate precisely the size of a cyst and its proportion to the rectum wall. Retrorectal cystectomy in perineal access is an effective method of treatment of this disease. This article, likewise other research works, describes a small group of patients, therefore, its conclusions should be treated as preliminary ones.*

Key words: rectal disease-ultrasonography-surgery; cysts

Introduction

Retrorectal cysts (RC) are unusual lesions. The majority of publications on this subject concerns a few cases at most or describe one casuistic patient.[1-5] In majority of cases (75%) the cysts are congenitally inborn.[6]

There are many classifications of retrorectal cysts and tumours. They are mostly based on a histopathological structure of the cysts which is connected with the embryonic development of these lesions. Levelady's and Deckerty's classification is the most frequent one and covers the following changes: dermoidal cysts, chordomas, myelomenin-gocele hernias, cysts on retrorectal intestine and other tumours, among them leiomyomas, neuromas and sarcomas.

Received 27 May 2005
Accepted 4 June 2005

Correspondence to: Iwona Sudoł-Szopińska, MD PhD, CIOP-PIB, ul. Czerniakowska 16, 00-701 Warszawa, Poland; E-mail: iwsud@ciop.pl

Dermoidal cysts are lined with stratified squamous epithelium and contain skin appendages. They are filled with liquid or greasy contents whereas chordomas are filled with thick jelly-like contents. Due to direct anastomosis with sacral and coccygeal bones chordomas cause deterioration of these osseous structures and, when growing, they can exert pressure on nervous trunks. Cysts on retrorectal intestine are mainly teratomas. In majority of the cases they contain histologically mature tissues i.e. elements of the skin and their appendages, teeth or osseous fragments. They occur more often in women.

Cysts are mainly of a mild character. However, they can be hormonally active[3,4] and can also undergo a malignant transformation. Dermoidal cysts turn malignant in 10-15% of the cases. A malignant transformation of chordomas occurs in 10% of the cases and a similar transformation of teratomas occurs in 10–20% of the cases.

Retrorectal cysts can be positioned differently and they can grow to different sizes. In a few cases of newborns with congenitally inborn cysts retrorectal tumours are placed behind pelvis minor[7] but they relocate and exert pressure on rectum. In adults RC are mainly positioned between the rectum and the sacral bone. The cysts can cause anal pain and sensation of tenesmus. They can suppurate. It may occur that patients suffering from such ailments are diagnosed with coccygodynia and they undergo a long-term ambulatory treatment with analgesics, steroid and non-steroid anti-inflammatory drugs. Per rectum the examination plays the decisive role in diagnosis of RC. It reveals tense tender resistance on the posterior wall of the rectum. It is sometimes difficult to differentiate between a cyst and a high extra levator abscess; the diagnosis depends on clinical symptoms. In many patients, who are diagnosed with retrorectal cysts, rectoscopy is an effective solution. Transrectal ultrasonography (TRUS) is an investigation which confirms the diagnosis and allows determining precisely the size of a cyst and its relation to the rectum wall.[1] Endosonography determines - to a certain point - whether the lesion merely models the rectum wall or infiltrates it. Transperineal ultrasound is an additional supplementing diagnostic investigation which together with TRUS gives a full picture of the lesion.

In the following article the authors present cases of five female patients who have been treated for retrorectal cysts and describe the diagnostics as well as the treatment of these patients.

Methods

Patients

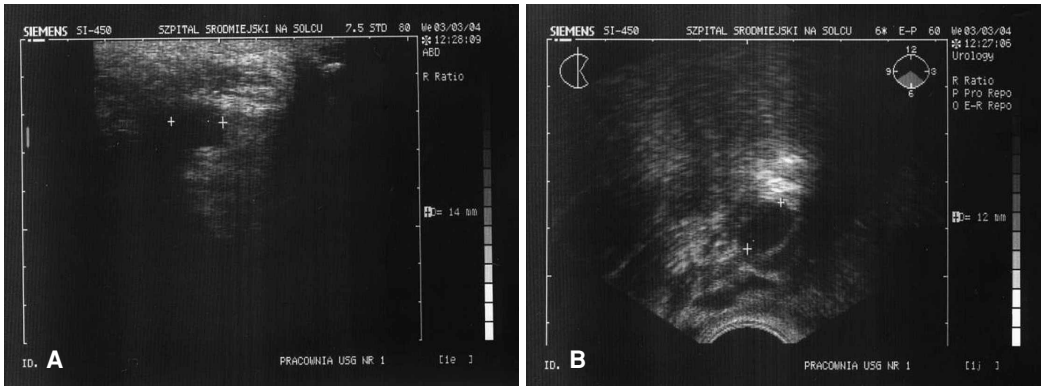
Five female patients from 36 to 55 years of age (the average 44 years) were operated on between 1 January 2001 and 30 June 2004 in Proctology Department of City Hospital at Solec (Table 1).

Diagnostics

The diagnostics of RC was based on the medical history of the patients. They all notified of severe pain and sensation of tenesmus which were growing in a sitting position. As the result of per rectum investigation elastic tender resistance of a different size was found and it was protruding from the posterior wall of rectum. The rectoscopic picture showed that the mucous membrane of rectum was unchanged. TRUS was the basic diagnostic investigation (Figures 1a, 1b).

Therapy

An operation to remove the cysts from perineal access was the treatment administered in these cases. The patients were placed on their side with legs pulled up. The incision was made between the anus and the coccygeal bone. In three cases it was necessary to perform a resection of the coccygeal bone. The wound was drained using Redon's method.



Figures 1a, 1b. Retrorectal cyst presented with transperineal and transrectal ultrasonography.

The material was sent for histopathological examination. In all these cases there were no complications in postoperative course.

Results

In three cases the histopathological examination showed cystis epidermalis. Its wall was formed with fibrous tissue epithelialized with cornifying stratified squamous epithelium. In another case a cyst epithelialized with ciliated epithelium was found. In the last case the result depicted bone tissue, fatty tissue and fibrous tissue, all in the state of chronic inflammation.

The patients had regular check-ups at Proctologic Hospital Clinic. In four cases the ailments subsided completely. One patient still suffers from ailments of different intensification. She also has degenerative changes in lumbosacral segment of vertebral column.

Discussion

In the presented material of all cases full compatibility between preoperative diagnostics

Table 1. Characteristics of patients with retrorectal cysts and their treatment

Age	Under 30 years old	0	0
	30 – 40 years old	2	40%
	over 40 years old	3	60%
Sex	Male	0	0
	Female	5	100%
Duration of symptoms	< 3 months	1	20%
	3 – 6 months	0	0
	6 – 12 months	1	20%
	> 12 months	3	60%
Type of surgical procedure	Cystectomy	2	40%
	Cystectomy combined with resection of the coccygeal bone	3	60%
Compatibility between surgery and transrectal ultrasonography	Compatible	5	100%
	Non-compatible	0	0
Position in relation to the rectum wall	Intramural	2	40%
	Adjacent to the rectum wall	3	60%

and surgical evaluation of the lesion was found.

In spite of an apparent easiness in the diagnostics of this disease, it often happens that patients have been treated with an ineffective method for many months before they finally receive professional help. The most probable reason for such a situation is the rarity of retrorectal cysts occurrence and physicians' lack of experience in their diagnostics.

Singer *et al* describe seven patients who suffered from ailment caused by RC but who were wrongly diagnosed with, for example, anal fistula, pilonidal cyst, anorectal abscess, psychiatric disease, pain after an injury, post partum pain or proctalgia fugax. They conclude that the best diagnostic investigation is an accurate per rectum examination supplemented with the computer tomography.[8]

There are investigators who recommend the use of magnetic resonance in RC diagnostics.[9] However, it is well known that this investigation is expensive and less available than the ultrasound scan.

Due to the risk of malignant transformation, suppuration and pressure symptoms, RCs should be removed in an operation in perineal or abdominal access.

Many investigators describe cystectomy combined with the resection of the coccygeal bone as a good operative method.[2] If the cyst is closely bound to the caudal bone, it has to be removed together with the fragment of the bone as it is the point where the cyst grows from. Leaving it behind may cause the regrowth of the cyst (local malignancy). There are cases that laparatomy ensures more accurate evaluation and surgical access.[1] The choice of surgical access depends on the size and location of the cyst, its anatomical position in relation to other organs and the experience of a surgeon. In order to qualify a patient for laparatopy it is advisable to supplement the preoperative diagnostics with CT of pelvis and abdominal cavity.

Conclusions

1. Per rectum digital exam is the basic examination decisive in making the diagnosis.

2. TRUS should be employed as the diagnostic investigation in order to estimate precisely the size of a cyst and its proportion to the rectum wall.

3. Retrorectal cystectomy in perineal access is an effective method of treatment of this disease.

4. This article, likewise other research works, describes a small group of patients, therefore its conclusions should be treated as preliminary ones.

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Radiol Oncol 2005; 39(3): 181-4.

case report

Communicating saccular pyloroduodenal duplication. Case report

Ivica Sjekavica[1], Marko Batinica[1], Mario Lušić[1], Irena Senečič-Čala[2], Božidar Oberman[1], Ranka Štern-Padovan[1]

[1] Clinical Institute for Diagnostic and Interventional Radiology, School of Medicine, University Hospital Center Zagreb – Rebro; [2] Clinical Department of Pediatrics, School of Medicine, University Hospital Center Zagreb – Rebro, Zagreb, Croatia

Background. *Duplication anomalies of pyloroduodenal region are not common. Intestinal duplications should be considered if additional specific development malformations are present.*

Case report. *We report a case of the pyloroduodenal duplication in 22-month-old girl by whom intermittent nausea and vomiting were the first symptoms. US revealed an anechoic cystic lesion between the stomach and the left liver lobe. The upper gastrointestinal contrast study revealed stenosis in the pylorobulbar region, as a result of the extrinsic compression. The diagnosis of the alimentary tract duplication cyst compressing the atypically formed head of pancreas was highly suspected by the contrast enhanced multi slice computerized tomography (MSCT). The intraoperative contrast application detected a communication between both, duplication and pyloric region. The patohistological examination confirmed a duplication cyst containing gastric and duodenal mucosa with no ectopic pancreatic tissue.*

Conclusions. *The ultrasound examination, as the initial diagnostic procedure of intestinal duplication, usually reveals a cystic anechoic lesion. Additional barium study, contrast enhanced CT or MRI scan are useful in diagnosis of alimentary tract duplications, providing supplementary information.*

Key words: pylorus-abnormalities; duodenum-abnormalities

Introduction

Isolated duplications of the alimentary tract are rare congenital malformations with a reported incidence of 1:5000.[1,2] Duplication anomalies of the pyloroduodenal region are not common as well. Intestinal duplications should be considered if additional specific development malformations are present. The aetiology of duplication cysts may be multifactorial.[3] The usual symptoms in patients with alimentary duplication cysts are gastrointestinal obstruction, vomiting, diffuse abdominal pain and sometimes melena. [2,4]

Received 12 September 2005

Accepted 20 September2005

Correspondence to: Marko Batinica, M.D., Clinical Institute for Diagnostic and Interventional Radiology, University Hospital Center Zagreb – Rebro, Kišpatićeva 12, 10000 Zagreb, Croatia; Phone: +385 1 2388 455; Fax: +385 1 2388 250; E-mail: marko.batinica@zg.htnet.hr

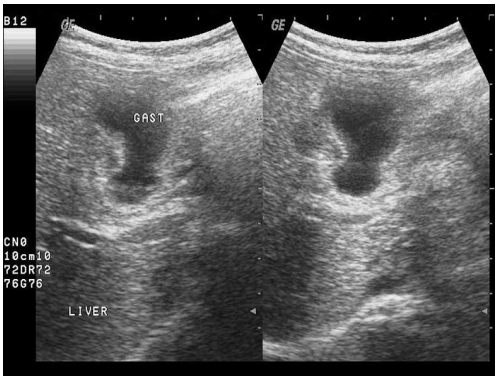


Figure 1. US if the upper abdomen. Anechoic oval structure between stomach and left liver lobe.

Case report

A 22-month-old girl with abdominal pain and recurrent vomiting was presented in the recent 15-month-period. Physical examination findings showed a small palpable mass in the left epigastrium. Early sonographic findings revealed an anechoic oval structure between the stomach and the left liver lobe suspected to be a duplication of the alimentary tract. There was no proof of any communication to intraperitoneal structures. No communication with the gastrointestinal tract could be demonstrated as well (Figure 1).

The radiological examination included the upper gastrointestinal contrast radiography which revealed stenosis in the pyloroduodenal region, 4 cm in length. Stenosis was considered as a sign of the extrinsic compression (Figure 2).

The contrast enhanced *multi* slice computerized tomography (MSCT) was compatible with US findings and contrast radiography. It revealed a well-defined cystic fluid collection, 3.3 x 3.9 cm, located between the left liver lobe and pylorus, suggesting an enteric duplication and extrinsic compression on the duodenal region. A mesenteric cyst, however, could not be excluded. The head of pancreas was severely deformed due to the cyst formation. There were no signs of acute pancreatitis (Figures 3,4).

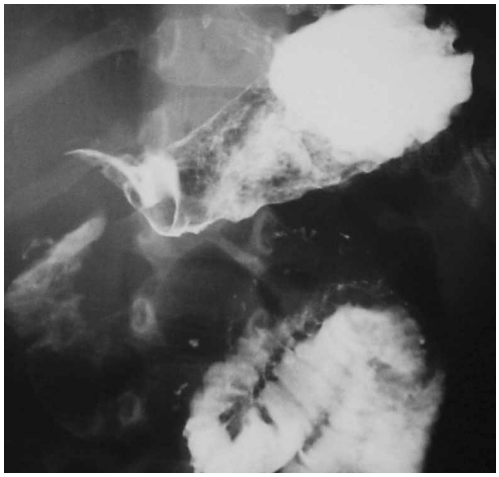


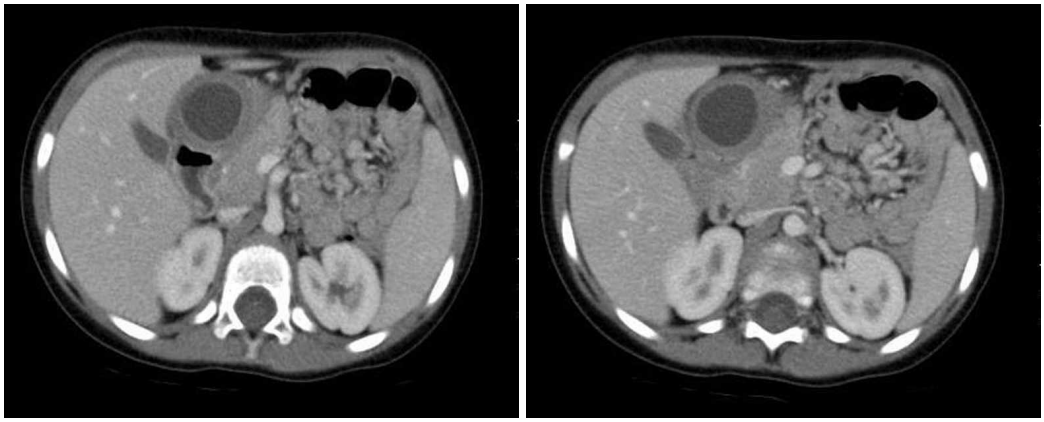
Figure 2. Upper gastrointestinal contrast radiography. Stenosis in pyloroduodenal region as sign of extrinsic compression.

The explorative surgery revealed a spherical duplication anterior to the pyloric region. The intraoperative contrast application through the cystic structure suggested a narrow communication between the duplication and alimentary tract. A partial resection was performed due to the common wall with pylorus shared in small segment. Mucosa of the remnant cyst wall was excised. The histopatological examination of specimen confirmed a pyloroduodenal duplication cyst containing gastric and duodenal mucosa.

Discussion

Duplication cysts are spherical or elongated hollow structures, lined by epithelium which is usually identical to a part of the alimentary tract they are aligned to, usually sharing common blood supply.[1]

Duplications occur due to a fault recanalization of the temporarily obliterated fetal intestine or incomplete embryogenic budding. They tend to be associated with other congenital malformations, mostly vertebral anomalies, intestinal atresia, double gallbladder or double uterus.[2,5] A gastrointestinal duplica-



Figures 3, 4. Contrast enhanced MSCT of the upper abdomen. Well-defined cystic fluid collection, 3,3x3,9 cm, between left liver lobe and pylorus, suggesting an enteric duplication.

tion may develop at any level of the gastrointestinal tract, often containing ectopic tissue. Gastric mucosa and pancreatic tissue are the only ones that have clinical significance. The usual localization of duplication development is enteromesenteric side of the alimentary tract. The majority of duplications are diagnosed in the early childhood due to symptoms developing in the first years of life.[3,6-7]

Differential diagnoses of duplications in children include cystic neoplasm, congenital and parasitic cysts and pancreatic pseudocyst.

Symptoms of intestinal duplications in children are mostly non-specific, depending on the localization. They may present as vomiting, palpable abdominal mass, problems with feeding and pancreatitis. Lesions in distal segments of intestine include flank abdominal pain, palpable tumour and melena.[3]

As a method of treatment, surgery should be attempted to remove the duplication radically, even if together with adjacent gut segment. If the cyst is closely related to vital structures, a total excision may not be possible. In such cases, the partial excision remains as a possible solution.

The diagnosis of a duplication cyst may be suspected on barium enhanced radiographs demonstrating the extrinsic pressure produced by abdominal mass.[8] US, CT and MR confirm a definitive diagnosis.

On US, duplications appear as anechoic mass with a thin echogenic rim representing mucosa, covered by a hypoechoic muscular wall. These findings are characteristic for the non-communicating type of a duplication cyst.[7,9]

CT demonstrates the location and extension of the duplication defining adjacent structures and excluding additional abnormalities. Rarely, CT demonstrates cyst wall calcifications.[7,10]

MR cholangiography is helpful in detecting biliary and ductal anomalies.[11,12] In addition, radionuclide imaging with ^{99m}Tc can show the increased uptake if a cyst contains gastric mucosa.[7]

Conclusions

Duodenal duplications constitute about 5% of all alimentary tract duplications. Patohistological findings in duplications usually show ectopic tissue such as gastric and/or pancreatic mucosa.[3] Complications as bleeding, perforation of ulceration may occur. A malignant alteration of duplication is extremely rare.[13]

In our case, the diagnosis of the alimentary tract saccular duplication compressing the atypically formed head of pancreas was highly suspected by US and contrast enhanced CT.

A contrast study of duplication during the surgical excision detected a communication between the duplication and pyloric region. The patohistological examination confirmed a duplication cyst containing gastric and duodenal mucosa.

The ultrasound examination, as an initial diagnostic procedure of the intestinal duplication, usually reveals a cystic anechoic lesion. Additional barium study, contrast enhanced CT or MRI scan can be useful in the diagnosis of alimentary tract duplications, providing the supplementary information.

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Radiol Oncol 2005; 39(3): 185-91.

Coronary artery calcium scoring in myocardial infarction

Šerif Bešlić, Faruk Dalagija

Institute of Radiology, Clinical Center University of Sarajevo, Bolnička 25, Sarajevo, Bosnia and Herzegovina

Background. *The aim of this study was to evaluate coronary artery calcium scoring and the assessment of the risk factors in patients with myocardial infarction (MI).*

Methods. *During the period of three years, 27 patients with MI were analyzed. The average age of patients was 66.1 years (46 to 81). Coronary arteries calcium was evaluated by multi row detector computed tomography (MTDC) «Somatom Volume Zoom Siemens«, and, retrospectively by ECG gating data acquisition. Semi automated calcium quantification to calculate Agatston calcium score (CS) was performed with 4 x 2.5 mm collimation, using 130 ml of contrast medium, injected with an automatic injector, with the flow rate of 4 ml/sec. The delay time was determined empirically. At the same time several risk factors were evaluated.*

Results. *Out of 27 patients with MI, 3 (11.1%) patients had low CS (10- 100), 5 (18.5%) moderate CS (101-499), and 19 (70.4%) patients high CS (>500). Of risk factors, smoking was confirmed in 17 (63.0%), high blood pressure (HTA) in 10 (57.0%), diabetes mellitus in 7 (25.9%), positive family history in 5 (18.5%), pathological lipids in 5 (18.5%), alcohol abuse in 4 (1.8%) patients. Six (22.2%) patients had symptoms of angina pectoris.*

Conclusions. *The research showed high correlation of MI and high CS (>500). Smoking, HTA, diabetes mellitus, positive family history and hypercholesterolemia are significant risk factors. Symptoms are relatively poor in large number of patients.*

Key words: myocardial infarction; coronary vessels; calcinosis; tomography; X-ray computed

Introduction

Atherosclerosis is a systemic generalized disease which usually occurs in different parts of arterial system, and affection of coronary arteries is of special interest.[1,2]

Coronary calcifications are almost always a sign of coronary atherosclerosis.[3] That is the reason why the level of coronary calcification can be considered as a risk factor.[4] Consequently, coronary artery calcium is taken as a predisposing marker of coronary atherosclerosis.[5,6] Therefore, the risk of future cardiac disease can be higher in patients with coronary calcifications than in those without them.

Received 7 March 2005
Accepted 20 April 2005

Correspondence to: Assist. Prof. Šerif Bešlić; MD, PhD, Institute of Radiology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina; Phone/Fax: +387 33 444 553; E-mail: sbeslic@bih.net.ba

Coronary calcifications are presented on CT scans as more than two consecutive pixels over 130 HU.[6] Coronary calcification has prognostic value in identification of asymptomatic patients who are at higher risk of coronary disease.[7]

Accurate and reproductive quantification of calcium is essential in the assessment of the progression of coronary calcification, as atherosclerosis markers, in a certain patient.[6]

Screening of coronary calcification started in 1990, primarily for the identification of patients with the coronary artery disease.[1] Agatston *et al*. have introduced this method for quantification of coronary artery calcium, by multiplication of calcified plaques zones based on plaque attenuation values.[6]

However, detection and quantification of coronary calcification is more adjusted for the risk evaluation of a sudden cardiac attack in asymptomatic patients than for the identification of symptomatic patients with the ischemic heart disease.[1]

The fact is that patients with higher Agatston score may have an increased risk for the future cardiac attack. That gives the fundamental motivation for the measurement of coronary calcium scoring, a better definition of patients who are at risk of myocardial infarction and of a sudden coronary death.[4]

The current stand-point of the American Society of Heart is that coronary heart disease (CHD) and atherosclerosis are less likely if a CT shows no coronary calcification. The risk of unexpected cardiac attack, like myocardial infarction and sudden death, can be very low in the period of consecutive two to five years. Besides, patients without coronary calcification will most probably have a normal finding at coronary angiography.[3]

The coronary calcification test is considered to be a strong indicator of cardiac mortality in elderly people, and it is independent of other cardiac risk factors.[8]

However, CHD cannot be confirmed, or ruled out only on the basis of coronary calcification.[3] Initial examinations found noncalcified plaques more often in patients with unstable angina, while calcified lesions were found mostly in patients with stable angina.

Early diagnosis is important for the plaque characterization, and the selection of treatable patients before the appearance of an ischemic attack. This helps a physician to distinguish lesions which are reversible with the medical treatment, from these that will need a surgical or endovascular treatment. It is believed, that the most promising techniques will be those which will be able to detect inflammatory processes in the plaque.[1]

CHD have been the most common cause of hospitalization and mortality in industrialized countries for many years.[9] It is usually caused by the rupture of an atherosclerotic plaque, which results with the total occlusion of the coronary artery. In developed world, 1/2 of a male and 1/3 of a female population will suffer from it after the age of 40 years.[7]

Currently, main available options for treatment are surgical revascularization with the coronary artery bypass graft (CABG), and interventional transluminal, catheter based procedures. Selection of treatment procedure depends on reliable diagnostic assessment of coronary arteries.[9] However, imaging of the coronary arteries is challenging. Their small dimension and position, together with breathing and heart pulsation artefacts, make visualization and detection of stenosis particularly difficult.[10]

Cardiac catheterization is a method of choice for determining the morphological status of coronary arteries, and it was often combined with interventional treatment procedures, like balloon angioplasty and stent implantation.[9] A selective catheterization of the heart primarily shows morphological changes combined with stenotic CHD, but also gives the parameters of myocardial function, and possibility for the measurement of haemodynamic parameters.

The main limitations of the coronary an-

giography are general contraindications, projection, and stenosis of the left branch, myocardial bypasses, endoluminal summation effects, and impossibility of the coronary artery wall visualization.[7] Cardiac catheterization is an invasive method which is connected with a certain risk and certain complications.

In recent years, many intensive researches have been undertaken with diagnostic procedures of low risk in order to replace and supplement, at least partially, current diagnostic cardiac procedures. Alternative imaging methods are: electron beam computed tomography (EBCT), multirow detector CT (MDCT) and magnetic resonance imaging (MRI).[9]

EBCT was the first CT modality which made possible the imaging of coronary arteries without movement artefacts. Agatston and co-operators proved EBCTs superiority in the detection of coronary calcification over fluoroscopy. Besides, they set up the quantification algorithm for the identification of patients with and without ischemic coronary artery disease.[3]

EBCT has the best overall accuracy, and is considered to be even better than MRI on the adequate visualization of proximal and middle segments of coronary artery, as well as on the detection of stenosis in these segments. Both modalities can be used, and they are complementary to each other. Being time-consuming, they cannot be alternative to the conventional coronary angiography for the time being.[10]

CT and MRI have a wide range of indications in non-invasive diagnostics, and they are partially overlapping in their clinical application.[9]

Besides the visualization of the coronary artery lumen, the vessel wall can also be seen on CT transversal scans.[3]

Non-invasive CT coronary angiography (CTA) may have even higher potential in the presumption of cardiac risk than calcium scoring. So, not only the lumen of the coronary artery can be visualized, but also non-calcified and non-stenotic atherosclerotic plaques can be detected on axial CT scans.[4] With contrast enhancement, both calcified and non-calcified lesions can be completely evaluated.[3]

A high negative predictive value of the coronary CTA can justify the examination of symptomatic patients with low or moderate pre-test probability of coronary artery disease. This technique could be used for the exclusion of coronary microangiopathy, and to avoid unnecessary cardiac catheterizations. Past researches proved that the wall of the coronary artery and its lumen can be seen by MDCT.[11] This method gives the possibility to follow-up the progression of coronary atherosclerosis in a non-invasive way.[5] MDCT coronary artery calcium scoring has been improved with retrospective ECG – gated data acquisition.[12]

CT and MRI have proved to be useful in the assessment of the changes in the vessel wall, and in the identification of highly risk patients who may benefit from treatment.[1]

MR angiography of the coronary arteries and MDCT angiography are the leading ways to supplement the diagnostic cardiac catheterization, whose role is mainly limited to the diagnosis of coronary atherosclerosis and measurement of the degree of stenosis.[13]

The aim of this study was to confirm coronary artery calcium scoring (CS), and risk factors in patients with the history of the previous myocardial infarction (MI). In this way, we wanted to indirectly confirm the relation of MI and the level of CS, as a risk factor.

Methods

During the three-year period, a large number of patients with various referral diagnoses were examined at our Institute of Radiology. Among them, 27 patients had the history of

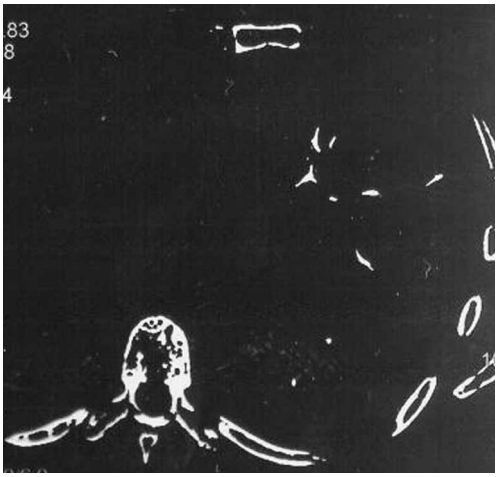

Figure 1. »Calcium Window« for identification of calcified plaques.

previous myocardial infarction. The average age of the patients was 66.1 years, the youngest was 46 and the oldest patient was 81 years old. Out of these patients, 23 (85.2%) were male and 4 (14.8%) female. In all patients, CS was determined according to the Agatston. The patients were divided into three categories based on the CS results: patients with the lowest CS (10-100), the intermediate CS (101-499), and the highest CS (>500) (Figure 1).

All patients were examined on MDCT machine with the four-row detectors, Siemens »Somatom Volume Zoom«. Calcium quantification Agatston calcium score program was used for examinations, native and contrast series were done, with non-ionic contrast medium applied by the automatic injector in the cubital vein. We used the collimation 4 x 2.5 mm, rotation time 500 msec, pitch 1.5 and FOV 200. 130 ml of contrast medium was injected, followed by 20 ml of saline, and a flow rate of 4ml/sec applied. The delay time was empirically determined, and it was in the range from 25 to 30 sec. The retrospective ECG gating was used during the examinations as well.

The following risk factors were taken from the patient's histories as relevant: smoking, arterial hypertension, diabetes mellitus, family history, increased lipids, alcohol abuse, and symptoms of angina pectoris.

Results

In the period from 2001 to 2003, we examined 27 patients with the history of myocardial infarction. The ratio of men to women was 5.7 to 1. In average, women were older than men for 3.9 years (Table 1).

In 27 patients with the history of myocardial infarction by whom we measured Agatston calcium score, 3 (11.1%) patients had low CS (10-100), 5 (18.5%) moderate CS (101-499), and 19 (70.4%) patients high CS (>500). Of risk factors, smoking was confirmed in 17 (63.0%) patients, high blood pressure (HTA) in 10 (37.0%), diabetes mellitus in 7 (25.9%), positive family history of cardiac disease in 5 (18.5%), pathological lipids in 5 (18.5%), and alcohol abuse in 4 (14.8%) patients. Six (22.2%) patients had symptoms of angina pectoris.

Discussion

As it has been shown by this study, coronary artery disease is predominantly a male disease because 85.2% of our patients were male, while only 14.8% were female. Therefore, male were 5.7 times more often victims of myocardial infarction. Besides, female who had myocardial infarction were in average older than male (69.7 to 65.8 years). This proves that age and male sex are significant risk factors, which is in accordance with the results from the literature.

Out of other risk factors related to the increased CS and development of myocardial infarction, smoking is at the first place, then hypertension, diabetes mellitus and hypercholesterolemia. It is also proved that only $^1/_4$ of the patients with the history of the my-

Table 1. Frequency of the risk factors in relation to age, sex and CS in patients with myocardial infarction

N	Age	Sex	Smoking	HTA	F. History	Diabetes	HHL	MI	Alcoholism	AP	CS
1	70	M	+	+	-	+	+	+	+	-	75
2	68	M	+	-	-	-	-	+	-	+	>500
3	44	M	+	+	-	+	+	+	-	-	>500
4	71	F	+	+	-	-	-	+	-	+	>500
5	72	F	+	+	+	+	-	+	-	-	>500
6	62	M	+	-	-	-	-	+	-	-	>500
7	62	M	+	+	-	+	-	+	+	-	>500
8	66	M	+	-	-	-	-	+	-	+	>500
9	70	M	+	-	+	-	+	+	-	+	>500
10	80	M	+	-	+	-	+	+	-	-	187
11	71	M	+	-	-	-	-	+	-	-	>500
12	61	M	-	-	-	-	-	+	-	-	**222**
13	46	M	-	-	-	-	-	+	-	-	**257**
14	68	M	+	+	+	-	-	+	-	+	**232**
15	81	M	+	-	-	-	-	+	+-	-	>500
16	63	M	+	-	-	-	-	+	-	-	>500
17	61	M	-	-	-	-	-	+	-	-	>500
18	78	F	-	-	-	-	-	+	-	-	**323**
19	77	M	-	-	-	+	-	+	-	-	>500
20	78	M	-	-	-	+	-	+	-	+	>500
21	72	M	+	+	-	-	-	+	-	-	>500
22	66	M	-	-	-	-	-	+	-	-	**97**
23	58	F	+	+	-	-	-	+	-	-	>500
24	64	M	-	-	-	-	-	+	-	-	>500
25	61	M	-	-	-	-	-	+	-	-	>500
26	75	M	+	+	-	-	-	+	-	-	>500
27	48	M	-	+	+	+	+	+	+	-	**10**
Total			**17**	**10**	**5**	**7**	**5**	**27**	**4**	**6**	
%			**63.0**	**37.0**	**18.5**	**25.9**	**18.5**	**100**	**14.8**	**22.2**	

N = number; HTA = high blood pressure; F. History = positive family history; HHL = Hypercholesterolemia; MI = myocardial infarction; AP = angina pectoris; CS = calcium score; M = male: F = female

ocardial infarction had symptoms of angina pectoris. That points out the importance of CS and the necessity of precaution in patients with high CS and those who are without any symptoms.

Data from the literature show the correlation between the high coronary artery calcium scores and the increased risk of the coronary artery disease and death.[8]

The same data show that the persons with the score over 500 had 2.7 times higher risk of death caused by heart attack than those with the score 101 or lower. Therefore we can conclude that 23.7 more deaths per 1000 people/per year are among patients with the highest score sets. Persons with scores from 101 to 500 have shown two-times higher risk of cardiac death in comparison to persons with scores lower than 101.[8]

In this study, CS score was measured in patients with the history of previous myocardial infarction, and, as it is showed in the Table 1, 19 (70.4%) patients had calcium score >500, while only 3 (11.1%) patients had a low

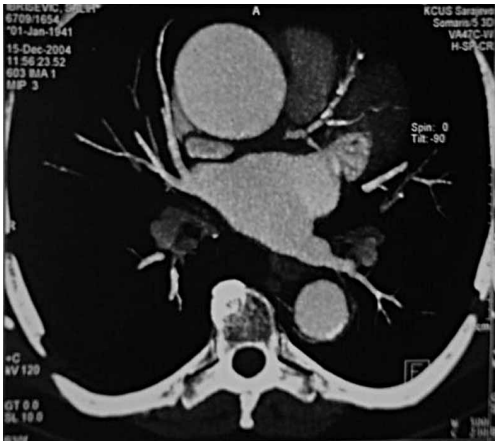

Figure 2a. Calcification of left coronary artery.

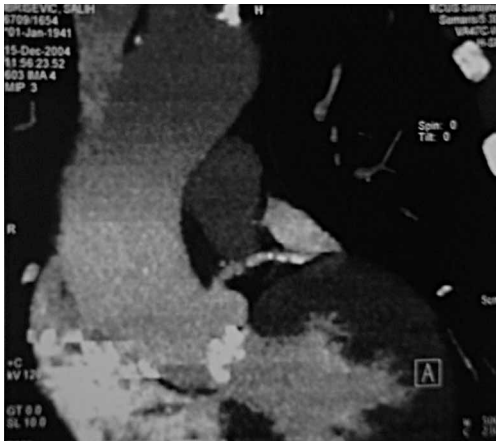

Figure 2b. Calcification of left coronary artery (arrow)

CS, and 5 (18.5%) patients had an intermediate CS. Therefore, among the patients with myocardial infarction, there were 6.3 times more those with the high CS than those with the low CS, and 3.8 times more than those with the intermediate CS.

During the study, it was noticed that the most of coronary calcification was in the proximal 2/3 segments of the coronary arteries, while the distal parts were less affected. Distal segments are also more difficult to analyze on the four-row detector MDCT machine. These findings are in accordance with the data from the literature (Figures 2a and 2b).

In autopsy studies, which included over 14.000 corpses with CHD, only 16% of stenosis was found in distal parts of coronary artery, while 66% of all haemodynamically relevant stenosis was located in a proximal third and 40% in a medial third of one or more coronary arteries.[9]

It can be visualized 68% of all segments of coronary artery by a four-row detector CT angiography (CTA). In these segments available for the analysis, sensitivity and specificity in detection of significant luminal stenosis, in comparation with conventional angiography, is 91% and 84%, respectively. This is in accordance with the previous reports.[14]

As shown in the literature, and proved by this study as well, the measurement of CS is important in patients suspect of CHD, it is predictive for coronary accident and correlates with the severity of it. The next step is going to be the analysis of the soft plaque, and the technical development of MDCT (64 row detectors); with its transversal plains it should make it possible. According to the literature, soft plaque can be even more dangerous than the calcified atherosclerotic plaque, although the latest contains soft parts too.

Previous data show that, besides the measurement of CS in CHD, CTA has a significant role as well. In comparison to cardiac catheterization, coronary CTA has positive and negative predictive value in coronary arterial stenosis 59-85% and 96-98%, respectively. In other words, coronary CTA can exclude CHD with highly negative predictive value. Patients with low to moderate pre-test values are particularly good candidates for the coronary CT examination.[3]

Some previous studies show that MDCT's negative predictive value of 96-98% for coronary artery stenosis, is sufficient for the identification of patients who do not need cardiac catheterization. Its positive predictive value, with the range from 60 to 85%, suggests that some improvements have to be made before it replaces catheterization.[13] Other studies on MDCT angiography (MDCTA) show mean sensitivity, specificity, accuracy, and positive

and negative predictive values for detecting significant coronary artery stenosis as 86%, 90%, 76% and 97%, respectively. This indicates that high negative predictive value of MDCTA can really exclude coronary artery disease.[11]

When talking about CS in patients with the history of previous myocardial infarction, a question arises - what was the condition before the infarction, and in what extent the coronary calcification, or high CS, is the result of reparatory mechanisms after the infarction?

Therefore, this problem needs further researches, to give the insight into the other factors significant for development of CHD, as well as for the position of CS and soft plaque in this context. Some of these solutions are already coming in sight with the further development of MDCT and MRI.

Conclusions

This study shows the high correlation between the level of coronary artery calcium scoring, calculated by Agatston method, and myocardial infarction, or that 70.4% patients with the previous myocardial infarction had CS > 500. The low CS was rarely found in patients who had a myocardial infarction, which presumes that the same is less commonly connected with the coronary artery disease. It leads to the conclusion that coronary CS is the significant screening method in predicting a potential coronary attack in asymptomatic patients, and in those with the symptoms of angina. Thanks to this method, it is often possible to avoid coronary angiography in certain number of patients. The main risk factors include: age, sex, smoking, hypertension, diabetes, heredity and hypercholesterolemia.

MDCT has shown to be an efficient method for the examination of coronary calcifications in proximal 2/3 segments of coronary arteries.

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Radiol Oncol 2005; 39(3): 193-6.

case report

Small-bowel carcinoid presenting with acute bleeding detected upon wireless capsule endoscopy

Živa Mrevlje[1], Marko Sever[2], Borut Kocijančič[1]

[1]*Clinical Department of Gastroenterology, University Medical Center Ljubljana, Slovenia*
[2]*Clinical Department of Abdominal Surgery, University Medical Ljubljana, Slovenia*

Background. *Intestine carcinoid usually presents with clinical symptoms and signs deriving from its endocrinological influences and rarely bleeds profusely.*
Case report. *We present a patient with intestinal bleeding of unknown origin. After conventional diagnostic procedures only wireless capsule endosopy was able to discover a tumour of small bowel, which was the reason of bleeding. On patohistological examination after the surgical resection it proved to be a small bowel carcinoid.*
Conclusions. *There are indications that WCE, besides being the first small bowel imaging technique, is a very important diagnostic tool, deserving consideration in the early phases of diagnosing small-bowel disease, especially in less intensive or occult bleeding.*

Key words: intestinal neoplasms-dignosis; carcinoid tumor; endoscopy

Introduction

The small intestine has to-date been a problematic section of the gastrointestinal (GI) tract for exploration. In patients with obscure or manifest GI bleeding the major part of the small bowel was unreachable by means of esophagogastroduodenoscopy (EGDS), push enteroscopy (PE) and coloileoscopy (CIS), the major limitations being its remoteness from GI tract openings and its length (3.4-7.9m approx.). Other conventional diagnostic procedures in small bowel bleeding are blood pool scintigraphy, angiography and barium small bowel series. Virtual endoscopy, employed lately, is an interesting alternative to conventional diagnostic techniques.[1]

In recent years a novel endoscopic tool, the wireless capsule endoscopy (WCE) has been developed.[2] It allows to endoscopically explore the small intestine in its entirety using a system composed by a peristalsis propelled video capsule with a radio transmitter, a sensor-array attached to the patients abdominal wall and a data recorder worn at the patient's belt. The data collected can then be retrieved and analyzed using a workstation.

Received 19 July 2005
Accepted 1 August 2005

Correspondence to: Živa Mrevlje, MD, Department of Gastroenterology, Clinical Center Ljubljana, Japljeva 2, 1000 Ljubljana, Slovenia; E-mail: ziva@mrevlje.org

Abbreviations: GI – gastrointestinal, EGDS – esophagogastroduodenoscopy, PE – push enteroscopy, WCE – wireless capsule endoscopy, RBC – red blood-cell count, MCV – medium red blood-cell volume

We present a case of manifest GI bleeding in which WCE facilitated identification of the bleeding site, its localization and treatment.

Case report

A 58-year-old man with maelena lasting for 3 days prior to the admission was referred to our hospital. On admission the patient was complaining of minor fatigue during the past few days. He had been on antihypertensive and statin therapy for several years. He was otherwise in good health, somewhat pale; on rectal examination black semi-fluid stools were found. The only pathological laboratory finding was normocytic anaemia (red blood-cell count - RBC 3.75 10^9/L, Hb 11.4 g/dL, medium red blood-cell volume - MCV 89.5 fL). He underwent oesophagogastroscopy with no positive finding. On colonoileoscopy, two polyps in the sigmoid without any sign of recent haemorrhage were found and frank maelena was seen to be flowing from the ileum into the caecum. Blood pool scintigraphy showed some active bleeding in a region projecting into the right upper abdominal quadrant, most probably a part of the small bowel. On angiography of the superior mesenteric artery and celiac trunk no extravasate was found in their course. On WCE performed with an M2A plus capsule and analyzed using the RAPID software (both Given Imaging Inc., Yoqneam, Israel) small bowel mucosa showed few small angiodisplasia-like mucosal changes in the proximal jejunal region. Following 3.5 hours of small bowel transit time we visualized a bleeding site in the vicinity of the tumour of 7 mm in diameter. The tumour was projected into the right lower quadrant of the abdomen (Figure 1).

On explorative laparotomy, a small umbilication of jejunal serosa lying 50 cm distally to the ligament of Treitz was found. At this site a 10 mm fixed tumour was palpable. Distally from it the lumen was filled with blood, which was even more evident on transillumination. A jejunal segmental resection of 5cm (Figure 2), followed by a one-layer terminoterminal anastomosis, was performed. The surgeon found no pathology on palpatory examination of the liver.

On patohistological examination the resected formation was found to be a well differentiated malignant (more than 10 mm in diameter) carcinoid of the small intestine, initial stage T2 N0. The tumour cells expressed serotonin, some of them somatostatin. There

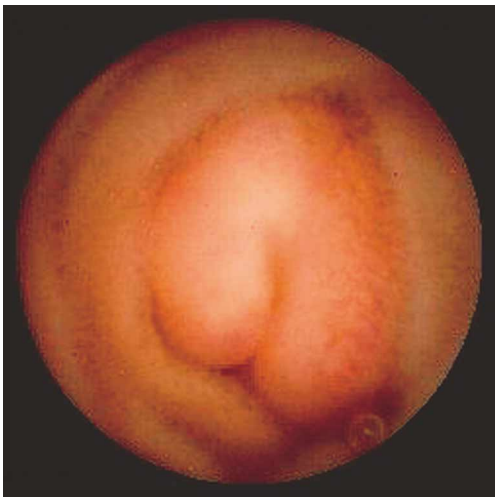

Figure 1. Capsule endoscopy view of the tumour.

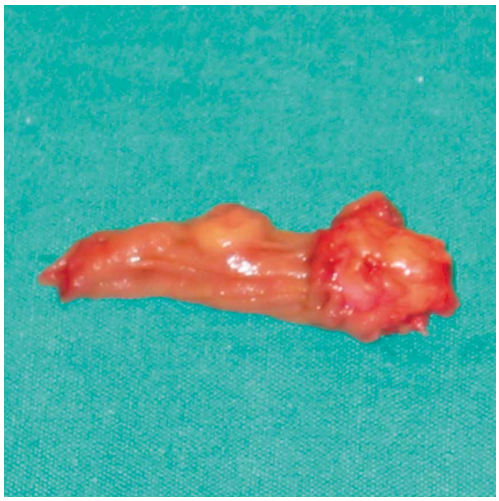

Figure 2. Tumour after excision.

was no need for the additional therapy, only the follow-up was recommended.

Discussion

When haemorrhage from the GI tract is suspected, we usually choose from, or combine, upper GI tract endoscopy and colonoscopy, which gain visual access to both end-sides of the GI tract and only to a small part of the small bowel, proximal jejunum and distal ileum. We performed both in this case, but didn't visualize any actively bleeding sites, and consequently deduced that bleeding derived from the small intestine.

PE has a diagnostic yield ranging between 13 and 38%; in a randomized trial its sensitivity was 37% compared to 64% for WCE.[3,4] It has the advantage of allowing treatment and specimen cropping and has higher specificity in its range.[5] Because of the proximity of the bleeding lesion to the ligament of Treitz (50cm) in our patient's case PE would have probably led to the diagnosis without any need to perform WCE, but we didn't perform it. In regard to its lower diagnostic yield and the possibility of performing WCE, we didn't perform barium small bowel series. Besides involving patient radiation, trial barium small bowel series were in different studies shown to be less diagnostic than WCE (27% vs. 45% of cases).[6,7]

The explorative surgery unaccompanied by additional techniques has a yield of approximately 10%.[8] The recognition of vascular lesions cannot be achieved without the aid of transillumination or intraoperative endoscopy. The latter is invasive and associated with many complications, i.e. postoperative paralytic ileus and perforation. We refrained from performing explorative surgery with intraoperative endoscopy, as the bleeding wasn't haemodinamically or otherwise threatening to the patient in the immediate time, not advocating for such an invasive technique.

Other morphologic and functional techniques, such as angiography of the superior mesenteric artery and blood pool scintigraphy with marked erythrocytes promised to bring some insight into the diagnostic problem.

Blood pool scintigraphy gives a positive scan with at least 5 ml of intraluminal blood. It may confirm small intestinal bleeding, it confers no information about the nature of the bleeding lesion and accurate localization is impossible. With sequential scanning it allows the detection of intermittent bleeding. Angiography of mesenteric arteries can demonstrate active bleeding and well vascularized nonbleeding lesions. Its diagnostic yield is 50-70%, but falls to 25-50% when the bleeding slows or stops; a positive find can only be gained with bleeding rates exceeding 0.5 or 1 ml/min.[9] In our case blood pool scintigraphy pinpointed to a bleeding site in the small intestine, whereas with angiography no bleeding site was identified. It might be that the bleeding site in our patient was smaller than required for identification, the more probable explanation is that at the time of angiographical examination there was no bleeding from the site.

Following angiography and blood pool scintigraphy we performed WCE. We visualized a bleeding site just before the tumorous formation and concluded it could be an angiodisplasia. When surgery was performed, besides the tumour, no angiodisplastic lesion was found. During WCE we probably wrongly interpreted blood in the lumen as deriving from a »lesion« of the intestinal mucosa, which, revising the WCE images, we concluded could well be an adherent coagulum or just superimposed blood. As we know of, our diagnostic mistake had no repercussions on the patients' well being.

Aftermath, we reconsidered the diagnostic path we took in view of the diagnostic yield of single diagnostic techniques and their cost. EGDS and colonoscopy were well employed

in our case as they helped eliminate the regions inspected as possible sites of bleeding and gave ground to suspicion of ongoing bleeding in the small intestine. From here we proceeded to angiography and blood pool scintigraphy, costly techniques, which drew us no nearer to the diagnosis. The cost of WCE is approximately that of angiography alone and in our case it gave the only definitive information, which in consequence led to the cessation of bleeding by removal of the tumour. Therefore, it would have been more cost-effective, if we had performed WCE before employing other techniques.

It has been demonstrated that WCE has many advantages over conventional procedures; it produces visual images and has a greater sensitivity in uncovering small bowel disease. It is also safe, easy for the patient, can be repeated many times, it has limited contraindications and a low complication rate. Its limitations are almost as obvious as its advantages; it confers diagnostic potential, but lacks possibilities of tissue sampling and treatment,[10] the exact site of the abnormality is not readily determined and it is demanding in view of the time needed to view the produced images.

More experience will be needed in this field, but there are indications that WCE, besides being the first small bowel imaging technique, is a very important diagnostic tool, deserving consideration in the early phases of diagnosing small-bowel disease, especially in less intensive, or occult bleeding.

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Radiol Oncol 2005; 39(3): 197-210.

review

Molecular biology of the lung cancer

Sasho Z. Panov

Laboratory for Molecular Biology, Institute of Biology, Faculty of Natural Sciences and Mathematics, "Ss. Cyril and Methodius" University, Skopje, Republic of Macedonia

Background. *Lung cancer is one of the most common malignant diseases and leading cause of cancer death worldwide. The advances in molecular biology and genetics, including the modern microarray technology and rapid sequencing techniques, have enabled a remarkable progress into elucidating the lung cancer ethiopathogenesis.*

Numerous studies suggest that more than 20 different genetic and epigenetic alterations are accumulating during the pathogenesis of clinically evident pulmonary cancers as a clonal, multistep process. Thus far, the most investigated alterations are the inactivational mutations and losses of tumour suppressor genes and the overexpression of growth-promoting oncogenes. More recently, the acquired epigenetic inactivation of tumour suppressor genes by promoter hypermethylation has been recognized. The early clonal genetic abnormalities that occur in preneoplastic bronchial epithelium damaged by smoking or other carcinogenes are being identified. The molecular distinctions between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), as well as between tumors with different clinical outcomes have been described. These investigations lead to the "hallmarks of lung cancer".

Conclusions. *It is realistic to expect that the molecular and cell culture-based investigations will lead to discoveries of new clinical applications with the potential to provide new avenues for early diagnosis, risk assessment, prevention, and most important, new more effective treatment approaches for the lung cancer patients.*

Key words: lung neoplasms-genetics; genes, tumor suppressor

Introduction

Lung cancer is one of the most common malignant diseases and leading cause of cancer death worldwide with estimated more than 1.3 million new cases each year.[1] The lung cancer incidence and mortality have risen into epidemic proportions in Western world during the 20th century.[2] The majority of lung cancer patients is inoperable or has disseminated disease at the time of diagnosis and displays a remarkable insensitiveness to chemotherapeutics and radiation therapy.[3] Over 85% of these patients eventually die from disseminated disease during the first 5 years and this extreme mortality has not changed significantly during the last three decades. Despite diagnostic and

Received 24 August 2005
Accepted 11 September 2005

Correspondence to: Sasho Z. Panov, PhD, Teaching and Research Assistant of Molecular Biology and Molecular Genetics, Institute of Biology, Faculty of Natural Sciences and Mathematics, "Ss. Cyril and Methodius" University, Arhimedova bb., MK-1000, Skopje, Republic of Macedonia; Phone: 389 70 248 790; Fax: 389 2 3228 141; E-mail: sasho@mt.net.mk

therapeutic improvements, the 5-year survival rate has barely increased from 7 to 14% since 1970-thies to the present. Moreover, the lung carcinoma is accounting for nearly 29% of all cancer-related deaths in both genders, that exceeds the sum of the next three leading causes of death due to breast, colon, and prostate cancer.[4]

It is believed that smoking is the primary etiologic agent in more than 80% of lung cancer patients.[5] The other risk factors include, but are not limited to, passive smoking, exposure to environmental pollutants, occupational exposure to chemicals (arsenic, asbestos, chromium, nickel and vinyl chloride) and to the natural radioactive gas radon.[2] Genetic predisposition, especially polymorphisms of the tumor suppressor genes and the allelic variants of the genes involved in detoxification, are implicated into the susceptibility to the disease.[6]

Based on the histopathological classification (WHO, 1977), lung cancer is divided into two main types: non–small cell (NSCLC) and small cell lung cancer (SCLC), which are delineated by their biological and clinical features. Furthermore, NSCLC consists of several subtypes, predominantly adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma. SCLC is a distinct clinicopathological entity with neuroendocrine pathophysiologic features and characteristic microscopic morphology.[7] SCLC represents roughly 20% of all pulmonary cancers. The histologic distinction between NSCLC and SCLC is clinically extremely important. There are considerable differences between those two groups in both, therapeutic approach and prognosis of the disease. Recently, molecular classification of lung carcinomas has been made using mRNA expression profiling by microarray technology.[8-10]

Molecular biology of lung cancer

It is generally accepted that the pathogenesis of human cancer involves the accumulation of multiple molecular abnormalities over time. Those alterations lead to acquired cellular capabilities that can be classified in the following six functional sets: a) self-sufficiency in growth signals due to mutations in proto-oncogenes, b) insensitivity to antiproliferative signals as a result of mutations affecting the tumour suppressor genes, c) evading of apoptosis by up-regulation of antiapoptotic or down-regulation of proapoptotic molecules, d) limitless replicative potential due to the activation of telomerase, e) sustained angiogenesis and f) capability for tissue invasion and capability for dissemination into distant sites (metastasis).[11] Those molecular alterations can occur at the level of gene up-regulation or down-regulation, DNA sequence changes (point mutations), loss of heterozygosity (i.e., deletion of one copy of allelic DNA sequences), DNA segment amplification or whole chromosome gains or losses with the simultaneous genomic instability and alterations in microsatellite DNA.[12,13]

The advances in molecular biology and genetics, including the modern microarray technology and rapid sequencing techniques, have enabled a remarkable progress into elucidating the lung cancer ethiopathogenesis. Numerous studies suggest that more than 20 different genetic and epigenetic alterations are accumulating during the pathogenesis of clinically evident pulmonary cancers as a clonal, multistep process.[14-16] Thus far, the most investigated alterations are the inactivational mutations and losses of tumor suppressor genes and overexpression of growth-promoting oncogenes. More recently, the acquired epigenetic inactivation of tumor suppressor genes by promoter hypermethylation has been recognized. The early clonal genetic abnormalities that occur in preneoplastic bronchial epithelium damaged by smoking or other carcinogenes are being identified. The molecular distinctions between SCLC and NSCLC, as well as between tumors with different clinical outcomes have been described.

These investigations lead to the "hallmarks of lung cancer".[3] It is realistic to expect that the molecular and cell culture-based investigations will lead to discoveries of new clinical applications with the potential to provide new avenues for early diagnosis, risk assessment, prevention, and most important, new more effective treatment approaches for the lung cancer patients.

Growth stimulation by oncogenes

Protein-tyrosine kinases (PTKs) are vital regulators of intracellular signal-transduction pathways that mediate development and cell-to-cell communication. Their activity is normally firmly controlled and regulated. Disturbances in the PTK signaling resulting from mutations and other genetic alterations contribute to the malignant transformation. A number of growth factors and their receptors are expressed by lung cancer cells or their neighboring stromal cells, thus producing autocrine or paracrine growth stimulation loops. Several are encoded for by proto-oncogenes which become activated in the course of the lung cancer development.[3] The overexpression of cell cycle regulatory proteins such as **cyclin D1**,[17] **cyclin E**,[18] and **cyclin B1**,[19] enhance the cell proliferation, decrease the cellular apoptotic potential and are commonly found in NSCLC tumor specimen.

Epidermal growth factor receptor (EGFR), also called ErbB-1, is the member of a subfamily of closely related proteins. After ligand-binding, the intracellular tyrosine kinase domain of the EGFR receptor is activated and undertakes autophosphorylation, which initiates a cascade of intracellular events. A downstream signaling pathway involves the activation of p21-Ras and mitogen-activated protein kinases (MAPKs). EGFR signaling is critical for the normal cell proliferation, but its deregulation is crucial for cancer pathogenesis, neoangiogenesis, metastasis, and apoptosis inhibition.[20] EGFR is overexpressed in the advanced NSCLC, and is associated with the poor survival and resistance to chemotherapeutic agents, including cisplatin. The results of different studies investigating the prognostic value of EGFR expression in lung cancer are contradictory.[3] However, since EGFR expression is clearly involved in the lung cancer pathogenesis, this molecule is an attractive target of different therapeutic approaches.[21] Few EGFR inhibitors (CP358774, ZD1839-Iressa and OSI774) are under intensive clinical trials in lung cancer patients.[3]

HER-2/neu (ErbB-2) gene is located on chromosome 17p21 and encodes for a 185-kDa transmembrane glycoprotein ($p185^{HER\text{-}2/neu}$) that has high homology with EGFR. *HER-2/neu* is overexpressed in about 30% of NSCLCs, particularly in adenocarcinomas and is associated with multiple drug resistance phenotype and high prevalence of metastases.[3] A point mutation resulting in the substitution of the amino acid residue 664 from valine to glutamic acid is commonly found, and this mutation contributes to the malignant transform of affected cells. Alterations and amplifications of *HER-2/neu* gene have been reported in NSCLC.[20] Chemotherapy combined with trastuzumab (Herceptin), a monoclonal antibody against the HER2/neu receptor is now under clinical trials.[3]

MYC proto-oncogene belongs to a family of related genes (*c-MYC, N-MYC, L-MYC*) which encode transcription factors that activate genes involved in the growth control and apoptosis. The MYC phosphoproteins are localized in the nucleus.[22] The transcriptional regulation by MYC proteins is mediated by heterodimerizing with partner proteins such as MAX, MAD or MX11.[23] MYC-MAX heterodimer binds to specific DNA sequences named E-box elements in the neighborhood of promoters of downstream target genes and activate their transcription. Histone acetylase

is activated and leads to alterations in chromatin structure, which, in turn, modulate the gene transcription. On the other hand, the MYC-MAX complex represses a transcriptional activation. MAX can bind MAD and MX11 proteins to repress transcription, antagonize MYC, and promote cellular differentiation.[20] The molecular abnormalities involving the *MYC* genes or their transcriptional deregulation were found to be an important molecular mechanism in the pathogenesis of human lung cancers.[23] The most frequent abnormality involving *MYC* members in lung cancer is gene amplification or gene overexpression without amplification. The overexpression of a *MYC* gene, with or without amplification, occurs in 80 to 90% of SCLCs.[22] In contrast to SCLC, the amplification of the *MYC* gene occurs only in approximately 10% of NSCLC samples. However, *MYC* overexpression without *MYC* gene amplification occurs in over 50% of NSCLC investigated specimens.[22] *MYC* gene overexpression has been identified to be a late event in lung cancer pathogenesis in the vast majority of SCLCs.[20] Lung tumor cell lines established from metastatic tumors have a high frequency of *MYC* amplification, and this probably explains the correlation of *MYC* amplification with a poor clinical prognosis.[24] The antisense oligonucleotides therapy models directed at downregulating *MYC* expression show encouraging results in cell culture.[3]

The dominant ***RAS* proto-oncogene** is extremely important for the transduction of the growth-promoting signals from the membrane to the nucleus and consequently for the cellular proliferation. The *RAS* family of genes includes: the *HRAS* gene (homologous to the oncogene of the Harvey rat sarcoma virus), the *KRAS2* gene (homologous to the oncogene of the Kirsten rat sarcoma virus) and the *NRAS* gene (initially cloned from human neuroblastoma cells). The *RAS* genes code for four highly homologous 21 kDa proteins called p21 anchored to the inner side of the plasma membrane, where they can effectively interact with their upstream activators and downstream targets. In active state RAS proteins binds to guanosine triphosphate (GTP) and through the intrinsic GTPase activity and conformational change of RAS, the GTP hydrolyze to guanine diphosphate (GDP) and after interacting with its substrate Raf1, RAS returns to the inactive state. The cell proliferation signal is subsequently transmitted by a cascade of RAS-dependent kinases, activating the MAPK, which translocate to the nucleus and initiate transcription factors.[20] This signal transduction pathway is sometimes called SOS-Ras-Raf-MAPK mitogenic cascade.[11] In malignant cells, the point mutation in the RAS gene can make the RAS protein defective in the intrinsic GTPase activity that becomes locked into the growth stimulatory GTP-bound form, constantly sending the signal stimulating cell proliferation signals to the nucleus.[25] *RAS* mutations are very rare or absent in SCLC, but can be identified in 15-20% of NSCLC. Up to 50% of the lung adenocarcinomas carry *RAS* mutations,[26] usually affecting codon 12 of *KRAS* (85% of cases), and rarely codon 13 of *HRAS*, or codon 61 of *NRAS* gene.[23] The majority (up to 70%) of these mutations are G→T transversions that are induced by benzopyrene diethyloxide (BPDE), nitrosamines and other DNA adducts-forming agents that are present in the tobacco smoke. It is believed that this is the reason for the correlation between smoking history and the frequency of *KRAS* mutations in NSCLC samples which are associated with poor prognosis.[27] Few clinical trials are conducted: using vaccination with mutant KRAS peptides, by suppression of the mutant *RAS* gene using antisense oligonucleotides, or by inhibition of the farnesylation of the RAS protein that is necessary for its activation.[3]

The distinguishing feature of SCLC tumors is the production and release of a broad range of neuropeptides from the neoplastic cells.

Angiotensin, bombesin, insulin-like growth factor 1, vasopressin, serotonin, and substance P are among the best studied signal molecules released by SCLC cells.[28] These peptides act as ligands for high-affinity receptors on the tumor cell surface, and their binding consequently activate the G-protein coupled receptors enabling a further intracellular transmission of the proliferative signal. By this, SCLC cells are self-stimulating the growth by autocrine and paracrine manner.

Insensitivity to anti-growth signals: tumor suppressor genes

Tumor suppressor genes (TSG) play a critical role in cell's antiproliferative circuitry and are also involved in the cellular response to DNA damage and consequent reparation processes. There is a frequent loss of tumor suppressor genes during the pathogenesis and progression of lung cancers, as in many epithelial cancers. The inactivation of the tumor suppressor genes occurs by loss of one allele from the chromosomal locus, termed loss of heterozygosity (LOH) and damage to the other allele by gene mutation or the epigenetic hypermethylation of its promoter. The chromosomal regions that where found to be most frequently affected by LOH in lung carcinomas are 1p, 3p, 4p, 4q, 5q, 8p, 9p (p16 TSG locus), 9q, 10p, 10q, 13q (*RB*-retinoblastoma locus), 15q, 17p (p53 locus), 18q, 19p, Xp, and Xq.3 The allelic loss at several loci on the chromosome arm 3p is one of the most frequent and earliest genetic events in lung cancer pathogenesis found in up to 96% of carcinomas and 78% of preneoplastic bronchoepithelial lesions.[29] The high frequencies of LOH and frequent homozygous deletions found in many lung cancer cell lines and tumor samples suggest that few potential tumor suppressor genes reside at this chromosome region.[23] Moreover, the frequency and size of the allelic loss of 3p correlate with the severity of histopathological preneoplastic/preinvasive grades. There are a number of other candidate tumor suppressor genes located at 3p and their allelic loss may probably be the earliest acquired genetic abnormality in the lung cancer pathogenesis.[3,30]

FHIT is a tumor-suppressor gene located at 3p14.2, coding for a dinucleoside 5′, 5‴-P1-P3-triphosphate hydrolase protein product (often denoted as pFHIT). The loss of the gene results in the accumulation of diadenosine tetraphosphate, thus stimulating DNA synthesis and cell proliferation. A decreased expression of *FHIT* has been found in 49% of NSCLC specimen by immunochemistry. pFHIT expression is significantly reduced in a large number of early-stage NSCLC and preneoplastic lesions in chronic smokers. The association between cigarette smoking and pFHIT expression suggests a role for *FHIT* in the initiation of smoking-related lung carcinogenesis.[20] It was demonstrated that the reintroduction of wild-type *FHIT* inhibits lung cancer in vitro growth and in vivo tumorigenicity in nude (athymic) mice.[23]

The ***RARβ.*** **(retinoic acid receptor beta) gene,** located at 3p24 is a strong TSG candidate. Low or absent *RARβ.* expression was detected with high frequency in lung cancer cell lines and primary lung tumours.[23] It appears to result from the aberrant promoter methylation of the *RARβ* and was observed in approximately 40% of primary SCLCs.

The ***TP53 tumor-suppressor gene (p53)*** is located at chromosome arm 17p13.1 and encodes a 53 kDa nuclear protein that acts as a DNA-binding, sequence-specific transcription factor that activates the expression of genes engaged in promoting growth arrest in the G1 phase or cell death in response to the genotoxic stress.[31] Thus, p53 has a role of "guardian of the genome", maintaining the genome integrity during the cellular stress from DNA damage, hypoxia, and activated oncogenes. Also, p53 prevents cells with damaged DNA from undergoing mitosis

when they enter the G_2 phase. p53 blocks cells at the G_2 checkpoint, at least partially, by inhibition of cdc2, the cyclin-dependent kinase required to enter mitosis. The ability of p53 to inhibit cellular proliferation or to induce apoptosis is suppressed by *HDM2* protein product, the human homologue of the murine double minute 2 *(MDM2)*. This protein blocks p53 regulation of target genes and enhances its proteasome dependent degradation.[31] On the other hand, p53 upregulates the expression of *HDM2* by directly binding and activating the *HDM2* promoter and thus p53 is downregulating its own expression. This autoregulatory loop keeps p53 at virtually undetectable levels in normal cells.[3] Missense mutations (mainly G→T transversions) clustered in the middle of the gene at codons 157, 245, 248, and 273 abolishes its tumor suppressing activity and extend the p53 mutant protein half-life that can be easily detected by immunohistochemistry. The *p53* gene mutations in lung cancer have been extensively investigated and were found that *p53* is inactivated in 75% of SCLCs and about 50% of NSCLCs and the frequency of mutations correlate with cigarette smoking.[20] It is intriguing that the mutations at codon 157 appear to be unique to pulmonary carcinomas, while codon 248 and 273 hot spots mutations occur in other cancers, *e.g.*, colon, liver, and prostate.[22] Nonsmokers who develop lung cancer have a completely different, almost random grouping of *p53* mutations.[22] Although the prognostic role of *p53* mutations in NSCLC p53 is still under debate, their presence influences the clinical response to cisplatin-based chemotherapy and radiotherapy.[3]

The ***RB* tumor-suppressor gene** is located on chromosome 13q14 and its protein product is a nuclear phosphoprotein initially identified in childhood retinoblastomas. RB protein cooperates with p53 in the regulation and control of cell cycle progression, the transcriptional level, and the equilibrium between the cell differentiation and proliferation. The phosphorylation status of the RB protein and its interaction with transcription factor E2F is most important for the regulation of G0/G1 cell cycle transition. When RB is dephosphorylated, it suppresses the G1 to S phase transition.[32] During G1 phase, cyclin D1 is associated with cyclin-dependent–kinases CDK2 and CDK4 that results in phosphorylation and activation of RB. Hypophosphorylated RB binds the E2F transcription factor, thus blocking the transcription of genes regulating the cell cycle. On the contrary, when RB is phosphorylated, E2F dissociates and activates the transcription, thus facilitating S phase entry.[23] Abnormalities of the *RB* gene in lung cancer include deletions, nonsense mutations, pathogenic splicing variations and chromosomal deletions. The disruption of the pRb pathway releases E2Fs allowing cell proliferation to proceed and making the cell insensitive to antigrowth factors that normally function to control a transition through the G1 phase of the cell cycle.[11] More than 90% of the SCLC and 15-30% of the NSCLC neoplasms have abnormal or no *RB* expression.[22] Although *RB* plays an important role in pulmonary cancer pathogenesis, pRB status has no prognostic significance in NSCLC patients.[20]

***PTEN* (Phosphatase Tensin Homolog Deleted on Chromosome Ten)** gene is located at chromosome 10q23 encodes a lipid phosphatase which dephosphorylates PIP3 and posses tumor suppressor activity *in vitro* and *in vivo*. Mutations or deletions of the PTEN gene have been found in a few lung cancer cell lines and tumor samples.[23]

Transforming growth factor-β (TGF-β) is multifunctional protein that inhibits the proliferation of many epithelial cells through binding with a set of cell receptors. It is a checkpoint inhibitor involved in the cell cycle regulation, causing cells to cease proliferation and arrest in G_1.[22] The reduced levels of TGF-β expression was found in NSCLC

samples by immunocytochemical staining studies.

Another candidate TSG on chromosome 10q25-26 is ***DMBT1.*** It is frequently down regulated and occasionally homozygously deleted in lung cancer.[23] The overexpression or activation of **insulin-like growth factor I receptor *(IGF-IR)*** has been observed in many human cancers including pulmonary carcinomas. The ***p16^{INK4}*** (also termed ***CDKN2A***) is a tumor-suppressor gene located on chromosome 9p21 and codes for two proteins translated by alternative mRNA splicing: α-transcript that is translated into p16 (p16^{INK4}) and β-transcript that is translated into p14^{ARF} protein. p16 protein that is part of the p16-cyclin D1-Cdk4-RB pathway.[32] p16 regulates cell-cycle progression through a G_1/S restriction point by inhibiting CDK4 and CDK6/cyclin D-mediated phosphorylation of pRB.[20] The disruption of *p16* function results in inappropriate hyperphosphorylation and, therefore, inactivation of pRB. The overexpression of the E2F transcription factor upregulates *p16* expression and inhibits cyclin D-dependent kinase activity, suggesting the presence of a feedback loop. **p14^{ARF}** protein binds to and stabilizes HDM2 (MDM2 homologue), increasing its availability of wild-type p53. The loss of p14^{ARF} or p53, which are common genetic lesions in lung cancer, permits an amplified *MYC* free opportunity for the cell proliferation and transformation. p14^{ARF} appears to bridge a gap between oncogenic signals and p53 whereby p14^{ARF}-induced activation would be critical to move the compromised cell toward apoptosis.[22, 31] The expression of p16^{INK4} gene in NSCLCs is frequently altered by abnormal promoter methylation (25% of cases) and homozygous deletions or point mutations (10%-40%).[23] It was found that the disturbances in both, the *p16/pRb* and *p53* pathways are essential for the enhanced proliferation of NSCLC cell lines. There is an inverse relation between p16 and Rb in pulmonary carcinomas: *Rb* is mutated and p16 is intact in SCLC, while p16 expression is disrupted and *Rb* is usually intact in NSCLC.[22] **p19^{ARF}** binds to the MDM2-p53 and prevents p53 degradation. The loss of p19^{ARF} is more frequent in lung tumours with neuroendocrine features.[23, 31]

Evading apoptosis

Apoptosis or programmed cell death is a genetically controlled process that is essential for tissue remodeling during embryogenesis and for the maintenance of the homeostatic balance of cell numbers during adult life. A deregulation of cell death pathways is implicated in tumor initiation, progression, and drug resistance in many human cancers and is one of the hallmarks of cancer.[11, 33] Two major intracellular apoptosis signaling pathways can lead to programmed cell death, the mitochondrial pathway (intrinsic) and the death receptor (extrinsic) pathway. Mediated by a cascade of caspase activations and other mediator proteins, both pathways finally lead to the proteolytic cleavage of a variety of cellular proteins, induces DNA fragmentation and numerous morphological changes that are characteristic of cells undergoing apoptosis. Key genes that regulate apoptosis include the *p53* tumour suppressor gene and the Bcl-2 gene family. Simplified, the *BCL-2* family members are major regulators of the apoptotic process, whereas caspases are the major executioners.

Bcl-2 (B-cell lymphoma-2) gene was the first oncogene found to function through the production of an inhibitor of apoptosis. The *bcl-2* gene family consists of more than 15 members, which either promote or inhibit the apoptosis.[34,35,36] The bcl-2 gene is located on chromosome arm 18q21 and the BCL-2 protein product is localized within the outer mitochondrial membrane, endoplasmic reticulum and the nuclear envelope, where it exerts anti-apoptotic effect within many cell types.[34] Following the apoptotic stimulation, pro-

apoptotic proteins are activated through post-transcriptional modifications or changes in their conformation. BCL-2 protein forms heterodimers with proapoptotic BCL-2 family members, leading to their inactivation. In addition, BCL-2 proteins may interfere with critical steps during the integration of proapoptotic signals at the level of mitochondria, thereby abrogating cytochrome-C release. BAX is a BCL-2-related protein which promotes apoptosis and is a downstream transcription target of p53. BCL-2 protein heterodimerizes with BAX consequently inhibits apoptosis. Tumor cells often escape apoptosis as the normal physiological response when challenged by cellular and DNA damage. BCL-2 overexpression, detected by immunohistochemistry, was found in 75%-95% of SCLC tumors, 25%-30% of the squamous cell carcinomas and in 10% of adenocarcinomas.[37] The significantly higher incidence of *bcl-2* overexpression in SCLC is unexpected as these tumors are more sensitive to chemotherapeutic agents that induce an apoptotic response.[3] Interestingly, the expression of BAX and BCL-2 proteins is inversely related in neuroendocrine cancers. Namely, high BCL-2 and low BAX expression occurs in most SCLC tumors which are also mostly *p53* deficient.[3] The significance of the *bcl-2* expression in lung cancer for the overall survival is controversial, but *bcl-2* expression was found to be associated with a better prognosis in NSCLC patients that may be associated with the lower tumor vascularization.[20,38]

Limitless replicative potential - telomeres and telomerases

Telomeres are specialized heterochromatin structures at the end of each chromosome that serves as protective caps and plays a role in the maintaining chromosome integrity, reversibly represses the transcription of neighboring genes and prevents the end-to-end fusion or degradation of the chromosomes.[39] Due to the inability of the conventional DNA polymerases to replicate the 5′-end of linear DNA, telomeres shorten during each cell division in the normal human somatic cells. This phenomenon is known as an end-replication problem. This shortening does not produce the loss of the essential genes in which each of the 46 human chromosomes is capped with long repeats of non-coding DNA sequences named telomeres. The human telomeres consists of highly repetitive DNA of tandem sequences TTAGGG)*n*.[40,41] It has been calculated that roughly 50–100 bp are lost with each round of cell division.[42] Human cells are estimated to have the potential to undergo on average 50–70 divisions. At this point the cell growth arrests and enters senescence. A dozen of telomeric proteins are needed to hide the telomeres from the cellular machinery that would normally treat the end of a linear DNA molecule as a broken strand needing repair.[43] The key telomeric DNA binding proteins are the telomeric repeat binding factors, Tankyrase, heterogeneous nuclear ribonucleoproteins and few other functionally related proteins. The physiologic maintenance of the telomere requires complex interactions among these proteins, telomeric DNA, and other cellular factors. Telomere integrity is also essential for the chromosome numerical and positional stability and the telomere shortening facilitates the evolution of cancer cells by promoting chromosome end-to-end fusions and the development of aneuploidy. The inhibition of telomerase in immortal cancer-cell lines by genetic or pharmacological methods results in telomere shortening and eventually halts cell proliferation.[44]

Telomerase is a specific ribonucleoprotein enzyme complex that elongates and maintains the preexisting telomeres of eukaryotic chromosomes, using an intrinsic RNA molecule as a template and thus is extending the number of divisions the cell may undertake.[45] Telomerase holoenzyme contains two main

components that are essential for the activity: hTERT subunit (RNA-directed DNA polymerase, *i.e.* reverse transcriptase, EC 2.7.7.), and hTR, 451-nt RNA chain that serves as a template. The enzyme complex also contains many proteins necessary for the full enzymatic activity that are collectively named as telomerase-associated proteins. The gene for the telomerase catalytic subunit *hTERT* is more than 37 kb in length and consists of 16 exons.[46] The telomerase activity is absent in the majority of normal cells in adult organisms, but is increased during the development and neoplasia.[47] Since over 90% of human neoplastic cells have increased telomerase activity, it is now generally accepted that this is a one of the cancer hallmarks and extremely frequent and consistent cancer-associated molecular abnormality. Generally, the telomerase expression in malignant tumors is determining the capacity for the unlimited proliferation and thus immortality. A high telomerase activity was detected in almost 100% of SCLC and 80% of NSCLC samples using a PCR-based telomeric repeat amplification protocol (TRAP assay). A high telomerase activity in primary NSCLC was found to be associated with the increased cell proliferation rates and advanced pathologic stage.[48] Recently, the telomere shortening was found to be an early molecular abnormality in bronchioepithelial carcinogenesis, preceding telomerase expression and p53/Rb inactivation that occurs in most high-grade preinvasive lesions.[49] Since the telomerase activity is associated with malignant growth, it is a marker for lung cancer detection, and a important target for novel therapeutic approaches.[23]

Tumor angiogenesis

New blood vessel growth (neovascularization or neoangiogenesis) is required for tumors to sustain and grow beyond 3 mm in diameter and for metastasis. Different inducers and inhibitors regulating endothelial cell proliferation and migration are involved in the process of angiogenesis. Growth factors that have been shown to stimulate angiogenesis include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived endothelial cell growth factor (PD-EGF) and platelet-derived growth factor (PDGF).[3,23] The productions of angiogenesis factors apparently influence the clinical outcome of lung cancer patients. Namely, the VEGF levels in plasma are correlated with the degree of angiogenesis in NSCLC and the VEGF expression was found to be associated with the decreased overall and disease-free survival in NSCLC patients.[50] Immunochemical studies demonstrated that bFGF is a prognostic indicator in lung adenocarcinoma, since the 5-year survival rate was significantly lower for bFGF positive patients and the more aggressive clinical behavior was associated with up-regulation of PDGF.[23] In a few clinical trials, impressive results were achieved by targeting VEGF with a "humanized" monoclonal anti-VEGF antibody. Unfortunately, unexpected bleeding from large necrotic lung neoplastic masses occurred in the initial trials, but this should be approachable by a more careful patient selection.[3]

Tissue invasion and metastasis

Molecular mechanisms that lead to the complex ability of the primary lung cancer cells to invade the adjacent tissue and to disseminate to the distant organs of the patient's body are mainly unknown.[3] This process involves degradation of the basement membrane, invasion of the surrounding stroma and the blood or lymphatic vessel, ability to growth without adhesion, angiogenesis, cell proliferation, and migration.[11] Few different genes and their protein products are identified to be important for the process of tissue invasion

and metastatic capability of the neoplastic cells.

E-cadherin is a cell adhesion molecule that is universally expressed on epithelial cells. During the pathogenesis of most epithelial cancers, E-cadherin function is lost by the mutational inactivation of the E-cadherin or **β-catenin** genes, as well as by the transcriptional repression, or enhanced proteolysis. This results in reduced E-cadherin-mediated cell-cell adhesion and enables the malignant cells to invade the tissues and to enter the blood or lymphatic vessels.[51] Therefore, E-cadherin gene is sometimes referred to as the "suppressor of invasion" gene.[52] It was demonstrated that E-cadherin loss in lung cancer is associated with the increased metastasis capability.[53] A degradation of the basal membrane and of the extracellular tissue matrix by proteases is very important for the local invasiveness and blood or lymphatic metastasis.

Matrix metalloproteinases (MMPs) are members of the family of zinc-containing proteolytic enzymes that facilitate the tumor invasion, the metastatic capabilities, and the tumor-related angiogenesis. Conversely, matrix metalloproteinase inhibitors (MMPIs) have been shown to inhibit tumour growth and dissemination in preclinical models. It is therefore not clear why not all lung cancers express the MMPs and there are conflicting reports about the prognostic importance of MMPs expression in lung cancer.[54]

It was found that **CRMP-1,** a protein that mediates the effect of collapsins, has reduced the expression in more aggressive and metastatic lung cancer samples.[55] This down-regulation is believed to enhance the cell migration ability, which is important for the process of metastasis. CRMP and other members of the collapsin/semaphorin protein families might control the cell's movement.[56]

Laminins and **integrins** are proteins involved in the adjacent tissue invasion through the basement membrane and further spread of the lung cancer cells. The reduced expression of laminin α chains (α3 and α5) in lung neoplastic tissue might result in the basal membrane fragmentation necessary for the cancer cell invasion.[57] Changes in the integrin expression are found in metastatic cells in many human neoplasms, including the lung cancer.[11] Recently, a study conducted by Manda and collaborators, identified that the ***LAMB3*** gene (coding for the laminin β3 chain, a component of laminin-5) was expressed only in NSCLC cells and not in SCLC tumor cells.[58] In the same study, the **α6β4** integrin, the specific laminin-5 binding receptor, was expressed only in NSCLC cells but not in SCLC cells. This suggests that laminin-5 might be a critical microenvironmental factor for the growth of NSCLC tumours.[58]

Overview of the molecular abnormalities in lung cancer pathogenesis

The model of lung cancer pathogenesis is depicted on the Figure 1 and was developed based on the previous studies.[59] The carcinogens from the tobacco or other environmental pollutants lead to the loss of the 3p21.3 allele in thousands of cells on different sites of the respiratory epithelium. Later, the tumor suppressor genes located in the 3p21.3 chromosome arm become haplo-insufficient. The next hit occurs in genes that are critical for the cell proliferation, such as *RB, p53, p16* or other genes either by the mutational inactivation or by the promoter hypermethylation. That permits a clonal outgrowth of the initially transformed cells. Some authors suggest that the molecular pathogenesis differs significantly between SCLC and NSCLC main tumor types.[30] It is proposed that during the pathogenesis of the SCLC neoplastic cells arise directly either from normal or hyperplastic epithelial cells without passing through characteristic preneoplastic intermediate pathological stages (parallel theory of lung cancer

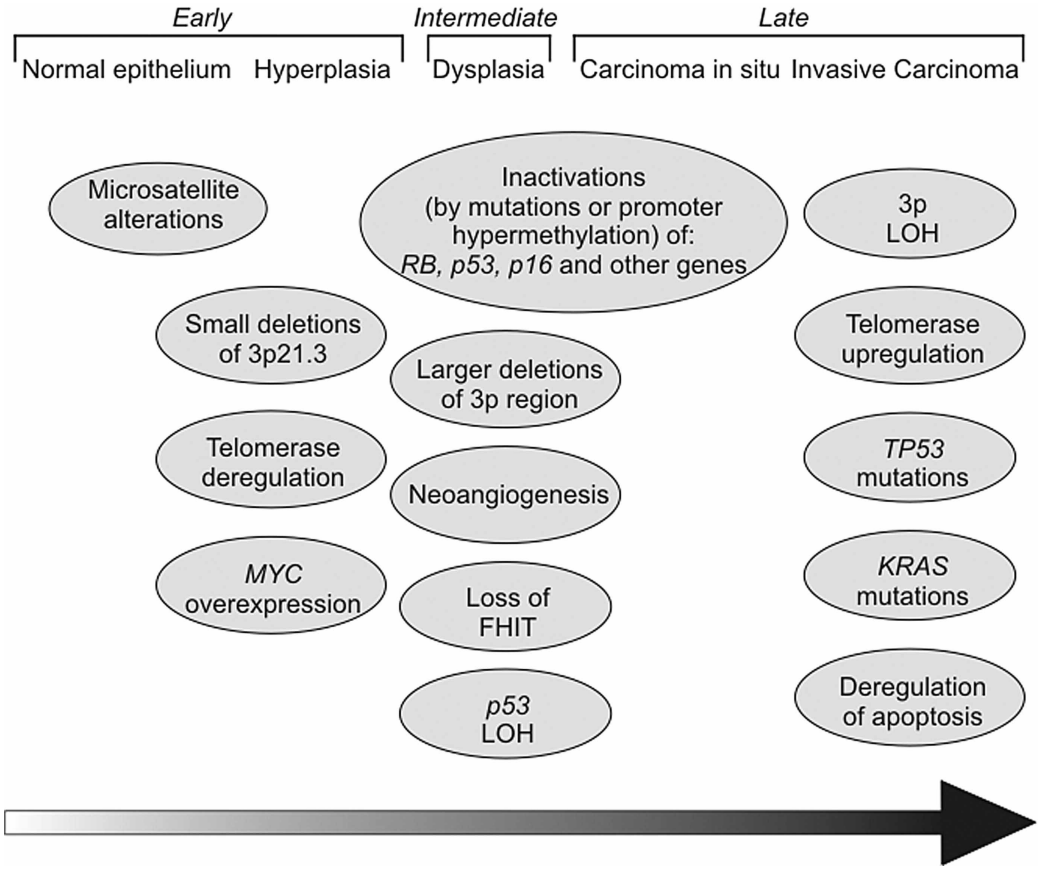

Figure 1. Main molecular abnormalities occurring during lung cancer pathogenesis (according to References 59 and 22).

pathogenesis). On the contrary, the NSCLC pathogenesis is accompanied with sequential morphological changes (sequential theory).

Conclusions

Recent progress into the elucidation of the molecular genetic abnormalities involved in the lung cancer has been achieved using modern technologies for the mutation detection as well as for the gene expression quantitation using microarray techniques. A precise characterization of those events and their association with the clinical and pathological types of the lung cancers are expected to result in the clarification of the pathogenesis of this complex disease and would led to the advance of novel molecular approaches for the early diagnosis and therapy of the pulmonary carcinomas.

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Radiol Oncol 2005; 39(3): 211-7.

Setup error and its effect on safety margin in conformal radiotherapy of the prostate

Borut Kragelj

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

Background. *In radiotherapy, setup errors in positioning the patients influence the size of safety margin and thereby also the size of irradiation field and toxicity of radiotherapy.*
Methods. *The setup errors were calculated by evaluating the deviations from the measured distance between the irradiation field margin and the bony pelvis.*
Results. *The research was performed on 23 patients. With respect to lateral, craniocaudal and anteroposterior axis, the observed systemic error ranged from -5 to + 9 mm, -4 to +5 mm, and from -4 to +4 mm, respectively, whereas the observed random error ranged from 0 to 7.5 mm, 0 to 3.6 mm, and from 0 to 4.2 mm, respectively. The safety margin, with the 90% probability to cover clinical target volume (CTV) and allowing for the prostate position variability, measured 9 mm, 9.5 mm, 7 mm, and 10 mm in the respective lateral, craniocaudal, anterior and dorsal direction.*
Conclusions. *Irradiation of the prostate with a 7 mm dorsal safety margin, allowing for 90% coverage probability of CTV, was feasible in 22/23 patients on condition that the gross systemic error (>3mm) was eliminated.*

Key words: prostatic neoplasms; radiotherapy, conformal

Introduction

Due to acute and particularly chronic postirradiation complications in radiotherapy of the prostate, the dose application, and consequently also the irradiation effect, are restricted. The incidence and grade of acute and chronic complications depend upon the dose and volume of the surrounding organs involved in the irradiation area.[1-4]

As the restrictions on dose application should in no way be disregarded, the irradiation of the prostate can be performed on condition that the beam is aimed as accurately at the target volume as possible. The size of the irradiation field is dependent on the width of safety margin around the target volume that ensures that the area to be irradiated is actually or most probably irradiated. However, the more the safety margin is extended, the

Received 15 August
Accepted 31 August

Correspondence to: Borut Kragelj, MD, PhD, Department of Radiation Oncology, Institute of Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia; Phone: +386 1 587 9489; Fax: +386 1 587 9400; E-mail: bkragelj@onko-i.si

greater is the exposure of the surrounding organs to irradiation and consequently also the risk of therapy-related complications.

In the radiotherapy of prostate cancer, the safety margin width is dependent upon the prostate motion and patient positioning errors. The aim of our research was therefore to estimate the setup errors, and from the obtained results, determine an optimal safety margin.

Methods

Patients

The patients who were irradiated at our Institute in the period from September 2004 to March 2005 were included into the study. These patients were given radiotherapy as a unique treatment or as adjuvant treatment after primary prostatectomy.

Irradiation technique

Irradiation was performed by a 15-MeV linear accelerator (Varian, Clinac 2100 C/D), using the four-field technique, at the angles of 0, 90, 180, and 270 degrees in the sense of 3D conformal radiotherapy. Irradiation simulation was carried out on Philips CT MX 8000 multislice simulator. Target volumes were mapped using the program CMS Focal, whereas the program CMS Xio 4.2.0 was used for irradiation planning that was carried out by beam-eye-view technique. The fields were framed by multileaf collimator.

The patients were irradiated in supine position with the feet resting on a support cushion (Sinmed Feetfix support cushion) and the knees provisionally supported. The isocenter was defined by three spots – one on the abdominal wall and two lateral spots. The position of each patient was additionally marked on the isocenter plane by four lines (with respect to the patient's axis, three longitudinal lines and one transversal line).

Irradiation area

Clinical target volume (CTV) included the prostate, seminal vesicles, and in the patients at high risk, also regional lymph nodes. The safety margin determining the planned target volume (PTV) was 1.5 cm wide; in the closing phase of radiotherapy, in which only the prostate was exposed to irradiation, the safety margin was reduced to 1 cm, and on the dorsal side, to 0.7 cm.

Irradiation precision

Irradiation precision was tested by amorphous silicon-based portal imaging system (EPI). The image was additionally processed by Varian's vision software, version 6.1 that allows a precise computerized reconstruction of irradiation field borders.

The setup error in patient positioning was calculated by comparing the distance between the field margin and selected bony pelvic structures of the digitally reconstructed radiographs (DRRs) obtained from the planning CT data and EPI. The display and comparison of images as well as measurements were made by computer program Multiaccess, version 8,00J0, Impac Medical Systems.

Methods

The setup error in patient positioning was defined by the deviations along the craniocaudal, anteroposterior and lateral axis. All deviations in the cranial direction, to the right and anterior were marked as positive and the deviations in the caudal direction, to the right and dorsum were marked as negative. In order to eliminate errors in deviation measurements, more measurements were performed yielding a higher mean value. Therefore, in final evaluations of safety margins, the inaccuracy of measurements was neglected.

From the above measurements, a systemic (SE) and a random setup error (RE) with re-

spect to each of the three axes was calculated for each individual patient. Systemic error was defined as a mean deviation of a patient positioning from the isocenter and random error as a deviation of each individual measurement from the mean value. The size of random error was marked as 1SD. The systemic and random setup errors were then calculated for the entire group of patients. The systemic error for the entire group (SEeg) was defined as arithmetic mean of all individual systemic errors.

In calculating the random error for the entire group (REeg), random deviations of individual SE from SEeg were also taken into account. The size of the random component of SE was estimated by 1 SD (SDse) and derived from an even distribution of individual SE around SEeg. The size of RE was also considered and was derived from an even distribution of individual RE around arithmetic mean of individual RE (AM RE). The size of individual RE deviations from AM RE was also defined as 1 SD (SDam). Adding AM RE and 1.63 SDam, SDre was obtained with 95% probability that all RE were comprised in SDre. In the calculation of REeg, SDse and SDre were considered as independent parameters. REeg, expressed as 1 SD, was obtained by the square root of SDse2+ SDre2.[5]

From the obtained systemic (SEeg) and random (REeg) setup errors, the size of safety margin was calculated in order to compensate for the errors in positioning the patient along each of the axis. Because of relatively high prevalence and severity of late rectal radiation toxicity, the anterior and posterior safety margins along the anteroposterior axis were calculated separately.

The safety margin calculation by adding SEeg and 1.5 SD REeg was based on Goitein's estimation[6] that 1.5 SD is a sensible compromise between the risk of underdosing the target volume and of excessive overdosing of the surrounding healthy tissue. This complies well with 90% confidence interval of random deviation in any of the directions. In further calculations of safety margin, the prostate position variability was taken into account in addition to the setup error. For the assessment of the position variability of the prostate, Zelefsky's data were used.[8] The safety margin was calculated by adding the arithmetic mean of the prostate movements and SEeg and 1.5 SD of the combined random error, calculated according to Rudat's recommendations, taking into account the random setup error as well as the random prostate movement error. The calculations of safety margins were made for each axis and separately for anterior and posterior directions.

Results

The research was performed on 23 patients in whom altogether 95 measurements were made for evaluating the position of a patient during irradiation. In each patient, three to maximum five positioning measurements were carried out.

The deviations along the lateral axis ranged from -10 to +12 mm, along the craniocaudal axis from -7 to 6 mm, and along the anteroposterior axis from -11 to +5 mm. The systemic error along the lateral axis was within the range of -5 to 9 mm, along the cranio-

Table 1. The range of the set up errors and the systemic and random components of the setup errors with respect to the direction of the positioning deviation

Deviation - direction	Lateral	Craniocaudal	Anteroposterior
Setup error-range (mm)	-10 do +12	-7 do +6	-11 do +5
Systemic error (mm)	-5.0 do +9.0	-4.2 do +4.8	-4.4 do +4.2
Random error (1SD in mm)	0 do 7.5	0 do 3.6	0-4.2

Table 2. Systemic (SEeg) and random (REeg) setup errors with respect to the entire group of patients (23) and the direction of pisitioning deviation by presenting SEeg, AMRE, SDam, SDre

Deviation - direction	**Lateral (**mm)	**Craniocaudal** (mm)	**Anteroposterior** (mm)
Systemic error (SE eg)	**+0.53**	**+0.17**	**-0.87**
SDse (1SD)	2.9	2.3	2.5
Random error (REeg)	**5.1**	**4.1**	**4.9**
AMRE	2.6	1.9	2.3
SDam	1.6	1.0	1.2
SDre	4.3	3.5	4.2

caudal axis -4.2 to +4.8 mm, and along the anteroposterior axis -4.4. to +4.2 mm. The random error with the size of 1SD varied along the lateral axis from 0 to 7.5 mm, along the craniocaudal axis from 0 to 3.6 mm, and along the anteroposterior axis from 0 to 4.2 mm (Table 1).

The calculated systemic error for the entire group along the lateral, craniocaudal, and anteroposterior axis was +0.57 mm, +0.17 mm, and -0.87 mm, respectively. The random error for the entire group in the lateral, craniocaudal, and anteroposterior axis was 5.1 mm, 4.1 mm and 4.9 mm, respectively. The two errors (SEeg and REeg) as well as SDse, AM RE, SDam, and SDre are presented in Table 2. The safety margin (SM) that would, with a 90% probability, cover an inaccurate positioning of a patient with respect to the lateral and craniocaudal axis is 8.2 mm and 6.3 mm, respectively, and with respect to the anteroposterior axis, 6.5 mm towards the anterior and 8.3 mm posteriorily. The safety margin that would, in addition to the setup errors, compensate also for the prostate position variability (SM total) along the lateral and craniocaudal axis with the same confidence interval is 9.2 mm and 9.5 mm, respectively, and along the anteroposterior axis, 6.7 mm towards the anterior and 10.3 mm posteriorily (Table 3).

Discussion

The aim of this study was to determine an adequate safety margin that would allow an acceptable exposure of a target area to irradiation. The difficulties of the prostate cancer patient radiotherapy that make this therapy unreliable are the prostate position variability as well as inaccuracy in all subsequent repositionings of the patient in the initial pose.

Monitoring the variability of prostate position is an exacting task, and so far, it has not been performed at our Institute. So, the size of safety margin, and thereby also the precision of irradiation, is dependent merely on the precision in repositioning the patient in the initial irradiation position. In comparing our data on the patient repositioning precision to the published data, it may be concluded that our precision was tolerably satisfactory. As reported by Rudat,[5] the random error along the lateral, craniocaudal, and anteroposterior axis was 3.1 mm, 5.4 mm, and 4.9 mm, respectively. In our patients, the random error calculated by using a similar method, was 3.9 mm, 2.9 mm, and 3.5 mm, respectively. In the study by Song, the data on the deviations greater than 5 mm in 40% of repositionings of his patients[9] also speak in favor of the satisfactory precision in repositioning of our patients.

Table 3. Safety margin depending on the setup error (SM) in conjunction with the prostate position variability (SMtotal)

Direction	**Lateral**	**Craniocaudalni**	**Anterior**	**Posterior**
SM (mm)	8.2	6.3	6.5	8.3
SM total (mm)	9.2	9.5	6.7	10.3

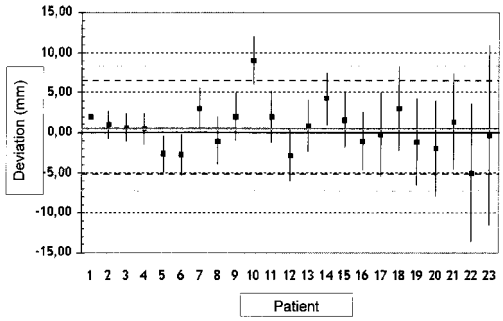

Figure 1. Systemic and random setup errors (1.5 SD) along the lateral axis in the patient positioning and safety margin at which CTV should have been included in the irradiation field with 90% probability.

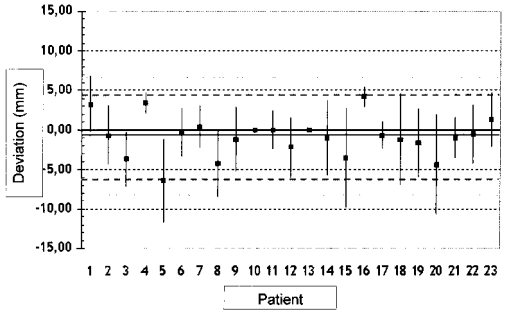

Figure 3. Systemic and random setup errors (1.5SD) along the anteroposterior axis in the patient positioning and safety margin at which CTV should have been included in the irradiation field with 90% probability.

The safety margin was calculated from the measurements of setup errors (in positioning of our patients) and from the data published on the prostate position variability. Our calculated safety margin – approximately 1 cm in all directions – is similar to the margins reported by various authors of the studies on prostate irradiation, except for the margin on the dorsal side, which was allowed to be smaller than 1 cm.[10] However, if the safety margin of less than 1 cm is not coordinated with the prostate position variability and setup error, the coverage of CTV may not be sufficient - according to Zelefsky, in the patient in prone position and at a safety margins of 1 cm in the anterior lateral and craniocaudal directions and of 0.6 cm at the dorsal side, the coverage of CTV at the dorsal side is 85 % before and 96% after the corrections for setup error and prostate displacement.[8] In our patients, the coverage of CTV can be evaluated only indirectly, by assessing the involvement of CTV dependent exclusively on the setup errors. The results are shown in Figures 1-3.

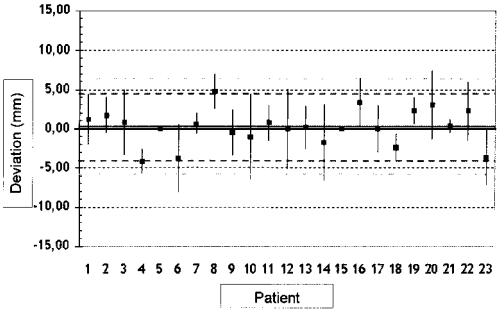

Figure 2. Systemic and random setup errors (1.5SD) along the craniocaudal axis in the patient positioning and safety margin at which CTV should have been included in the irradiation field with 90% probability

The 90% probability of CTV coverage of the irradiation field at the safety margin of 1 cm along the lateral axis is achieved in 91% of patients, and in cranial and caudal directions in 91 % and 87% of patients, respectively, and on the anterior and posterior side in 96 % and 78 % of patients, respectively on side. By reducing the dorsal margin to 0.7 cm, the 90% probability of CTV involvement in the irradiation field would be obtained only in 74% of patients.

The irradiation precision may not be improved either by changing the patient position or by additional support using various positioning aids. The prone position during irradiation may helps to reduce the exposure of the rectum to irradiation;[8,11] however, there is no data proving that this position can improve the positioning precision, given that it somehow deprives the patient of comfort during irradiation. Additional disadvantage of the prone position is that, in this position,

Table 4. Systemic and random setup errors in patients with less than 90 % probability of CTV coverage and the direction of the setup errors

Direction	Patient's no.	Systemic error mm	Random error mm
Right	16	9	2
	19	0.3	7.5
Left	15	5.0	5.8
	19	0.3	7.5
Cranial	8	4.8	1.5
	20	3.0	2.9
Caudal	6	3.8	2.9
	14	1.8	3.3
	23	3.7	2.3
Anterior	1	3.2	2.4
Posterior	5	6.4	3.5
	15	3.5	4.2
	20	4.4	4.2
Posterior	3	3.7	2.3
(0.7cm)	8	4.2	2.9
	18	1.2	3.9

urethrography is hard to perform and, hence, the apex of the prostate cannot be reliably located. Considering the precision of the patient positioning, even the use of support cushions may be questionable. Comparing different support systems, Song reported that a similar percentage of most evident errors, approx. 40%, was made in positioning the patients by using any type of support as in positioning them with no support at all.[9]

On the other hand, a better irradiation precision may be achieved by eliminating most apparent systemic errors (Table 4). By determining the systemic and random positioning errors, it is possible to asses an appropriate safety margin and, by eliminating the systemic error, the probability of CTV involvement into the irradiation field may increase. By correcting the systemic error, due to which the probability of involving CTV along one of the axes during the positioning was lower than 90%, an adequate CTV coverage may be obtained along the lateral axis in 96% of patients, in the cranial and caudal directions, in 100% and 96%, respectively, and along the anteroposterior axis, in 100% of patients. In cases when the dorsal safety margin is reduced to 0.7 cm, the correction of the most evident systemic error may help to achieve an adequate exposure of CTV to irradiation in as much as 96% of patients. In that case, the correction of isocenter would be required in 10/23 patients.

From the estimates of systemic and random error, it is possible to identify the patients in whom CTV would have been included in the irradiation field with 90% probability provided that the systemic error had been eliminated and the patients in which the estimated exposure of CTV to irradiation would have been obtained only by increasing the safety margin. By redefining the isocenter, which would be required in almost half of our patients, an optimal exposure of the most critical part of the prostate to irradiation, i.e. of the dorsal part, would be obtained in 22/23 patients, even though the safety margin was reduced to 0.7 cm.

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case report

Missing tissue compensation with wax filter compensators in radiotherapy of the head and neck region

Daša Grabec, Primož Strojan

Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background. *In the conventional radiotherapy of the head and neck region, the inhomogeneity of the absorbed dose in certain clinical situations can exceed ? 5% of the nominal dose. Depending on the pattern of dose inhomogeneity, treatment related toxicity is more pronounced and disease control reduced. The aim of our report is to present the wax filter compensation technique used in our department.*

Case report. *A 46-year-old male with inoperable carcinoma of the oropharynx of clinical stage T3N2c was irradiated with 5 MV linear accelerator photon beams and conventional 3-field technique. In order to obtain more homogenous dose distribution in treated volume, the opposed lateral fields were modified using 2D-wax filter compensators.*

Results. *Using conventional wedge filter compensation, the planed absorbed dose deviations in the treated volume were in the range of 94% to 113% of the prescribed dose. By modification of the opposed lateral fields with 2D wax filter compensators, the variations of the absorbed dose were reduced to the range from 93% to 105% of the prescribed dose. In the article, the planning and manufacturing as well as dosimetric checking of wax filter compensators are described.*

Conclusions. With the use of 2D wax filter compensators, the inhomogeneity of absorbed dose distribution was significantly reduced, and the quality of treatment considerably improved.

Key words: head and neck neoplasms-radiotherapy; radiotherapy dosage

Introduction

The conventional teleradiotherapy technique for head and neck tumors consists of two opposing lateral fields, encompassing primary tumor and upper neck lymphatics, and one anterior field to cover the lower neck and supraclavicular regions. To provide a homogenous dose distribution, the most elementary compensation technique is the wedge compensation of lateral fields. Even though, the precalculated variations of the delivered dose inside of the target volume can, in certain cas-

Received 8 January 2005

Accepted 10 March 2005

Correspondence to: Daša Grabec, PhD, Radiophysics Unit, Department of Radiotherapy, Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia; Phone: +386 1 5225238; Fax: +386 1 4319108; E-mail: dgrabec@onko-i.si

Acknowledgement

This work was supported by the Ministry of Science and Technology of Republic Slovenia, Grant No. Z3-6144-0302-04/3.04.

es, highly exceed ± 5 % of the nominal dose as recommended by ICRU.[1,2] The following two factors contribute to the inhomogeneity: *(1)* the difference in the amount of tissue between different levels inside of the head and neck region that is more pronounced in thin patients and after extensive neck surgery ("geese neck"); *(2)* the difference in the tissue structure, i.e. different electronic tissue density of various structures in the head and neck region (bones, soft tissue, air cavities).

Both, the volume and the position of the low/high dose regions, together with the level of variations from the nominal (reference) dose, can significantly compromise the quality of treatment. »Hot spots« result in more pronounced acute side effects of irradiation, which could influence the scheduled radiotherapy course, and consequent late toxicity could importantly decrease the patient's quality of life during post-treatment period. In addition, »cold spots« reduce the probability for controlling the disease and, therefore, the patient's chance for cure.

When absorbed dose inhomogeneities in the treated region are considered to be unacceptable, the need for more sophisticated compensational technique emerges.[3] The compensation technique should be chosen according to the individual clinical situation and technical and logistic possibilities in particular radiotherapy department. When the full skin-sparing effect of megavoltage treatment beam is desirable, the use of filter compensators is indicated.[4]

The filter compensator material is chosen according to the electron density of the material and according to the quality of irradiating beam.[5] The filter compensator material should also not significantly change the beam quality.[6] Several studies showed that wax can be successfully used as a material for filter compensators.[5] The required dose reductions for compensating purposes are usually up to 20 %. For 5 MV photon beam that is achieved using approximately around 5 cm of wax.

The aim of our report is to present the wax filter compensation technique used in our department.

Case report

A 46-year-old male with inoperable carcinoma of the oropharynx of clinical stage T3N2c was referred to the Department of Radiotherapy at the Institute of Oncology Ljubljana, Slovenia, for curative treatment with radiotherapy. The patient was simulated on conventional simulator with CT option (Philips SLS-CT). Irradiation technique consisted of two opposed lateral fields (270° and 90°: 11.5 cm × 13.5 cm) to cower the region of primary tumor and upper neck lymphatic basins, and one anterior field (0°: 21 cm × 9 cm) to cower lower neck and supraclavicular regions. The parts of the fields to be spared of

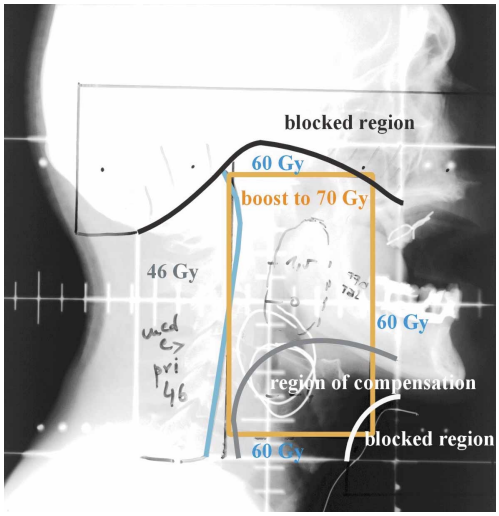

Figure 1. The simulator film of the right lateral field (270¡). The positions of the CT images are indicated (central slice, through the isocenter; upper slice, 1.5 cm above the isocenter; lower slice, 4 cm below the isocenter). The blocked regions and the high dose region that should be compensated are delineated. The three phases of the photon treatment are indicated: the whole treatment volume up to 46 Gy, avoiding medulla from 46 to 60 Gy and boost to gross disease from 60 to 70 Gy.

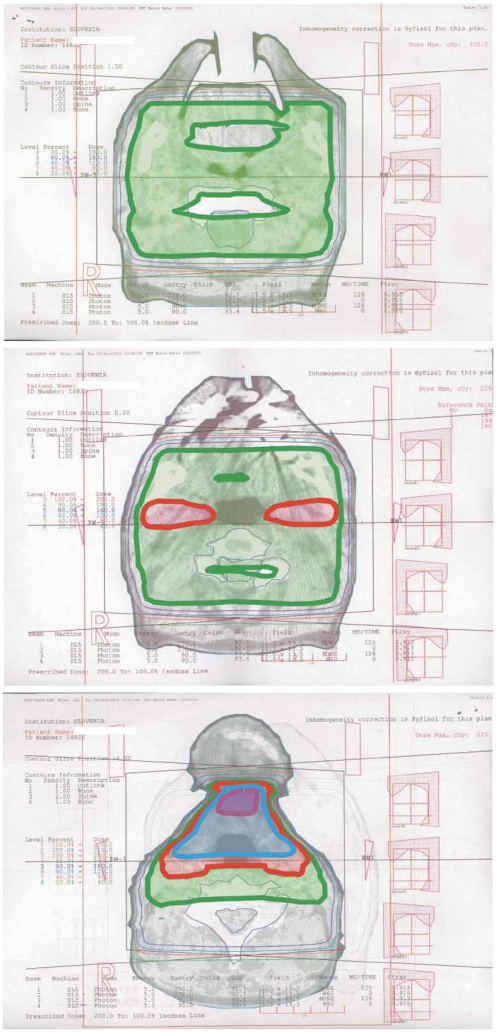

Figure 2. The optimized dose distribution was calculated using three CT slices (see Fig. 1). Applying only wedge filter compensators, the calculated inhomogenieties inside the treated volume were significant. The regions of different absorbed doses, expressed in the percentage of prescribed dose, are colored: 95 % ≤ green <100 %; 100 % ≤ red <105 %, 105 % ≤ blue <110 %, 110 % ≤ purple < 115 %. On the central slice (through isocenter), the dose varied from 95% to 100% of prescribed dose.

On the lower slice (4 cm below isocenter), the absorbed dose exceeded 110% of the prescribed dose. On the upper slice (1.5 cm above isocenter), the absorbed dose hardly reached 95 % of the prescribed dose. The planed overall inhomogeniety range applying only wedge filter compensators was 19 % of the prescribed dose.

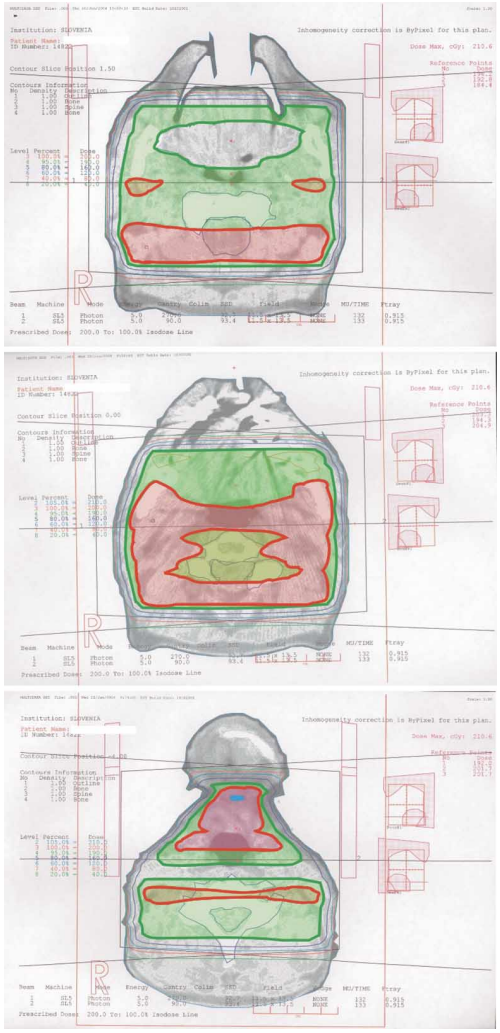

Figure 3. Applying the 2D paraffin wax filter compensator, the optimized dose distribution was calculated. In the high-dose region, the filter compensator was introduced as a block of 85% transmission. Dose distribution is presented on the same slice levels as on Fig.1 (central slice, +1.5 cm, - 4 cm). As the result, the dose distribution is much more homogenous as it was applying only wedge filter compensators (Fig.2). At the central slice, the absorbed dose is almost homogenous (100% of the prescribed dose), at the lower slice, the maximum dose hardly reaches the 105%, and it ranges from 93% to 100% of the prescribed dose on the upper slice.

irradiation were delineated on simulator film. The three CT slices were taken at three different levels: central slice (through isocenter); upper slice, 1.5 cm above the isocenter; lower slice, 4 cm below the isocenter (Figure 1).

The treatment was carried out in three phases. Phase 1: using 5 MV linear accelerator photon beams and 2 Gy daily fractions up to 46 Gy. Phase 2: from 46 Gy to 60 Gy; the lateral fields were shielded in the region of spinal cord which was boosted with 9 MeV electron beams. Phase 3: boost to gross disease to cumulative dose of 70 Gy

The optimal use of wedge filters and the irradiation times for each individual field were calculated with 2D planning algorithm with correction for tissue electron density (MultiData DSS, Multidata System International Corp., St. Louis, Missouri, USA). Applying wedge filters only, the planed inhomogeneities inside the treated volume covered with the opposed lateral fields ranged from 94% to 113% of the prescribed dose.

In this particular clinical situation, the degree of dose inhomogeneity (19%) indicated the use of compensator. The bolus type compensator was not suitable because we wished to preserve the skin sparing effect of megavoltage photon beams. Therefore, the use of 2D wax filter compensator was indicated. The region of dose compensation (the »high dose« area) was indicated on the film as shown on Figure 2.

The optimal dose compensation of the high dose region was calculated using the MultiData DSS planning system. The compensated region was introduced into the planning system as a block of a certain transmission T. The optimized transmission of the compensated region was found to be 85%, as shown on Figure 3. With the compensation of high-dose region, we could prolong the irradiation time of each individual opposed lateral field by 5%, thereby also increasing the delivered dose to previously low-dose regions.

Figure 4. The foam blocks with blocking filters made of Wood alloy and filter compensators made of paraffin wax, were manufactured for each of the lateral opposed fields (gantries 270¡ and 90¡). The central hole was drilled in each of the foam block in order to see the center of the optical fields. The positioning holes were drilled in the corners of the blocks. The 30 × 30 × 8 cm3 foam blocks had to be cut to the suitable dimension for Philips SL 75/5 linear accelerator, i.e. to 21 × 30× 8 cm3. The foam blocks were fixed on the positioning trays, ready to use.

The paraffin wax compensator filter assembling technique

The negative cut of the individual blocking filter and the negative cut of the compensator filter were milled in the previously calibrated 8 cm thick foam blocks (block dimensions: 30 cm × 30cm × 8cm) by the computer-guided milling machine (ACD – 5, Par Scientific, Denmark).

For the selected field, both negatives, that of the blocking filter and that of the compensator block, were cut in the same foam block. For the blocking filters, the Wood alloy is used because of its high electronic density. For the same reason, Wood alloy is not suitable as the compensator material. To increase compensating precision, the paraffin wax was used as the compensator material.

The negative cuts of the compensated and blocked regions were separated from each other with thin paper wall. First, the blocking region was filled up with the Wood alloy, and consequently, as soon as the Wood alloy so-

lidified, the region of compensating filter was filled with the liquid paraffin wax.

In order to irradiate at gantry 270° and 90° (opposed lateral fields), the foam blocks with shieldings and compensators were fixed on the holding trays as can be seen on Figure 4. As the largest dimension of the foam blocks fixed on the holding trays, used in irradiation, is 21 × 30 × 9 cm^3, the foam blocks of original dimensions 30 × 30 × 8 cm^3, had to be cut off (the original dimensions just at the end of the positioning holes = 21 cm). The central hole was drilled in the center of the foam, allowing for the center of the irradiating field and the position of the blocks and compensator to be verified.

Dosimetry

Prior to the irradiation of the patient, the filter compensators were checked by dosimetry of filtered beam. The delivered dose was also measured in vivo during the irradiation.7 For dosimetry checks, the micro-rod thermoluminescence dosimeters LiF:Mg:Ti (TLD 100) were used.[8]

Preheated TLD micro-rods were calibrated with 5 MV photon beam. Two TLDs were placed in the centre of the plastic water block (which simulated the patient's head) and were irradiated with two opposed lateral fields. The beams set-up conditions were the same as planned for the treatment without compensators. The response for the delivered dose of 197 cGy in the center of plastic block was measured.

Next, prior to patient treatment, the plastic water block with calibrated TLDs was irradiated according to the treatment plan, using shields and compensators. With applying compensators, we could increase the overall irradiation time and simultaneously the dose delivered at isocenter. The dose measured at the center of the plastic water block was 200 cGy. As it was the same as planned dose, we agreed that the filter compensator was appropriate for clinical use.

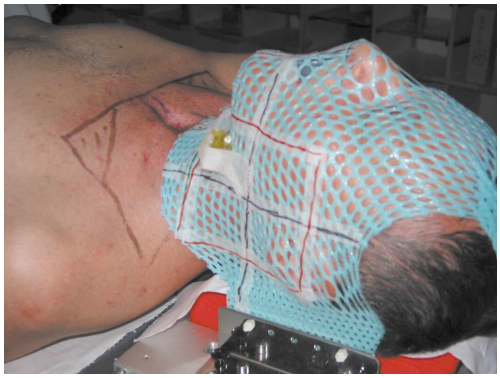

Figure 5. In vivo dosimetry is performed with the preheated and calibrated LiF:Mg:Ti micro-rod thermo-luminescence dosimeters (TLD - 100). TLD were placed in the tubes, covered with the 1.5 cm thick jelly and fixed on the patient. The delivered dose measured in the centers of the lateral opposed fields were 208 cGy on the left patient side and 197 cGy on the right patient side (104% and 98.5% of the planned dose, respectively). The delivered dose in the center of the compensated region on the left patient side was 189 cGy, 94.5% of the prescribed dose. Without the compensation, the dose absorbed in this region would be in the range from 210 cGy to 220 cGy (from 105% to 110% of the prescribed dose 200 cGy).

In vivo TL dosimetry was preformed twice during the irradiation. The first *in vivo* measurement was preformed on day 1 of the radiotherapy course. The two TL dosimeters were placed under the 1.5 cm thick jelly bolus in the center axis of each of the two opposed lateral fields. The delivered doses in the center of the irradiation fields were 208 cGy on the left and 197 cGy on the right patient's side (i.e. 104% and 98.5% of the planned dose, respectively).

The second measurement was done in the region of the compensated dose. On the left patient's side, the measured dose in the center of the compensated region was 189 cGy, 94.5% of the prescribed dose. Without the compensation, the dose absorbed in this region would be in the range from 210 cGy to 220 cGy (from 105% to 110% of the prescribed dose 200 cGy). On the right patient's side, the dosimeter was placed too close to the blocked

region and revealed the dose in the penumbra region. The in vivo dosimetry of the compensated region is presented on Figure 5.

The dose reduction was measured also with film dosimetry. The portal image conditions (5 monitor units [MU], open field; 3 MU, shielded field) were simulated with the planning system. The portal image was calibrated and used for the dose measurements. The overall delivered dose was in the range of 3% of the planned dose, whereas in the region of the dose lowered by the filter compensator the measured dose did not differ for more than 2 % from the planned dose.

Conclusions

Our method of missing tissue compensation using wax filter compensators proved to be precise enough to meet the expectations in clinical setting. Even though the manufacturing process of wax filter compensators is driven by computer-guided machinery, it is time consuming and should be properly scheduled and planned in advance. Anyhow, the quality of treatment was considerably improved.

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Radiol Oncol 2005; 39(3): 171-5.

Endoluminalni ultrazvok pri ugotavljanju ponavljajočih analnih fistul

Sudoł-Szopinska I, Jakubowski W, Kolodziejczak M, Szopinski T, Panorska AK

Izhodišča. Namen raziskave je bil primerjati endoluminalno ultrazvočno preiskavo brez kontrastnega sredstva in s kontrastnim sredstvom pri ugotavljanju ponavljajočih in primarnih analnih fistul.

Metode. V letih 1999-2002 smo pri 148 bolnikih ugotovili analno fistulo. Med njimi je bilo 51 bolnikov, ki so imeli ponavljajočo fistulo, 97 pa jih je imelo primarno. Endoluminalne ultrazvočne preiskave smo opravljali z Bruel & Kjaer skenerjem in 7,0 MHz sondo. Preiskavi brez kontrastnega sredstva je sledila preiskava s kontrastnim sredstvom, kjer smo uporabili 3% raztopino hidrogenega peroksida. Nato smo primerjali izsledke obeh preiskav.

Rezultati. Pri ugotavljanju ponavljajočih fistul je bila ultrazvočna preiskava, kjer smo uporabili kontrastno sredstvo, 35,3% bolj natančna kot preiskava brez kontrastnega sredstva (95% interval zaupanja 50,5% - 20,19%). Pri ugotavljanju primarnih fistul je bila razlika le 4,5% (95% interval zaupanja 11,1% - 2,0%).

Zaključki. Endoluminalna ultrazvočna preiskava s kontrastnim sredstvom statistično značilno izboljša natančnost glede na preiskavo brez kontrastnega sredstva pri ugotavljanju ponavljajočih analnih fistul. Pri ugotavljanju primarnih analnih fistul pa so rezultati obeh preiskav primerljivi in nismo našli značilne razlike.

Radiol Oncol 2005; 39(3): 177-80.

Diagnosticiranje in kirurško zdravljenje retrorektalnih cist – opis petih primerov

Kołodziejczak M, Grochowicz M, Sudoł-Szopińska I, Kosim A, Stefański R

Izhodišča. Retrorektalne ciste so redka bolezen, pravtako so redke objave, ki opisujejo to bolezen. Običajno poročajo le o nekaj primerih.
Metode. Avtorji opisujejo 5 bolnikov, ki so jim diagnosticirali retrorektalne ciste. Bolezen so ugotovilili s pomočjo anamneze, kliničnega pregleda in transrektalnega ultrazvoka. Ciste so operativno perinealno odstranili.
Rezultati. Pri treh bolnikih je bila histološka diagnoza epidermalna cista. Pri četrtem bolniku so ugotovili, da je bila cista epitelizirana z migetalčnim epitelijem, pri zadnjem pa so odkrili kostno, maščobno in vezivno tkivo kot del vnetnega stanja.
Zaključki. Digitalni rektalni klinični pregled je osnovni pregled pri diagnosticiranju retrorektalne ciste. Transrektalni ultrazvok je potreben za bolj natačno opredelitev velikosti ciste in lege glede na steno rektuma. Perinealna retrorektalna cistektomija je učinkovita metoda pri zdravljenju te bolezni. Dosedanji objavljeni primeri bolezni pa so maloštevilni, zato so lahko zaključki le preliminarni.

Radiol Oncol 2005; 39(3): 181-4.

Komunikacijska sakularna piloroduodenalna podvojitev – prikaz primera

Sjekavica I, Batinica M, Lušić M, Senečič-Čala I, Oberman B, Štern-Padovan R

Izhodišča. Podvojitvene anomalije piloroduodenalne regije so redke. Ob črevesnih podvojitvah običajno ugotovimo še dodatne malformacije.

Prikaz primera. Opisujemo primer piloroduodenalne podvojitve pri 22-mesečni deklici, kjer so bili prvi bolezenski znaki intermitentne slabosti in bruhanje. Ultrazvočna preiskava je pokazala anehogeno cistično spremembo med želodcem in levim jeternim režnjem. Preiskava zgornjega črevesa s kontrastom je pokazala stenozo v pilorobulbarni regiji kot posledico zunanjega pritiska. Na cistično podvojitev v prebavnem traktu s pritiskom na glavo pankreasa smo posumili ob preiskavi z večlistnim CT-jem s kontrastom. Med opracijo pa smo s kontarstom ugotovili komunikacijo med podvojitvijo in pilorno regijo. Patohistološka preiskava je potrdila podvojitveno cisto, ki je vseboval želodčno in duodenalno mukozo brez ektopičnega pankreatičnega tkiva.

Zaključki. Ultrazvočna preiskava je prva slikovna preiskava pri ugotavljanju črevesnih podvojitev in običajno pokaže cistično anehogeno spremembo. Dodatne preiskave: rentgenska preiskava z barijem, kontrastna preiskava s CT-jem ali MRI-jem nam lahko pomagajo bolj natančno diagnosticirati podvojitve v prebavnem traktu.

Radiol Oncol 2005; 39(3): 185-91.

Ugotavljanje koronarne kalcifikacije pri miokardnem infarktu

Bešlić Š, Dalagija F

Izhodišča. Namen raziskave je bil ocenitev pomembnosti ugotavljanja koronarne kalcifikacije kot dejavnika tveganja pri bolnikih z miokardnim infarktom.

Metode. V obdobju treh let smo pri 27 bolnikih z miokardnim infarktom ugotavljali stopnjo koronarne kalcifikacije. Povprečna starost bolnikov je bila 66,1 let (46-81). Za merjenje kalcija v koronarnih arterijah smo uporabljali večrezno računalniško tomografijo (MTDC) »Somatom Volume Zoom Siemens« in retrospektivno obdelali podatke glede na z EKG-jem merjen srčni ritem. Polavtomatsko smo izračunali količino kalcija po Agatstonu (CS). Uporabljali smo 4 x 2,5 mm veliki kolimator in 130 ml kontrastnega sredstava, ki smo ga vbrizgali z avtomatskim injektorjem s hitrostjo 4 ml/s. Empirično smo določili zakasnitveni čas. Ocenili smo tudi različne dejavnike tveganja za miokardni infarkt.

Rezultati. Med 27 bolniki z miokardnim infarktom so 3 (11,1%) imeli nizek CS (10-100), 5 (18,5%) sreden CS (101-499), 19 (70,4%) bolnikov pa je imelo visok CS (>500). Ko smo ugotavljali druge dejavnike tveganja za miokardni infarkt, smo ugotovili, da je bilo 17 (63,0%) bolnikov kadilcev, 10 (57,0%) bolnikov je imelo povišan arterijski krvni tlak, 7 (25,9%) sladkorno bolezen, 5 (18,5%) srčno bolezen v družini, 5 (18,5%) zvišane lipide v krvi, 4 (1,8%) pa so bili alkoholiki. Le šest (22,2%) bolnikov je navajalo simptome angine pektoris.

Zaključki. Raziskava je pokazala veliko soodvisnost miokardnega infarkta in stopnje kalcifikacije koronarnih arterij (CS>500). Tudi v naši skupini preiskovanih bolnikov smo ugotovili večjo prisotnost preostalih dejavnikov tveganja za miokardni infarkt, kot so kajenje, zvišanje arterijskega krvnega tlaka, sladkorna bolezen, miokarni infarkt v družini in povišan holesterol v krvi. Pri večini bolnikov pa nismo ugotovili izrazitih simptomov.

Radiol Oncol 2005; 39(3): 193-6.

Karcinoid tankega črevesa z akutno krvavitvijo, ki smo ga diagnosticirali s kapsulno endoskopijo

Mrevlje Ž, Sever M, Kocijančič B

Izhodišča. Karcinoid tankega črevesa običajno diagnosticiramo zaradi njegovih endokrinoloških simptomov, saj redko močneje krvavi.

Prikaz primera. Predstavljamo primer bolnika z nepojasnjeno krvavitvijo iz prebavil. S standardnimi diagnostičnimi preiskavami nismo ugotoviti mesta krvavitve. S kapsulno endoskopijo smo ugotovili manjši tumor tankega črevesa, ki je bil vzrok krvavitve. Patohistološki pregled po kirurški resekciji je pokazal karcinoid tankega črevesa.

Zaključki. Kapsulna endoskopija je pomembna preiskava tankega črevesa in jo moramo upoštevati kot eno prvih preiskav pri ugotavljanju začetnih oblik bolezni, še zlasti pri neizrazitih in okultnih krvavitvah.

Radiol Oncol 2005; 39(3): 197-210.

Molekularna biologija pljučnega raka

Panov SZ

Izhodišča. Pljučni rak je najpogostejše maligno obolenje in tudi glavni vzrok smrti rakavih bolnikov. Neverjeten napredek pri poznavanju etiopatogeneze pri raku pljuč sta doprinesli molekularna biologija in genetika z moderno tehnologijo mikromrež in sekveniranja.

Številne raziskave so ugotovile, da je kljub klonalnemu nastanku pljučnega raka potreben večstopenjski proces z več kot 20 različnimi genetskimi ali epigenetskimi spremembami. Do sedaj najpogosteje raziskovana področja so mutacije in druge genetske spremembe na onkogenih in na tumor supresorskih genih. V zadnjem času je vse več raziskav usmerjenih v ugotavljanje pridobljenih okvar na tumor supresorskih genih s hipermetilacijo promotorske regije. Poleg tega sedaj odkrivajo tudi zgodnje klonalne spremembe, ki nastajajo na preneoplastičnem bronhialnem epiteliju kot posledica kajenja ali drugih karcinogenov. Poznanih je že tudi veliko razlik na molekularni ravni med drobnoceličnimi in nedrobnoceličnimi karcinomi, ugotavljajo pa tudi razlike med tumorji z različnim biološkim potekom bolezni. Te raziskave vodijo v temeljitejše poznavanje biologije pljučnega raka.

Zaključki. Pričakujemo lahko, da bodo take raziskave doprinesle k boljši diagnostiki pljučnega raka, kot tudi boljšemu ocenjevanju tveganja, zgodnji prevenciji in novim prostopkom učinkovitega zdravljenja bolnikov s pljučnim rakom.

Radiol Oncol 2005; 39(3): 225-32.

Radiol Oncol 2005; 39(3): 211-7.

Napaka nastavitve bolnika in njen vpliv na varnostni rob pri konformnem obsevanju prostate

Kragelj B

Izhodišča. Napake pri nastavitvi položaja bolnikov med obsevanjem določajo velikost varnostnega roba in s tem tudi velikost obsevalnih polj.
Metode. Napako pri nastavitvi bolnikov smo ugotavljali z merjenjem odmikov robov obsevalnega polja od kosti medeničnega obroča.
Rezultati. V raziskavo je bilo vključenih 23 bolnikov, pri katerih je bila glede na lateralno, kraniokaudalno in anteroposteriorno os ugotovljena sistematska napaka od -5 do +9 mm, -4 do +5 mm in -4 do +4 mm ter naključna napaka od 0 do7,5 mm, 0-3,6 mm ter 0-4,2 mm. Varnostni rob za 90% verjetnost zajetja kliničnega tarčnega volumna (CTV) z upoštevanjem tudi gibanje prostate je bil 9 mm v lateralni, 9,5 mm v kraniokaudalni, 7 mm v anteriorni in 10 mm v dorzalni smeri.
Zaključek. Obsevanje prostate s 7 mm dorzalnim varnostnim robom je možno z odpravo izrazite sistematske napake(>3 mm), pri čemer je dosežena 90% verjetnost zajetja CTV pri 22/23 bolnikov.

Radiol Oncol 2005; 39(3): 219-24.

Voščeni filterski kompenzatorji pri obsevanju tumorjev glave in vratu

Grabec D, Strojan P

Izhodišča. Ob uporabi konvencionalne radioterapije področja glave in vratu lahko odstopanja absorbirane doze od predpisane presežejo ± 5%. Vzorec dozne nehomogenosti lahko vpliva na stopnjo izraženosti obsevalnih poškodb in uspeh zdravljenja. V članku želimo predstaviti uporabo voščenih filterskih kompenzatorjev na Onkološkem inštitutu v Ljubljani.

Prikaz primera. 46-letni bolnik z neoperabilnim karcinomom ustnega žrela kliničnega stadija T3N2cM0, je bil obsevan na linearnem pospeševalniku s fotonskim snopom energije 5MV in konvencionalno tehniko treh polj. Za dosego večje stopnje homogenosti razporeditve doze v obsevanem volumnu, sta bili nasprotno ležeči lateralni polji modificirani z voščenima 2D-filtrskima kompenzatorjema.

Rezultati. Ob uporabi konvencionalne kompenzacije s klinastimi filtri je znašalo predvideno odstopanje absorbirane doze znotraj obsevalnega volumna med 94% in 113% predpisane doze. Z modifikacijo nasprotno ležečih lateralnih polj z voščenima 2D filtrskima kompenzatorjema se je zmanjšalo nihanje absorbirane doze na vrednosti od 93% do 105% predpisane doze. V članku predstavljamo načrtovanje obsevanja z voščenimi filtrskimi kompenzatorji, njihovo izdelavo, ter rezultate dozimetričnega preverjanja pred in med obsevanjem.

Zaključki. Z uporabo 2D-voščenih filtrskih kompenzatorjev smo uspeli znatno zmanjšati nehomogenost v porazdelitvi absorbirane doze, s tem pa občutno izboljšali kakovost zdravljenja.

Notices

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Radiobiology

October 2-6, 2005

The ESTRO course »Basic Clinical Radiobiology« will take place in Izmir, Turkey.

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Oncology

October 7, 2005

The EORTC (European Organisation for Research and Treatment of Cancer) annual course »One-Day Introduction to EORTC Trials« will take place in Brussels, Belgium.

Contact 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 62 33; or e-mail dzi@eortc.be; or see http://www.eortco.be /Seminar/Educationpgm/Programs/prog2005.htm

Lung cancer

October 16-20, 2005

The IASLC workshop »Biology and Prevention of Lung Cancer« will be offered in Woodstock, Vermont, USA.

Contact Taryn Klocke at Envision Communications; call +1 770 763 5690; or see www.lungcancerprevention.net

Clinical oncology

October 19, 2005

The advanced cancer course »Molecular Oncology« will be offered in Rio de Janeiro, Brazil.

Contact: ASCO International Affairs Department, 1900 Duke Street, Suite 200, Alexandria, VA 22314, USA; or cal +1 703 519 1448; or fax +1 703 299 1044; or e-mail: international@asco.org; or see http://www/asco.org

Oncology

October 30 – November 3, 2005

The ESTRO 24 / ECCO 13 Conference will take place in Paris, France.

Contact FECS office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see http://www.fecs.be

Thoracic oncology

November 12, 2005

The 7th Annual UCSF/UC Davis Thoracic Oncology Conference will be held in San Francisco, California, USA

Contact University of California, San Francisco, Office of Continuing Medical Education, Box 0742, 3333 California St., San Francisco, CA 94143; or e-mail CME@ocme.ucsf.edu; or http://www.ucsfcme.com

Radiation oncology

November 13-18, 2005

The ESTRO course »Evidence-Based Radiation Oncology: Methodological Basis and Clinical Application« will take place in Dubrovnik, Croatia.

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Clinical oncology

November 14-15, 2005

The advanced cancer course »Doctor-Patient Communication« will be offered in Brisbane, Australia.

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Neuropsychiatry

November 16-18, 2005

The European Federation of Neuropsychiatry Annual Congress will be offered in Munich, Germany

Contact: EFNP Secretariat, RPA Congress, Nottingham; or cal +44 (0)115 969 2016; or e-mail: info@efnp.org; or see http:// www.efnp.org

Oncology

November 21-25, 2005

The EORTC (European Organisation for Research and Treatment of Cancer) course »Organization and Implementation of Cancer Clinical Trials« will take place in Leuven, Belgium.

Contact 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 62 33; or e-mail dzi@eortc.be; or see http://www.eortco.be /Seminar/Educationpgm/Programs/prog2005.htm

Mesothelioma

November 22-27, 2005

The »International Mesothelioma Symposium« will take place in Antalya, Turkey.

Contact: Taryn Klocke; call +1 770-984-5113; fax: +90 232 278 33 73.

Lung cancer

December 9-10, 2005

The 6th European conference »Perspectives in Lung Cancer« will be offered in Amsterdam, The Netherlands.

Contact Imedex, Alpharetta, Georgia, 30005-3969 USA; or call +1 770 751 7332; or fax +1 770 751 7334; or e-mail meetings@imedex.com; or see www.imedex.com

Thoracic oncology

January 13-15, 2006

The »5th Annual UCSF Clinical Cancer Update» will be held in Lake Tahoe, California, USA.

Contact University of California, San Francisco, Office of Continuing Medical Education, Box 0742, 3333 California St., San Francisco, CA 94143; or e-mail CME@ocme.ucsf.edu; or http://www.ucsfcme.com

Oncology

March 9-12, 2006

The ESO advanced course »Modifying Cancer Response to Therapy: From Molecular signalling to Cancer Care« will be offered in Lugano, Switzerland.

Contact: Chatrina Melcher, European School of Oncology, ESO Bellinzona Office, IOSI, Ospedale Regionale Bellinzona e Valli, CH-6500 Bellinzona, Switzerland; or cal +41 91 8111 8050; or fax +41 91 811 8051; or e-mail: eso2@esoncology.org

Oncology

March 12-15, 2006

ICTR 2006, the »3rd International Conference on Translation Research and Pre-Clinical Strategies in Radiation Oncology« will be offered in Lugano, Switzerland.

Contact: ICTR 2006 Secretariat, Department of Radio-Oncology, Oncology Institute of Southern Switzerland, CH-6504 Bellinzona, Switzerland; or fax +41 91 811 8678; or http://www.iosi.ch/ictr2006.html

Lung cancer

April 19-26, 2006

The »2nd Latin American Conference on Lung Cancer« will be offered in Cancun, Mexico.

Contact E-mail: LungCancerLA@meet-ics.com: or see http:// www.LCLA2006.com

Clinical oncology

May, 2006

The 42nd ASCO Meeting will be offered in Atlanta, USA.

Contact E mail: enews@asco.org; or see http:// www/asco.org

Lung cancer

June 18-21, 2006

The »10th Central European Lung Cancer Conference« will be offered in Prague, Czech Republic.

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Bronchology

June 25-28, 2006

The 14th Word Congress of Bronchology and the 14th Word Congress of Bronchoesophagology will take place in Buenos Aires, Republica Argentina.

Contact: General Secretariat, Ms. MarÛa Graziani & Asociados with phone +4394 7726 4393 3437; or Fax: +541 439 33436; or E-mail: mg@mariagraziani.com

Lung cancer

September 28-30, 2006

The »2nd International Workshop Early Invasive Lung Cancer: New Diagnostic Tools & Treatment Strategies« will be held in Turin, Italy.

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Lung and head & neck

October 26-28, 2006

The »4th Lung & Head and Neck Conference« will be offered in Sheraton Hotel, Chicago, Illinois.

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Lung cancer

November 8-12, 2006

The »3rd IASLC/ASCO/ESMO International Conference on Targeted Therapies in Lung Cancer« will be held in Taormina, Sicily. Italy.

Contact E-mail: fred.hirsch@UCHSC.edu

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

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Activity of »dr. J. Cholewa« foundation for cancer research and education - a report for the third quarter of 2005

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to support activities associated with cancer research and education in Slovenia with different grant applications and other applications for various types of financial support were being dealt by the responsible bodies formed by Foundation members with clinical and cancer research experience and members with important experience in finance.

The Dr. J. Cholewa Foundation for Cancer Research and Education also continues to support the regular publication of »Radiology and Oncology« international scientific journal, which is edited, published and printed in Ljubljana, Slovenia, as it has done over the last couple of years and is considering it one of its permanent commitments.

The Foundation bestowed various grants and other forms of financial support to interested individuals with projects dealing with problems in oncology affecting general population and patients with cancer in Slovenia. Among the recipients were also some reputed non-government organisations, such as Slovenian Cancer Association and others. With this in mind and as already noted before, the Foundation acknowledges the importance of the commitment of various public companies and private individuals to its cause.

Borut Štabuc, MD, PhD
Tomaž Benulič, MD; MSc
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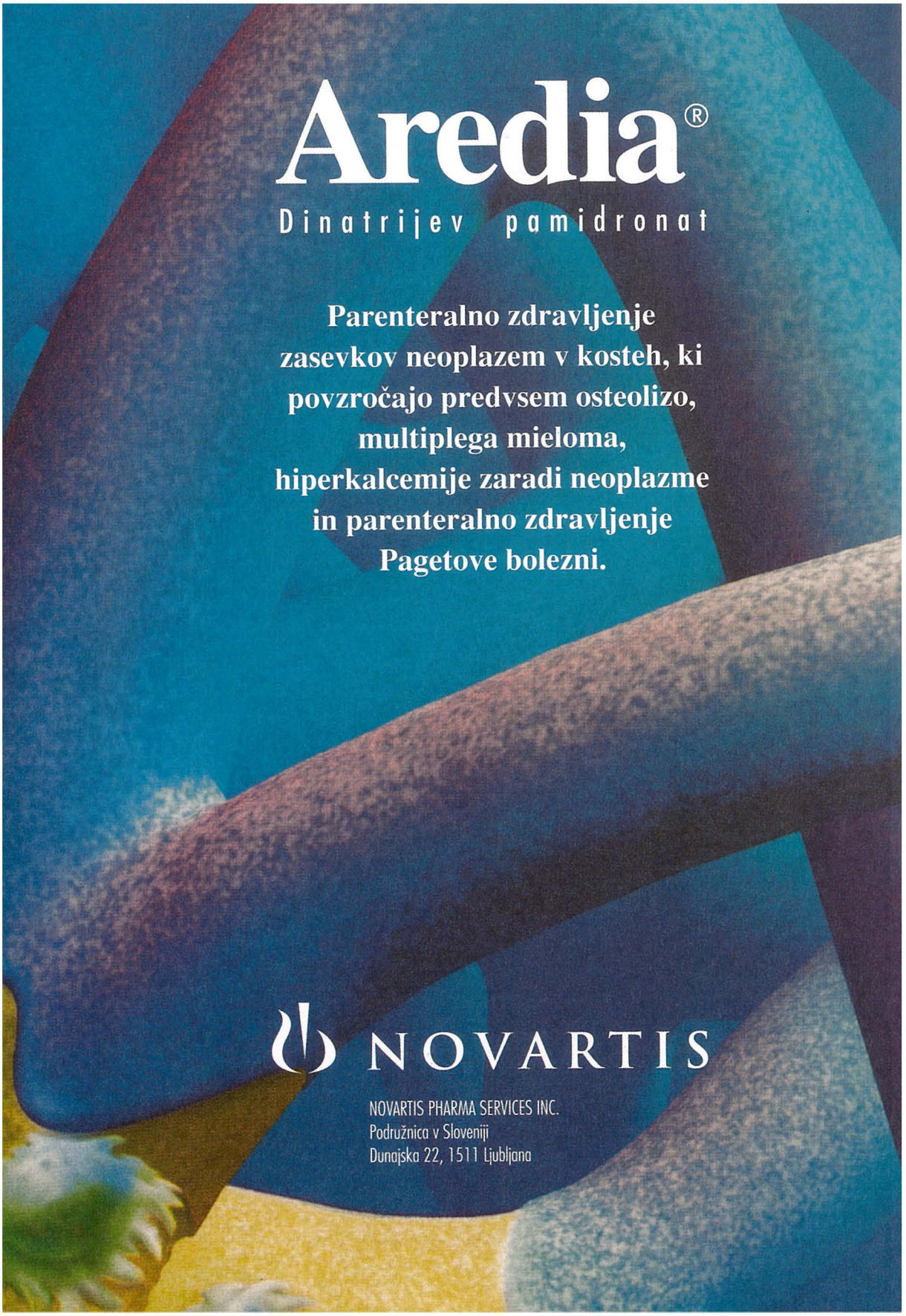
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Schering-Plough CE AG **[bolnišnična enota]** Dunajska 22, 1000 Ljubljana, t: 01 3001070, f: 01 3001080

Ime zdravila Temodal® 100 mg, 20 mg, 250 mg. Sestava zdravila Vsaka kapsula zdravila Temodal vsebuje 20 mg, 100 mg ali 250 mg temozolomida. Terapevtske indikacije KapsuleTemodal so indicirane za zdravljenje bolnikov z malignimi gliomi, kakor sta npr. multiformni glioblastom ali anaplastični astrocitom, ki se po standardnem zdravljenju ponovijo ali napredujejo. Odmerjanje in način uporabe Odrasli bolniki in pediatrični bolniki, stari 3 leta ali starejši: 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, potem pa naj sledi 23-dnevni premor (skupaj 28 dni). Pri bolnikih, ki so bili že prej zdravljeni s kemoterapijo, je začetni odmerek 150 mg/m² enkrat na dan, v drugem ciklusu pa se poveča na 200 mg/m² na dan, pod pogojem, da je na 1. dan naslednjega ciklusa absolutno število nevtrofilcev (ANC) ≥1,5 x 109/l in število trombocitov ≥100 x 109/l. Uporaba pri bolnikih z motenim delovanjem jeter ali ledvic: Pri bolnikih z blago ali zmerno jetrno okvaro je farmakokinetika temozolomida podobna kot pri tistih z normalnim delovanjem jeter. Kljub temu svetujemo previdnost pri uporabi Temodala pri teh bolnikih. Uporaba pri starejših bolnikih: Analiza farmakokinetike je pokazala, da starost ne vpliva na očistek temozolomida. Kljub temu svetujemo posebno previdnost pri uporabi zdravila Temodal pri starejših bolnikih. Način uporabe Temodal mora bolnik jemati na tešče. Kapsule Temodal 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 Pri bolnikih, ki so močno bruhali (stopnja 3 ali 4) v prejšnjih ciklusih zdravljenja, bo lahko potreben antiemetik. Uporaba pri otrocih: Kliničnih izkušenj z zdravilom Temodal pri otrocih, mlajših od 3 let, še ni. Uporaba pri starejših bolnikih: Zdi se, da je pri starejših bolnikih (starost >70 let) tveganje za nevtropenijo ali trombocitopenijo večje kot pri mlajših, zato svetujemo posebno previdnost pri uporabi zdravila Temodal pri starejših bolnikih. Moški bolniki: Temozolomid lahko deluje genotoksično. Interakcije Sočasna uporaba zdravila Temodal in ranitidina ni povzročila spremembe obsega absorpcije temozolomida. Jemanje zdravila Temodal s hrano je povzročilo 33 % zmanjšanje Cmax in 9 % zmanjšanje AUC. Ker ne moremo izključiti možnosti, da bi bila sprememba Cmax lahko klinično pomembna, priporočamo jemanje zdravila Temodal brez hrane. Analiza populacijske farmakokinetike temozolomida v raziskavah druge faze je pokazala, da sočasna uporaba deksametazona, proklorperazina, fenitoina, karbamazepina, ondansetrona, antagonistov receptorjev H2 ali fenobarbitala ne spremeni očistka temozolomida. Sočasno jemanje z valproinsko kislino je bilo povezano z majhnim, a statistično značilnim zmanjšanjem očistka temozolomida. Uporaba zdravila Temodal v kombinaciji z drugimi mielosupresivi lahko poveča verjetnost mielosupresije. Neželeni učinki V kliničnih raziskavah so bili najpogostnejši neželeni učinki, povezani z zdravljenjem, prebavne motnje, natančneje slabost (43 %) in bruhanje (36 %).Pogostnost hude slabosti in bruhanja je bila 4 %. Drugi pogostejši neželeni učinki so: utrujenost (22 %), zaprtje (17 %) in glavobol (14 %). Poročali so tudi o anoreksiji (11 %), driski (8 %) te izpuščaju, zvišani telesni temperaturi in zaspanosti.Laboratorijski izvidi: trombocitopenija oz. nevtropenija 3. oz. 4. stopnje sta se pojavili pri 19 % oz. 17 % bolnikov, zdravljenih zaradi glioma. 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 1-2 tednih. Znakov kumulativne mielosupresije niso ugotavljali. Imetnik dovoljenja za promet z zdravilom Schering-Plough Central East AG, Luzern, Švica, Predstavništvo v Sloveniji, Dunajska 22, 1000 Ljubljana 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 2005. Podrobnejše informacije o zdravilu so vam na voljo pri proizvajalcu.

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Datum priprave besedila januar 2005

Podrobnejše informacije so na voljo pri proizvajalcu.

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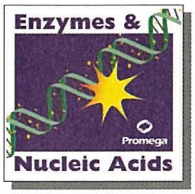

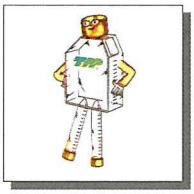

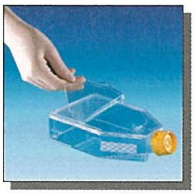

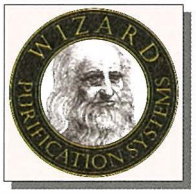

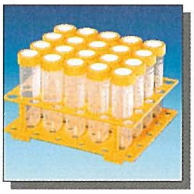

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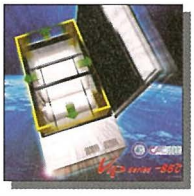

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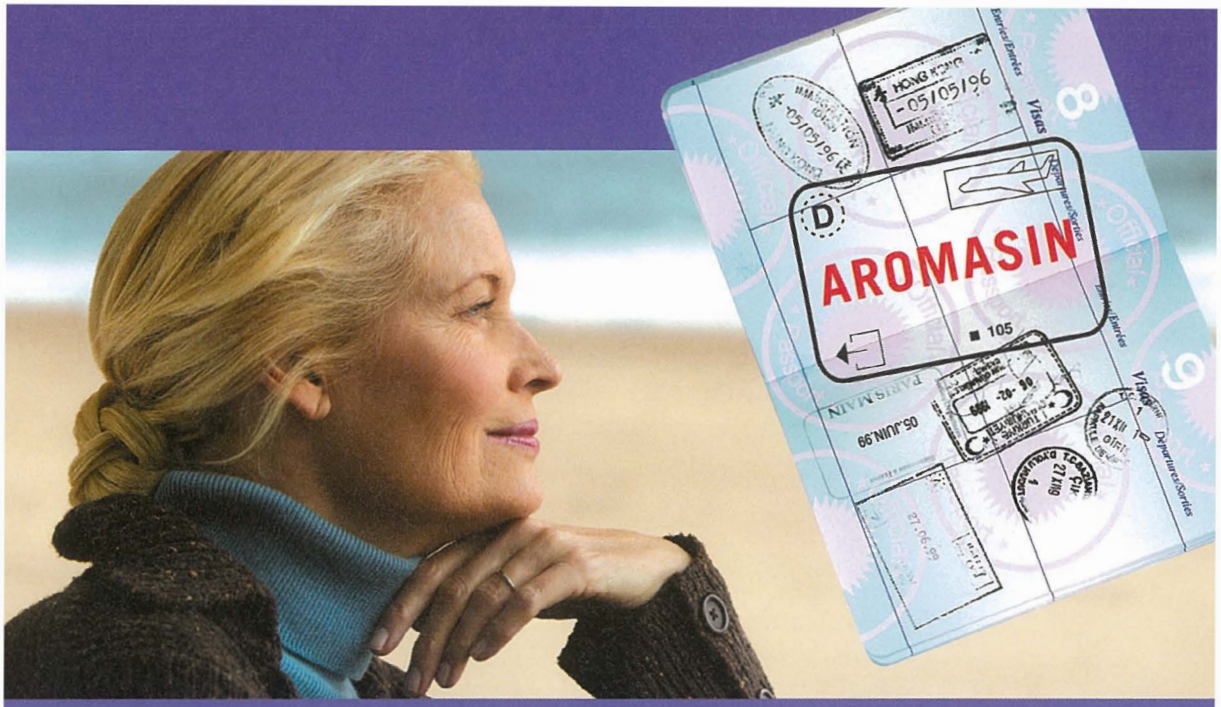

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Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

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

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

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

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

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

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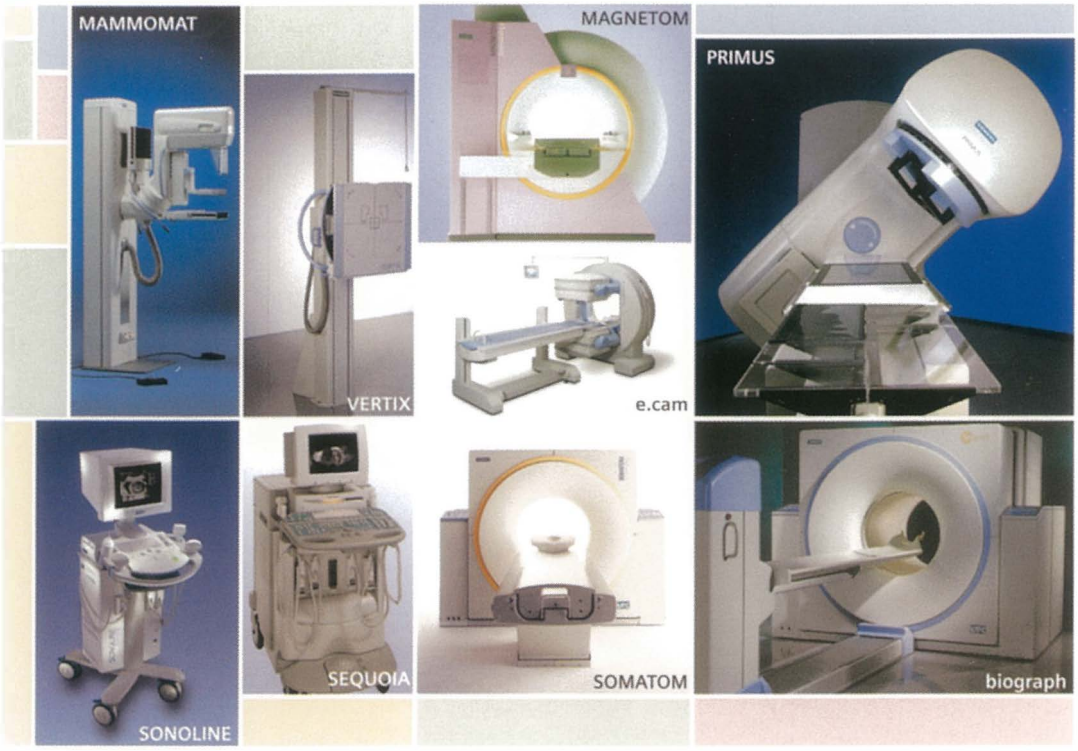

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