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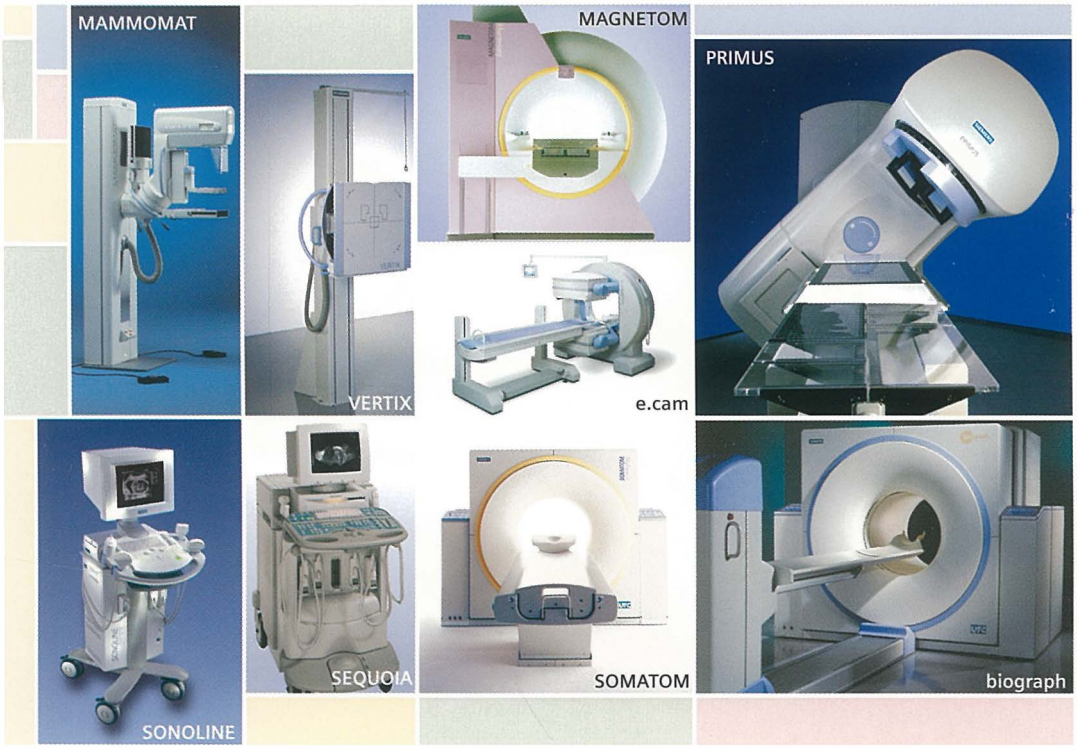

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Primary breast tuberculosis. A case report

Dimitrios C. Filippou, Spiros Rizos, Athanasios Nissiotis

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Background. *The differential diagnosis of primary breast tuberculosis with other benign or malignant conditions can be difficult with the current imaging techniques that used to recognize breast pathologies. In many cases mammographic and ultrasound characteristics of breast tuberculosis are similar to those of breast cancer.*

Case report. *We present a case of primary breast tuberculosis, with no previous history of the disease, which was diagnosed during the operation.*

Conclusions. *Primary breast tuberculosis can be misdiagnosed. In these cases a tuberculosis infection history is negative, the mammographic and radiological findings obscure and the mass can be misdiagnosed as carcinoma. The diagnosis is achieved after the surgical removal of the mass and histological examination of the specimen.*

Key words: breast diseases; tuberculosis; female genital

Introduction

Breast tuberculosis is a rare pathology, with a very low incidence ranging from 0.1-0.5%. Breast, spleen and skeletal muscles seem to be relatively immune to tuberculous infection. In non-endemic countries breast tuberculosis is 3-4.5% of all breast pathologies. In non-endemic countries breast tuberculosis is rare, and usually is secondary through haematogenous spreading from other infected organ.[1-3]

Primary breast tuberculosis in non-endemic countries is so rare that only a few cases had been reported till now. The clinical and radiological (mammographic, ultrasound) characteristics of breast tuberculosis are similar to those of other breast pathologies; in young masquerades as abscess and in elderly ones as cancer. So, if there is no history known, then, the diagnosis is very difficult to be established.[4-6]

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Case report

A 65-year-old woman admitted to our surgical department complaining of a mass in the upper quadrant of the right breast. The patient discovered the palpable mass 12 days ago. The patient's and family history were clear, except of a mild hypertension pharmaceutically treated. The findings at physical exami-

nation were a non-tender, palpable, mobile mass extending from the skin to the chest wall. No skin or nipple alterations observed. Auxiliary lymph nodes were present consisting block. The examination of the other breast showed no findings. We performed mammography (craniocaudal and lateral view), which showed a mass in the upper quadrant of the right breast, with mild skin retraction, with malignant characteristics (Figure 1). Breast ultrasound showed a well-defined nodular lesion with heterogeneous echo pattern posterior to acoustic enhancement. The lesion considered being malignant, and no fine needle aspiration cytology received. The resection of the tumour and auxiliary lymph nodes dissection decided to be performed therapeutically.

At operation tumour was excised in healthy tissue and sent to cryobiopsy, which showed no malignant cell, but tyroid necrosis of the tissue, compatible with the inflammatory disease. No lymph nodes were removed. The pathological examination of the specimen showed that the mass was tuberculous. Mantoux test was positive. The full examination (x-ray, CT, etc) showed that tuberculosis was nowhere else; that means that breast tuberculosis was primary. The patient received anti-tuberculosis therapy (3 drugs combined therapy) for 9 months. There has not been recurrence for 4 years of the follow-up.

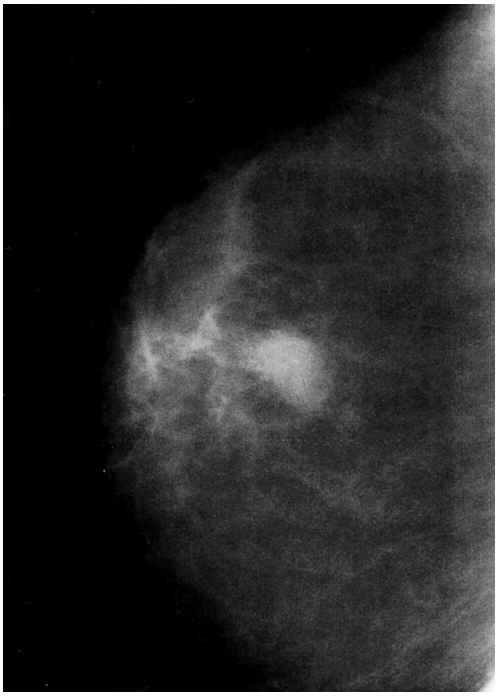

Figure 1. Mammography of primary breast tuberculosis mimics breast cancer. The findings were obscure and the diagnosis set by cold biopsy.

Discussion

Breast tuberculosis identified as primary and secondary. In the primary, breast is the only site of the disease in patients with no history of tuberculosis. In the secondary, mainly haematogenous spreading or direct extension infects breast after a contact with an infected material. The mycobacterium can infect breast haematogenous from auxilla, lungs, ribs and articular lesions, or can be infected by a direct contact through nipple, abrasions of the skin or lactiferous duct.[1,4,5,7]

Three types of breast tuberculosis have been described. The most common type is nodular disease, which is growing slowly and masquerades carcinoma on mammography. The second type, which also mimics carcinoma, is the diffuse type, which presents multiple foci. The third type is the sclerosing, which is painful and more common in the elderly.[3,4,8,9]

The differential diagnosis is quite difficult, and includes cancer, mastitis, sarcoma, actinomycosis, granulomatous mastitis, etc., although it's not uncommon that more than one pathologies in the same breast coexist.[9,10]

The most common symptoms are a palpable breast with or with no auxiliary lymph nodes, usually painful with sometimes nipple discharge.[5,7]

Mammographic findings are not always specific for breast tuberculosis, which can be

misdiagnosed as fibroadenoma or adenocarcinoma (inflammatory or scirrous). The two mammographic findings that are specific for breast tuberculosis are »skin bulge« and the »sinus tract site«. Ultrasonography may resemble cystic lesion, or indicates a hypoechoic heterogeneous mass with irregular borders. CT is useful in the diagnosis, particularly between primary and secondary tuberculosis as can indicate lesions in other sites.[4,6,8-10]

More accurate information can be achieved by fine needle aspiration biopsy, which can demonstrate a granulomatous inflammatory lesion with central cessation.[7]

Many cases can be misdiagnosed and the diagnosis achieved after the surgical removal of the mass and histological examination of the specimen. In these cases a tuberculosis infection history is negative, the mammographic and radiological findings obscure and the mass misdiagnosed as carcinoma.[3,7,9]

In primary breast tuberculosis the indicated treatment consists of the surgical removal of the mass and the anti-tuberculosis therapy with isoniazide, pyrazimanide, ethamboutole and rifampikin for the period from 9 months to 2 years.[2,10]

The increasing tuberculosis incidence in Western countries may also increase the incidence of breast tuberculosis.

In conclusion, primary breast tuberculosis is an uncommon breast pathology, which can mimic adenoma or carcinoma and can be misdiagnosed especially in patients with no previous history of the disease. The fine needle aspiration biopsy can lead to a correct diagnosis, which is finally achieved with the histological examination of the specimen. Patients with breast tuberculosis should undergo a surgical removal of the tumour and a long time anti-tuberculosis therapy.

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Mammographic oblique views 45°versus 60°: breast thickness, breast exposure and image quality

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Background. *Standard screening mammography includes two views: craniocaudal and mediolateral oblique. In the mediolateral oblique projection a central beam angle can varies between 30° and 60°.*

Patients and methods. *We compare the thickness of the compressed breast, time-current product, exposures and image quality in two different mammographic oblique views: 45°versus 60°. Our study population consisted of 33 women in whom additional 60°-films after standard 45°-films were obtained for the objective diagnostic reasons.*

Results. *The mean thickness of the compressed breast was significantly lower with an angle of 60° than with an angle of 45° (47.8 vs. 50.7 mm, p<0.01); the mean time-current product and the mean breast exposure were significantly lower with an angle of 60° than with an angle of 45° (42.6 vs. 46.7 mAs, p<0.01; 0.67 vs. 0.78 mGy, p<0.01). The difference in the image quality has not reached statistical significance (but it exists!).*

Conclusions. *By introducing 60°-films instead of commonly used 45°-films, mammograms of at least the same quality can be obtained with lower radiation dose, which is of great importance when we remind the great radiosensitivity of glandular breast tissue.*

Key words: mammography, radiation dosage; thermoluminiscent dosimetry

Introduction

Standard mammography includes two views: the craniocaudal and the mediolateral oblique.[1,2] In the mediolateral oblique projection a central beam angle can vary between 30° and 60°, with 45° routinely used for the majority of patients.[3] Mammography may include supplemental views tailored to a specific problem. Although the use of mammography has been increasing rapidly, contributing to the breast radiation burden, the benefits of mammography substantially outweigh the risk of radiation induced carcinoma, which is small but inevitable.[4,5] The study was aimed to compare the thickness of the compressed breast, time-current product (mAs), exposures and image quality in two different

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mammographic oblique views: 45°versus 60°.

Patients and methods

Our study population consisted of 33 women in whom additional 60°-films after standard 45°-films were obtained. Additional 60°-films were obtained for clarifying suspect or indeterminate focal lesions or microcalcifications. Additional oblique films were done after the informed consent (we explained to our patients the potential benefit of early cancer detection versus a small carcinogenic risk related to the additional exposure). All our patients were ≥40 years old. Women with breast implants, prior lumpectomy and radiotherapy were excluded from the study.

Film-screen mammography was done with Mammomat 300 (Siemens, Erlangen, Germany) with Mo-anode and 0.03 Mo-filtration. A film-screen combination MIN-2000 (Kodak, Windsor, CO, USA) and an automatic processor for developing Curix 400 (Agfa Gevaert N.V., Brussels, Belgium) were used. To avoid bias, additional 60°-films were obtained and developed under the same conditions several minutes after 45°-films. This included the same positioning technique, compression force (15 kp), tube voltage, AEC (automatic exposure control) detector position and the same radiographer who was unaware of the purpose of the study.

Exposures were measured using thermoluminescent dosimeters (TLD), which were positioned at the breast support plate as near as possible to the nipple, but not to obscure any part of the breast tissue. TLDs used for exposure measurements were TLD-700 (LiF:Mg, Ti) lithium flouride TLD (manufactured by Harshaw), 3x3 mm chips 0.9 mm thick, which were packed in pairs of two in rubber holders. TLDs were annealed prior to each irradiation (at 400°C for one our + 100°C for 2 hours (calibration). Before the readout, the external (100 °C for 20 min) and the internal (100 °C for 6 hours) pre-heat treatment for all TLDs were used.[6] Reading of TLDs was performed by using Toledo 654 (Pitman/Winten) system. The digital readout of compressed breast thickness (mm) and time-current product (mAs) was recorded at the mammography unit control table. The contrast and spatial resolution were subjectively assessed using 0-3 scale (0=unsatisfyed, 3=excellent) by two skilled radiologists who were unaware of the view angle, and who analysed the mammograms independently.

For quantitative data (the breast thickness, time-current product and exposures) mean values and the standard deviation were calculated. The significance of differences was assessed by means of the differention method and the Student t-test. For qualitative data (contrast and spatial resolution) an average score was calculated (0-3 scale). The significance of differences was assessed by means of the McNemar χ^2-test.

Results

The study was performed on 33 women aged between 40 and 71 years (mean age was 51.2 +/- 8.8 years), in whom additional 60°-films after standard 45°-films were obtained. The mean thickness of the compressed breast was significantly lower with an angle of 60° than with an angle of 45° (47.8 versus 50.7 mm, $p<0.01$) (Table 1). The mean time-current product (mAs values) was significantly lower with an angle of 60° than with an angle of 45° (42.6 versus 46.7 mAs, $p<0.01$) (Table2). The mean exposure was significantly lower with

Table 1. Thickness of the compressed breast (in mm): 45°versus 60°

Mammographic mediolateral oblique view	45°	60°
Mean	50.7	47.8
S.D.	11.5	10.7
Significance	p<0.01	

Table 2. Time-current product (mAs values): 45°versus 60°

Mammographic mediolateral oblique view	45°	60°
Mean	46.7	42.6
S.D.	17.1	15.2
Significance	p<0.01	

Table 3. Breast exposure (in mGy): 45°versus 60°

Mammographic mediolateral oblique view	45°	60°
Mean	0.78	0.67
S.D.	0.31	0.27
Significance	p<0.01	

an angle of 60° than with an angle of 45° 0.67 *versus* 0.78, p<0.01) (Table 3). The average spatial resolution was insignificantly better with an angle of 60° than with an angle of 45° (0-3 scale; 1.53 versus 1.37, p>0.05). There was no difference in the average contrast resolution (0-3 scale; 1.50 *versus* 1.51).

Discussion

Due to the great radiosensitivity of glandular breast tissue there is small but inevitable risk of inducing breast cancer during mammography (6.6 radiation induced breast cancers per million women per year per 0.01 Gy per all western women exposed after age of 20).[7] The incidence of radiation induced breast cancer depends on the radiation dose and the age at the exposure. It progressively decreases after the age of 40 years because of the lower proportion of glandular breast tissue and fatty substitution.[8] The minimal latent period was estimated to 10 years from the radiation exposure until breast cancer develops and it was unaffected by dose.[7,9] A linear dose-response curve without a threshold is generally accepted for the radiation induced breast cancer.[8,10]

It is obvious that a theoretical carcinogenic risk from mammography appears to be negligible compared to benefits of early cancer detection, even in women beginning annual screening at age of 35 and continuing until age 75 years the benefit widely outweigh the risk.[4] Regardless of this »theoretical risk« of carcinogenesis, we consider that efforts made to reduce radiation dose during mammography are welcome, especially when we take into account rapidly increased number of women attending to the mammographic examination. According to the prior statement, intention of this study was to indicate a way to reduce radiation dose during mammography, without impairing image quality.

Routinely used 45°-films were proved to be suitable for the majority of patients considering different body constitution and breast types. We were curious, what will happen with the thickness of the compressed breast, time-current product, exposure and image quality if we choose another central beam angle? It is well known that the proper breast compression is a prerequisite for obtaining mammograms of satisfying quality and for reducing radiation dose. Gentry and DeWerd state that exposure dose and compressed breast thickness were linearly correlated.[9] It reinforces the importance of the firm breast compression during mammography in order not only to reduce the exposure but also to achieve some additional benefits affecting image quality: lower scatter, reduced motion artefacts, reduced geometric unsharpness (shorter object-film distance), reduced breast tissue superimposition and equalised breast thickness.[11,12] If we intend to obtain good image quality with as low as possible radiation dose a central beam angle, which allows a better breast compression, should be chosen.

Considering the radiation dose measurement two approaches are available: recording the exposure parameters (tube voltage, focus-film distance, mAs, the thickness of the compressed breast) or the direct assessment using TLDs, which was performed in our study.[13] In a previous study[14] the authors es-

timated the breast irradiation indirectly recording exposure parameters and found differences in favour of 60°-films which agrees with the results of this study.

In both studies »fixed kVp protocol« was used: the tube voltage was constant and the variable breast thickness was compensated by mAs values. Mc Parland and Boyd investigated the patient's dose in »fixed kVp protocol« *versus* »variable kVp protocol« and found a lower radiation dose for thicker breast when »variable kVp protocol« was used, with a small reduction in image quality.[15] In spite of this, we used »fixed kVp protocol« because we consider that the patient's dose reduction should not interfere with the image quality.

We are aware of the possible shortages of our study: We did not assess the mean glandular dose (MGD) which is of the greatest importance in assessing the carcinogenic risk. But, when we are aware of the linear correlation between MGD and the exposure, we can assume that by reducing exposures we will reduce MGD and the carcinogenic risk, as well. We also did not take into consideration the patient's body constitution and the constitution of the breasts. It was found in a previous study that the breast compressibility with an angle of 60° was the best in thin women with the pendulous breast.[14]

We conclude that 60°-films were obtained with better breast compressibility comparing to 45°-films, which results in lower time-current product and exposure whereby the image quality was the same or even better. By introducing 60°-films instead of 45°-films the mammograms of at least the same quality can be obtained with a lower radiation dose and a lower carcinogenic risk.

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Scintigraphic detection of peptic lesions with the method of radiolabelled sucralfate

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Background. *Sucralfate is an antiulcer agent that after peroral application strongly adheres to mucosal defects and in that way provides a protective barrier to further damage from acid and pepsin. If radiolabelled with a gamma isotope, it could be detected under a gamma camera pointing lesions to which it adhered. With the aim to confirm a suitable noninvasive method for investigation of caustic lesions of the upper gastrointestinal tract we evaluated in a preliminary study the validity of the radiolabelled Sucralfate scintigraphy in detection of peptic disease.*

Patients and methods. *With that purpose, 35 patients after an endoscopic examination underwent scintigraphy with Tc-99m-DTPA sucralfate. Patients were divided in two groups: a group of 20 patients with endoscopic confirmed peptic disease and a control group of 15 persons who had not any disease of the upper gastrointestinal tract.*

Results. *Using the test for clinical evaluation of a new method, the scan showed sensitivity of 75 %, specificity of 100 % and accuracy of 85.7 %.*

Conclusions. *Scintigraphy with Tc-99m-DTPA Sucralfate promoting it as an additional method, complementary to routine investigations in detecting mucosal lesions.*

Key words: peptic ulcer-radionuclide imaging; sucralfate; isotope labelling

Introduction

Sucralfate, a complex polyaluminium hydroxide salt of polysulphated sucrose, is used in medical treatment of peptic disease as a coating agent that provides a protective barrier to further damage from acid and pepsin. Its actions are principally local and at acid pH becomes highly polar and binds by way of strong electrostatic interaction to ulcer tissue for up to 12 hours, while relatively little binds to intact gastric or duodenal mucosa.[1]

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Utilizing its selective binding characteristics, Vasquez et al. first radiolabelled it with a gamma emitting isotope, developing a new method for detection of gastrointestinal ulcerations.[2] Since its original publication, this method has been used in different modifications to detect and to evaluate other diseases in addition to peptic ulcers, such as oral microlesions, oesophagitis, oesophageal transit time, gastric carcinoma, inflammatory bowel diseases and many other that have underlying mucosal defects.[3-6]

The presence of mucosal and submucosal lesions at peroral caustic ingestion allows the idea that the detection of these injuries is possible with this method. With aim to evaluate the efficacy of the method of radiolabelled sucralfate and gain primary experience about its technique and interpretation of results, a preliminary study was undertaken on a group of patients with and without peptic disease.

Patients and methods

Subjects

After a fiber-endoscopic investigation of the upper gastrointestinal tract, 35 patients (18 male, 17 female; medium age 38.5, range 15 - 72 years) were divided in two groups: an index group, consisting of 20 patients, with endoscopic verified peptic disease and a control group, consisting of 15 patients, who underwent endoscopy because of the suspicion of a peptic disease and the same excluded.

Preparation of radiolabelled sucralfate

After suspending 500 mg sucralfate (1/2 a tablet of Venter, Krka, Slovenia) in 5 ml of normal physiological saline in a test tube, 1 ml DTPA was added and incubated for 2 minutes. 2 mCi of TcO4 was added, rotated and centrifuged for 10 minutes. After decanting the supernatant, pellet is resuspended in 20 ml water and applicated *per os* (modification of the method of Scopinaro et al.).[7] The paper chromatography of the supernatant showed a consistently labeling efficiency of 87-91%.

Patient imaging

Isotope scan was carried out in the morning after an overnight fasting within 48 hours of endoscopy. Images of the upper gastrointestinal tract were obtained using a large field of view gamma camera with the patient in the supine position. Images were initially obtained in the anterior position and, if necessary, additional images were made in the left and right decubitus. Serial analog images on 30 minutes were taken for 2 hours and if gastric emptying was slow, we continued. To hurry up the gastric emptying we gave 100 ml of water by mouth and a intra- muscular injection of metoclopropamid.

Positive images appeared as areas of accumulation of radiopharmaceutical and remained so with no changes of position, time and after drinking 100 ml of water. Negative results were interpreted if the first seen accumulation changed position with time or vanished after drinking water.

Results

The number of detected peptic lesions visualized with both investigations, fiber-endoscopy and radiolabelled sucralfate scintigraphy, are given in Table 1.

After comparing the results obtained from the radiolabelled sucralfate scans with the endoscopic findings, they were estimated as

Table 1. Number of detected peptic lesions with both methods

peptic lesion	FE	Sc
reflux esophagit	4	3
gastric ulcer	7	5
duodenal ulcer	9	7
control group*	0	0
total	20	15

FE=fiber-endoscopy; Sc =scans; * no lesions

true positive (TP), true negative (TN), false positive (FP) and false negative (FN). This study gave 15 TP, 15 TN, no FP and 5 FN results.

Using the methods of clinical est evaluation (Bayesian analysis), the sensitivity (Sn=TP/TP+FN), the specificity Sp=TN/TN+FP), positive predictive value (PPV=TP/TP+FP), negative predictive value (NPV=TN/TN+FN) and the accuracy (Ac=TP+TN/TP+TN+FP+FN) were calculated as Sn=75%, Sp=100%, PPV= 100%, NPV=75% and Ac= 85.7%.

Discussion and conclusion

Many authors found this method sensitive for detecting various mucosal defects in the upper and lower gastrointestinal tract. With variable successes in visualizing lesions, reported sensitivity was in the range from 67-75 % in the cases of gastroduodenal ulcers and up to 95% in the cases of detecting inflammatory bowel disease.[5,6,8] In all these studies the Sp was constantly high 97- 100 %. Lesions as small as 0.5-2 mm were detected after biopsy of gastric mucosa.[9] Although of many optimistic reports, some authors reported unsatisfactory results and discontinued studies in the assessment of localization and extent of inflammatory bowel disease mostly because of the need of purgation in severely ill patients.[10] Our preparing of the patient was only an overnight fasting. Only severe oesophagitis was detected in other studies explaining unfavorable conditions while drinking the radiopharmaceutic in erect position and giving short time of contact to the not enough proteinaceus excudate overlying lesser degrees of esophageal inflammation.[4,11]

In our study we got similar results as the previously reported in the literature. The false negative results may be due to the »inactivity« of the peptic disease that means reepitelisation of the visualized ulcer craters. The peptic lesions in this study were not histologically verified and mostly depended on morphological judgment and experience of the endoscopist. However, acute and »active« peptic lesion with mucosal denudation seems to be detectable and not chronic »inactive« structural ulcers. How the aim of this study was to get experience with this method and later on to apply it in the investigation of caustic ingestion that is acute and sometimes deeper than the mucosal and submucosal layer, these preliminary results give an opportunity to try.

Most authors conclude that this method is insufficient in comparison with endoscopy, with equal reliability to contrast x-rays, but admits its advantage to be noninvasive, easy to perform, not needing active collaboration from the patients and gives an opportunity to evaluate any seriously ill patient not in condition for endoscopythe or barium meal.[5,12]

Although the group is small, the results suggest that this method could be useful as noninvasive help in the clinical follow up and the detection of mucosal lesions. It seems to be a preferable option for patients after the ingestion of a caustic that would be an aim of a further clinical trial.

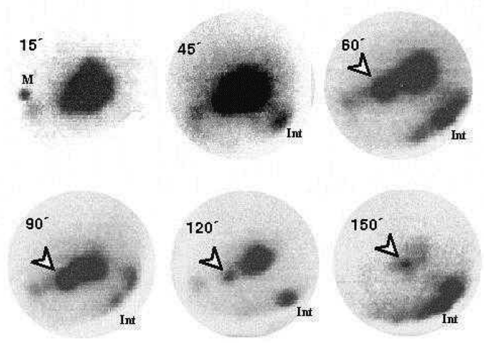

Figure 1. Scintigraphy visualization of gastric region on 30 minute intervals after drinking a portion with radio labeled Sucralfate in a patient with previously endoscopic verified antral ulcer.
(Arrow pointing to the radiotracer accumulation, matching endoscopic location of peptic ulcer; M-Marker , Int - Intestinal loops)

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The accuracy of chest sonography in the diagnosis of small pleural effusion

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Background. *The aim of the study was to evaluate the accuracy of chest sonography in the radiological diagnosis of small pleural effusions.*

Patients and methods. *Patients referred for abdominal and/or chest sonographies for various reasons were examined for sonographic features of pleural effusion. From January 1997 till January 2000, 69 patients were included into the study. Fifty-two patients were found to have pleural effusion not exceeding 15 mm in depth, the rest of them served as controls. Subsequently erect posteroanterior and expiratory lateral decubitus projections were done in all patients.*

Results. *Compared to radiological examination chest sonography had a positive predictive value of 92% in the diagnosis of small pleural effusions in our study population. The mean thickness of fluid was 9.2 mm on ultrasonography and 7.6 mm on expiratory lateral decubitus views (P<0.01).*

Conclusions. *Chest sonography showed a high degree of accuracy for demonstrating small pleural effusions and could replace lateral decubitus chest radiographs adequately.*

Key words: pleural effusion-ultrasonography; thoracic radiography

Introduction

A small amount of fluid (5-10 ml) is often present in the pleural space of healthy individuals.[1] Small pleural effusions are not readily identified on conventional radiographic views of the chest.[2] Lateral decubitus radiographs or chest ultrasonography proved to be more efficient methods for demonstrating small amounts of free pleural fluid.[3-6] The data on the smallest amount of pleural fluid detectable vary considerably, but they are essentially within the same broad range whether computed tomography, sonography or X-ray examination are used.[1,3,6-12]

Rigler used lateral decubitus chest radiographs for the detection of small pleural effusions.[13] Other investigators[3,14] have developed the technique and using cadaveric studies[15] have shown that volumes of pleural fluid as little as 5 ml may be detected. Recent reports have proved that minute pleural effusions can be detected using chest ultrasonography.[6,7,17] No formal comparison has been

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made between the thickness of the pleural effusion as seen on sonography with X-ray and the amount of aspirated fluid.

We have compared sonographically detected small pleural effusions with expiratory lateral decubitus radiographs.

Patients and methods

Patients referred for abdominal sonography for a variety of clinical conditions were also examined for unsuspected pleural effusion. Small control group was made up of 17 patients, examined only for clinically suspected pleural effusion, which was not sonographically confirmed.

Between January 1997 and January 2000, 69 patients (51 males, 18 females, 28-80 years old, with the mean age of 57.1 years) were included into the study. Their condition was clinically diagnosed as lung cancer in 30, cardiac failure in 13, metastasis to the lung in 11, pneumonia and pulmonary tuberculosis in 6 and liver cirrhosis in 3 cases.

Following abdominal sonography, the patient was positioned in the lateral decubitus position for 5 minutes; sonography of the lower pleural space was performed with the patient leaning on the elbow.[17] During the examination maximal fluid thickness was measured, with the position of the probe perpendicular to the thoracic wall.[18]

A Toshiba SSA-340A ultrasound unit was used with a 3.7 or 6 MHz convex transducer.

Radiological examination followed if sonography showed a small pleural effusion. A 140 kV Siemens unit was used, with a 2 m film-focus distance for the erect views of the chest, and 1.5 m film-focus distance for lateral decubitus views. For these, the patient was put into lateral decubitus position with 10^0 hip elevations, for 5 minutes prior to exposure. Exposures were taken in expiration, with the central beam aimed at the lateral chest wall and the patient slightly rotated onto the back. The films were evaluated independently by two experienced radiologists with no knowledge of the sonographic findings.

On sonography, the criteria for determining the presence of pleural fluid were: a non/hypo - echogenic zone between the parietal and the visceral pleura and/or changing between expiration and inspiration as well as changing with different positions of the patient or fluttering of the pulmonary edge during respiration.[6,9,19,20]

On x - ray, the criteria were as follows: minimum 3 mm thick density with horizontal level on lateral decubitus view and costophrenic angle density with meniscus sign on erect views.[3,21]

Matching pair's *t*-test was used for analysis of differences between measurements of the fluid layer thickness on chest sonography and expiratory lateral decubitus projections.

The study was approved by relevant ethic committee.

Results

On erect posteroanterior chest radiographs pleural fluid was demonstrated in only 17 of 52 (33%) patients.

Lateral decubitus views were positive in 48 of 52 patients (ie, a positive predictive value of 92%) with sonographically visible fluid. In two cases pleural effusions detected sonographically were confirmed by thoracocentesis. In one patient sonographically positive result was not confirmed either way. In the last case radiography revealed diagnostic error occurred on sonography (Figure 1). The range of fluid thickness was 3-6 mm in these three patients.

In a small control group of 17 patients pleural fluid was not confirmed sonographically nor radiographically.

The mean thickness of fluid was 9.2 mm (SD= +/- 3.3 mm) on sonography and 7.6 mm

(SD= +/- 4.0 mm) on expiratory lateral decubitus views (P<0.01). The ranges of fluid thickness on gray-scale sonography and lateral decubitus radiography were 3-15 mm and 3-11 mm, respectively (Figures 1a, 1b).

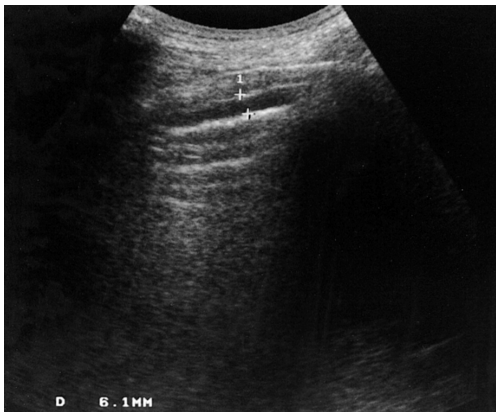

Figure 1a. A 6-mm-thick hypoechogenic zone (calipers) between the parietal and the visceral pleura suggestive of a small pleural effusion.

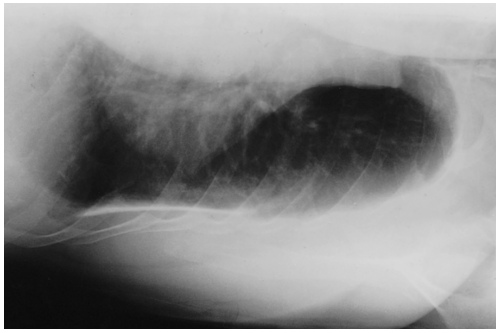

Figure 1b. Left lateral decubitus radiograph clearly shows a flat pleural thickness with calcified plaque on the visceral pleura.

Discussion

In the literature we could not find any exact definition of small pleural effusions. So, our term of small pleural effusions includes clinically silent effusions, which are usually unexpected finding on x-ray or sonographic examinations undertaken for other reasons.

Rigler[13] was the first to use lateral decubitus views for pleural fluid demonstration. He did not use exposure in expiration, however, nor did he expose with central beam aimed at the lateral chest wall, parallel to the expected fluid level. The latter technical improvement was introduced by Hessen[3] together with the elevation of the patient's hip, while obtaining radiograph during expiration was tested in the work of Kocijančič et al.[17] The amounts of pleural fluid detectable this way have been assessed in cadaveric experiments[15] and has been shown to be as little as 5 ml in experimental conditions. This is probably less reliable in practice, because the fluid may not always be completely aspirated with thoracocentesis.

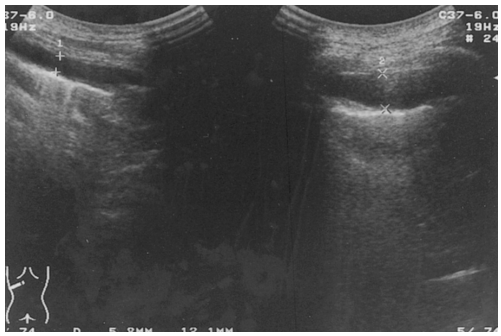

Figure 2a. Sonograms show a thin fluid layer (6 mm) visible during inspiration (left image, calipers). Pleural effusion became much more apparent during expiration and allowed the reliable diagnosis (right image, calipers).

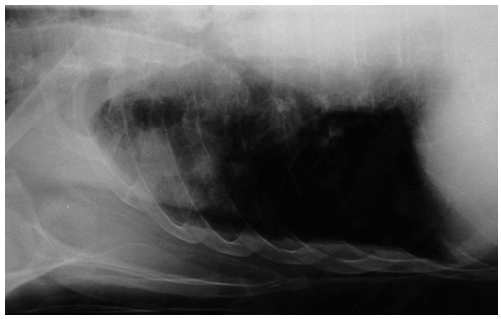

Figure 2b. Lateral expiratory decubitus radiograph, clearly showing a horizontal fluid layer of approximately the same thickness in a 52-year-old male patient with obstructive pneumonia of the right upper lobe due to lung cancer.

With the advent of sonography it was shown that very small amounts of pleural fluid can be demonstrated this way.[4-8] However no one precisely determined the sonographic criteria that should be fulfilled for reliable diagnosis of small pleural effusions. In our study population all effusions were anechogenic, the only case with hypoechogenic »fluid« turned out to be pleural thickness. Interestingly, the main sign, allowing the demonstration of the smallest effusions on sonography as well as on radiography,[17] was changing of the fluid layer during inspiration - expiration (Figures 2a, 2b).

In the course of our study searching for small pleural effusions of about 200 ml or less,[12,18] we have achieved comparable results using sonography and radiography, but sonography appears to assess the thickness of fluid layer more accurately.

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Endosonographic and manometric assessment of the anal sphincters after ileal pouch-anal anastomosis

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Background. *The aim of this study was to compare endosonography and manometry of the anal sphincters in patients after ileal pouch-anal anastomosis (IPAA).*
Patients and methods. *Ten patients aged between 23 and 50 years with IPAA performed for ulcerative colitis were examined with anal endosonography (AES) and manometry.*
Results. *AES visualised abnormal image of the internal anal sphincter (IAS) in 9 patients (90%). Defects of the external anal sphincter (EAS) and puborectalis muscle (PR) were shown in 4 patients (40%). In 5 patients (50%) correlation between endosonographic and manometric assessment for the all analysed muscles: IAS, EAS and PR was found. In 4 cases (40%) both methods correlated with the evaluation of the EAS only and in 1 patient (10%) no correlation was found. Correlation between both methods for the IAS was found in half of the patients (50%) while in the evaluation of the EAS and PR dynamic activity, it was found in 9 cases (90%).*
Conclusions. *Anal endosonography and manometry allow us to assess the morphology as well as the function of the anal sphincters in patients with IPAA. The methods mentioned above show high correlation in the assessment of the EAS function (9 cases; 90%) whereas in the case of IAS, manometry frequently (5 patients; 50%) does not confirm endosonografically detected defects.*

Key words: colitis, ulcerative; anus-ultrasonography; manometry; proctocolectomy, restorative

Introduction

Ileal pouch-anal anastomosis (IPAA) has become the operation of choice for most patients with ulcerative colitis. Patients prefer this form of therapy to formation of the stomy although it is accompanied by a noticeable percentage of anal incontinence which affects even 84% of patients.[1-4] Anal sphincters defects can be partially responsible for this high incidence of incontinence. The aim

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of this study was to visualise the suspected defects of the anal sphincters on anal endosonography (AES) and to compare them with the results of the ano-rectal manometry.

Patients and methods

Ten patients (8 women and 2 men) aged between 23 and 50 years (median age 33.2 years) with J - pouch and stapled IPAA performed without mucosal dissection for the ulcerative colitis were examined with the use of anal endosonography and ano-rectal manometry. Examinations were performed after 3-11 years after IPAA formation (mean 5,5 years). None of them had any operation on the anal canal prior to IPAA formation and none of the women had a complicated delivery. In order to assess the severity of anal incontinence, the Jorge- Wexner's grading system was used.[5] Anal endosonography was performed with the use of Bruel and Kjaer scanner type 1846 with a 7.0 MHz rotating endoprobe that provides a 360° image. The probe was covered with a plastic cone with an external diameter of 17 mm, which was filled with degassed water for acoustic coupling. The cone was covered with a condom. Patients were examined in the prone position, and no preparation was required prior to AES. As the probe was withdrawn from the anal canal, images of the puborectalis muscle (PR), external anal sphincter (EAS) and internal anal sphincter (IAS) were documented. The thickness, echogenicity and outlines of the IAS and echogenicity of the EAS were assessed on each level of the anal canal. The thickness of the IAS was measured at 3 and 9 o'clock position of the coronal plane of imaging, using electronic calipers on the monitor. The normal IAS was defined as a homogenous, hypoechoic ring with thickness greater than 1mm.[6] Increased and nonhomogenous echogenicity and ill-defined margins of the IAS were diagnosed as abnormal. The EAS was identified as non-homogenous muscle with striated echogenicity and was defined as abnormal if hypoechoic areas were visible within it.[6] Dynamic activity of EAS and PR was assessed as good (++), poor (+) or lack (0) of contraction using a subjective scale which depends on comparing their image at rest and during maximal voluntary contraction.

Anorectal manometry was performed with the patients in the left lateral position. No enema was given. A lower gastrointestinal manometry system (PC Polygraf HR; Synectics Medical Stockholm, Sweden) with four - lumen polyvinyl chloride catheter with rectal distending balloon (AMC4-B; Zinectics Medical, Stockholm, Sweden) was used. Perfusion ports were located in 1 cm intervals arranged circumferentially. After positioning at the depth of 6 cm from the anal verge the catheter was allowed to accommodate for several minutes. Maximum resting anal pressure (MRP), maximum voluntary pressure (MVP) and maximal duration of squeeze (D) were recorded. Pouch capacity was also recorded by distending air-filled, thin- walled balloon positioned 6 cm within the pouch to assess maximal tolerable volume (MTV).

Results

The results of anal endosonography and anorectal manometry are presented in Tables 1 and 2.

In anal endosonography, thinning of the IAS was visible in all but one patient (9 cases; 90%). Increased echogenicity of the IAS in 6 (60%) and ill-defined borders was detected in 3 patients (30%). Echogenicity defect of the EAS was visible in 3 cases (30%).

Dynamic examination revealed good EAS and PR contraction in 6 patients (60%), poor in 3 (30%) and lack in 1 patient (10%).

Manometry revealed decreased maximum resting anal pressure suggesting dysfunction of the IAS in 3 cases (30%), decreased maxi-

Table 1. Anal endosonography in patients with IPAA

No	IAS			Echogenicity defect of the EAS	Dynamic exam
	Thickness [mm]	Increased echogenicity	Il-defined borders		
1. BA	<1	+			++
2. EB	<1	+	+		++
3. GP	<1				++
4. ME	<1	+			+
5. NM	2.5				++
6. SK	<1			+	+
7. ST	<1	+	+	+	+
8. WE	<1	+	+		++
9. WM	<1				++
10. Wm	0	+	+	+	0

Table 2. Ano-rectal manometry in patients with IPAA (sequence of patients as in Table 1)

No	MRP*	MVP	D	MTV	I
1. BA	30	180	16	150	8
2. EB	60	180	48	100	0
3. GP	60	200	40	190	0
4. ME	60	81	40	150	0
5. NM	80	110	30	200	6
6. SK	45	125	64	120	12
7. ST	60	200	40	350	0
8. WE	60	257	80	/-/	/-/
9. WM	75	148	50	260	0
10. Wm	30	45	/-/	160	9
Normal values	60-80	100-250	>40	>150	0

*MRP - Maximum resting anal pressure [mmHg],

MVP -Maximum voluntary pressure [mmHg],

D - Maximal duration of squeeze (sec)

MTV- Maximal tolerable volume [ml],

I - Jorge-Wexner's fecal incontinence severity score (points)

/-/ - not assessed: in one patient - MTV and I - because of pouch-vaginal fistula and in one patient - D - because of low MVP

mal voluntary anal pressure in 3 patients (30%), implying dysfunction of the EAS and PR, and in another 2 patients (cases 1 and 5 from the Table 2) the shortage of the maximal duration of squeeze indicating dysfunction of the EAS and PR was revealed as well.

In all cases manometry correlated with clinical examination (Table 2). Correlation between endosonography and manometry was found in 5 patients (50%) for all analysed muscles (IAS, EAS and PR), and in 4 patients (40%) for the EAS and PR only. No correlation between the methods was found in 1 patient (10%). Although in this case AES showed thin, hyperechoic, with ill-defined marginated IAS, and also poor contraction and scars within EAS, manometry revealed preserved function of the anal sphincters.

The analysis of the each assessed element of the IAS (thickness, echogenicity and bor-

ders) showed that normal image of this sphincter, which was observed in only 1 patient correlated with its preserved function in manometry. However, the abnormal image, which was visible in the remaining 9 patients correlated with its dysfunction in manometry in 4 cases only (44.4%). This included 2 out of 3 patients with thin IAS (66.6% correlation) and 2 out of 6 patients who had thin and hyperechoic IAS (33.4%).

Correlation between AES and manometry in the assessment of the EAS and PR function was found in the majority of the patients (9 cases; 90%). In the remaining one case, endosonographic image of the PR and EAS showing their poor contraction and scars did not corresponded with their preserved function (case 7 from the tables 1 and 2).

Discussion

Anal endosonography, apart from magnetic resonance imaging using endorectal coil, is the most appropriate method to assess the morphology of the anal sphincters.

Ileal pauch-anal anastomosis has become an operation of choice for most patients with ulcerative colitis.[2,4,7-9] Patients prefer the pelvic reservoir to an ileostomy, although the results of the IPAA formation are not fully satisfactory, its greatest problem being the loss of continence after treatment.[2,4,7-9] The images of the anal sphincters and their function after IPAA have not been precisely investigated so far. Individual reports in the literature concentrated on the results of anal endosonography and ano-rectal manometry after IPAA and show the thinning of the IAS and the reduction of the maximum anal resting pressure in most of the operated patients.[2,7,9] These disturbances are present after endoanal manipulation (handsewn transanal anastomosis with or without mucosectomy) as well as after stapled anastomosis.[4,7] Nevertheless, avoidance of endoanal procedures and transabdominal anal pursestring placement and stapled IPAA without mucosectomy provides higher anal resting pressure comparing to endoanal manipulations.[4,7] The thinning of the IAS was also the most frequent abnormality we observed in our study in all but one patient (9 patients; 90%). There are several reasons leading to the thinning of the IAS, such as denervation, ischemia or a direct trauma to the IAS as a result of transanal mucosectomy, and also, as mentioned above, hand sewn anastomosis.[2,7,9] During the IPAA, the formation dissection and mobilisation of the anorectum is responsible for the IAS trauma as a result of damage to the extrinsic autonomic nerve supply, which plays an important role in the IAS function.[3] Additionally, the transsection of

Table 3. Jorge-Wexner's grading system of anal incontinence

Type of Incontinence	Frequency				
	Never*	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

*Never = 0
Rarely ≤1/month
Sometimes ≤1/week, ≥1/month
Usually ≥1/day

the rectal wall at the level of the levator ani muscles may cut through the layer of specialised circular muscle which forms the IAS. This could cause damage of the intramural nerve plexus and blood supply.[2] The sphincter trauma at this level is presumably inevitable.[2]

In our study only one patient had a normal image and pressure of the IAS. In the remaining 9 cases, endosonography suggested its degeneration in 6 out of 9 patients. Correlation with manometry was found in less than half of these patients (4 out of 9; 44.4%). Generally, manometry revealed preserved function of the sphincters in the majority of the patients. Our results were as in other studies, for instance in Stryker et al.,[7] who found no differences in anal canal resting and squeeze pressures between patients with IPAA and controls as well as no correlation between them regarding clinical data. Although our small study does not lead to definite conclusions, such a high incidence of patients with abnormal image of the IAS, but without functional disturbances is striking. Undoubtedly, our group of patients with aged 33.2 years on the average is young, and it is well known that the thickness of the IAS normally increases with age.[10] So in the young population thickness is the smallest. It is expected to be over 1.9 mm at the age of 19-65 years.[10] Norms of the thickness of the sphincter may need to be verified. Increased echogenicity of the IAS was the most likely consequence of surgery and represented fibrosis of the sphincter. The possibility of the IAS degeneration related to age, which manifests typically as thinning, increased echogenicity, and ill-defined borders of the IAS, is excluded because of the young age of our patients. On the other hand, there were predominantly women in our group of patients (8 versus 2) and it has been shown in the literature[11] that a relevant number of women, who have had uncomplicated deliveries, endosonographically show sphincter defects. The results of the findings would be more reliable if patients had been examined before and after the pauch procedure, which was not the case in our study. Dynamic anal endosonography appeared a valuable adjunct to the examination at rest. Dynamic endosonography is especially valuable in diagnosing anal sphincters trauma, and shows high correlation with electromyography.[10] In our study, correlation between dynamic anal endosonography and manometry was found in 9 cases (90%).

The assessment of the anal sphincters in both ano-rectal manometry and anal endosonography in patients with IPAA enables structural and functional evaluation of the sphincters. The lack of high correlation between these methods in our group of patients emphasizes the complexity of the many mechanisms that contribute to normal continence. One of the examinations of anal sphincter function, besides clinical investigation, is anal manometry, which showed normal function of the anal sphincters in most of our patients. Anal endosonography visualised defects of the IAS in 90% of the patients. They might reflect the presence of subtle (not disturbing the function) changes of the sphincter, as a consequence of surgery, which in the future might predispose to further trauma (for instance obstetric), with the risk of anal incontinence development.

Conclusions

Ano-rectal monometry and anal endosonography are complementary methods in the assessment of the anal sphincters after IPAA. Although in our study manometry showed preserved function of the IAS in most of the cases, the abnormal image of this sphincter might be indicative of its subtle or imminent dysfunction. Dynamic anal endosonography supplements manometric evaluation of anal sphincters and enables prognosis of the sphincter function.

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Malignant lymphomas of the testis

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Background. *The aim of the study was to analyse 10 patients with malignant lymphomas of the testis, and to discuss the necessity of immunocytochemical staining to confirm the histologic diagnosis and an effective treatment policy.*

Patients and methods. *Ten patients with malignant lymphomas of the testis were reviewed in order to identify and study the incidence, histologic findings, the type of treatment administered and the overall outcome.*

Results. *Testicular malignant lymphomas were identified ten times between 1984 and 1999. Bilateral tumours occurred simultaneously in 4 patients, and a metachronous malignancy and testicular relapses developed in 2 patients. Of the remaining patients 4 had unilateral testicular involvement. None had elevated AFP and β-HCG or a history of undecided testis. Eight of patients were younger than 50 years. Five of the lymphomas were high grade, 3 were intermediate and 2 were low grade diffuse non-Hodgkin's lymphoma. All patients were initially treated with radical orchiectomy and were, according to their clinical stage, treated with chemotherapy and/or radiotherapy. Five of 10 patients were alive with no evidence of disease with follow-up ranging from 9 to 62 months. The remaining 5 patients died between 3 and 42 months respectively.*

Conclusions. *Testicular lymphomas are similar to those of testicular germ cell tumours and account for approximately 5% of all testis tumours and represents 1% of all lymphomas. Testicular lymphomas differ from germ cell tumours of the testis by following points: (1) Testicular lymphomas tend to occur in the middle ages, (2) tumour markers AFP and β-HCG are in normal limits, (3) a development in cryptorchid testis is extremely rare, (4) an early systemic therapy is indicated and watchful waiting policy can not be performed, (5) the prognosis is poor. The recognition of histologic diagnosis with immunocytochemical staining for leukocyte common antigen (LCA) is essential and should help the future treatment policy.*

Key words: testicular neoplasms, lymphoma; germinoma; lymphoma, non-Hodgkin

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Introduction

The average incidence of testis tumours is in the range of 2.1 to 2.3 per 100 000 males and remains the most common solid cancer in men between the ages of 20 and 34 years.[1-3]

Testicular lymphomas account for approximately 5% of testis tumours and constitute the most frequent of all testicular tumours in patients over 50 years of age. The median age of occurrence is about 60 years. Primary lymphoma of the testis rarely occurs in children.[4-7] Testicular involvement by lymphoma may be a manifestation of primary extranodal disease, an initial manifestation of clinically nodal disease or a later manifestation of disseminated nodal lymphoma. The most common histologic pattern is a diffuse histiocytic lymphoma and testicular lymphomas are sometimes misdiagnosed as spermatocytic or anaplastic seminomas. The prognosis is poor within one year after the diagnosis if a disseminated disease is evident.[5,6,9]

The aim of this paper was to analyse a group of patients with malignant lymphomas of the testis and to discuss the necessity of performing leukocyte common antigen (LCA) in pathologically reported anaplastic or spermatocystic seminomas in order to confirm the histologic diagnosis.

Patients and methods

From 1984 to 1996, 1201 patients, 17 to 73 years of age were treated for a testicular tumours in Ankara Oncology Education and Research Hospital. We reviewed medical records of these patients to identify and study lymphomas in the testis with respect to their incidence, histologic findings, the type of treatment administered and the overall outcome.

Results

Malignant lymphomas of the testis were identified in 10 patients. The information recorded for each patients included age, date of diagnosis, initial symptoms and physical findings, initial haematologic data, clinical stage, histology, mode of therapy, response to therapy, survival time in months and the patient's condition to the last date of follow-up. The data are summarised in Table 1.

The common clinical presentation was a painless enlargement of the testis. Of 10 patients 7 had generalized constitutional symptoms including anaemia (3 patients), anorexia (6 patients), weakness and weight loss (2 patients). The investigation included a complete blood count, peripheral smears, chest radiographs, ultrasonography and/or computerised tomography of abdomen, ultrasound of testes, tumour markers AFP and β-HCG. None of patients had elevated AFP and β-HCG. Bilateral tumours were identified in six patients (60 %). The tumours occurred simultaneously in 4 patients, and metachronous tumours plus testicular relapses developed in 2 patients after one and 6 months of the diagnosis.

Initially, all patients were treated with radical orchiectomy. Five of the testicular lymphomas were high grade, 3 were intermediate and 2 were low grade diffuse non-Hodgkin's lymphoma.

Discussion

Cancer of the testis accounts for less than 3 % of all malignant tumours in males. Most of these malignancies are of germinal cell origin.[1-3] To date, approximately 100 % of germ cell tumours can be cured.

The involvement of the testis by lymphomas accounts for almost 5 % of testicular tumours and 50% of patients with bilateral tumours have lymphoma.[3,7,8,10] Testicular lymphomas differ from germ cell tumours in regard to age, incidence, relation to cryptorchidism, frequency of bilateral involvement, normal tumour marker levels of AFP and β-HCG, and prognosis. Despite reports that the median age of occurrence is about 60 years, in our series the age ranged from 32 to

73 years with a median of 49. In contrast, 8 of 10 patients were younger than 50 years at diagnosis. Risk factors, like cryptorchidism, have been reported to range between 7 and 35 % of the total number of patients with testicular germ cell cancer.[11-13] In the medical literature, to our knowledge, testicular lymphoma arising in cryptorchid testis was reported only once.[5] None of our patients had a history of cryptorchidism.

In principle, bilateral tumours can occur synchronously or metachronously and bilateral testicular involvement is reported to be a more common feature of malignant lymphomas of the testis than of germ cell tumours.[14-16] The relative incidence of bilateral testis tumours, reported in the literature from 1981 to 1995, can be calculated as 2.38 %.[17-22] Our study doesn't confirm this, bilateral testis tumours comprise 1.17 %, and lymphoma of the testis comprises 60 % of the total incidence of bilateral testicular carcinomas.

Four of 10 patients had radical inguinal orchiectomy in different hospitals. Tissue specimens of all patients were reviewed in our pathology department to confirm the pathologic diagnosis, because testicular lymphomas are sometimes pathologically misdiagnosed as spermatocytic or anaplastic seminomas. Our study confirms this in 2 of 10 patients (20 %). There were 2 patients initially misdiagnosed as spermatocytic seminoma. In order not only to prevent misdiagnosis but also for further evaluation and treatment, we recommended to perform immunocytochemical staining with LCA if the levels of β-HCG and AFP are normal in the sera, especially in the clinical stages to IIC to IV seminomas.

Until several years ago, the traditional treatment for testicular lymphoma was radiation therapy for the localized and regional spread and chemotherapy for distant metastasis. To date multiagent chemotherapy, the combined modality treatment has become more frequently used as the initial one.[23] Irradiation of contra lateral testicle as a prophylactic treatment for patients with testicular lymphoma is controversial.[6,24,25] Even though, prophylaxis for the normal opposite testis can be performed safely to the elder patients, the need to preserve testicular function may be vital for young cases. Most previous reports have also indicated a poor prognosis for patients with testicular lymphoma, especially in patients with bilateral disease and there were no 5-year survivors. In centres cumulating a sufficient number of cases, even

Table 1. Patients' data presenting with testicular lymphomas

Patients	Age (months)	Laterality	Clinical stage	Treatment	Disease free interval (months)	Status
1	32	Right	III	Chemo	24	Alive with NED
2	38	Right	I	XRT	11	DD
3	38	Left	IV	Chemo	42	DD
4	43	Bilateral, M	I	Chemo+XRT	52	Alive with NED
5	36	Bilateral, M	IV	Chemo	10	DD
6	48	Bilateral, S	I	XRT	62	Alive with NED
7	48	Bilateral, S	I	XRT	18	Alive with NED
8	58	Left	IV	Chemo	9	Alive with NED
9	70	Bilateral, S	IV	Chemo	6	DD
10	73	Bilateral, S	IV	Chemo	3	DD

S = simultaneously; M = metachronous; Chemo = chemotherapy; XRT = radiotherapy; NED = no evidence of disease; DD = died of disease

in patients with low-stage tumours, a 5-year survival rate has been documented as 30 %.[6,12,13,26-29] Thus, even patients whose disease seems to be limited to the testis may have a relatively short survival time. In patients with lymphoma at other sites and who later experience testicular relapses a poor prognostic factor exisists.[5,6,9] The reported incidence of relapse in the contra lateral testicle is 0 to 35 % for patients with testicular lymphoma.[13,24,26,27,30] Testicular relapse was occurred in our 2 cases (20 %). Disease free mean survival times in reported series ranges between 16 months to 30 months.[4,6] Five of our cases were alive with no evidence of disease with follow-up ranging from 9 to 62 months. The remaining 5 patients died of disseminated disease, with survival ranging 3 - 42 months. Even though we treated our patients with combine modality, we did not obtain good results.

Conclusions

Testicular tumours of germ cell origin reach their peak incidence in the age group 20 and 34 years. Malignant lymphomas of the testis account for almost 5% of all testis tumours. The common clinical presentation, initial treatment and the pattern of dissemination of testicular lymphomas are similar to those of testicular germ cell tumours. In contrast, by the following points testicular lymphomas differs from germ cell tumours: (1) Lymphoma of the testis tends to occur in the middle ages; (2) The levels of AFP and β-HCG are in normal limits; (3) Development of testicular lymphoma in cryptorchid testis is extremely rare; (4) In view of aggressive behaviour, an early systemic chemotherapy is indicated and a watchful waiting policy is contraindicated; (5) Patients with disease apparently confined to the testis and who have no clinical evidence of generalised disease 1 year after therapy may or may not have a high probability of cure; (6) Survival is poor especially with bilateral disease, and later experiencing a testicular relapse.

Since testicular lymphomas are sometimes misdiagnosed as spermatocytic and anaplastic seminomas, immunocytochemical staining for LCA should be performed in order to confirm the histologic diagnosis. The recognition of histologic diagnosis in testicular lymphoma is essential and should help the future treatment policy.

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The urokinase plasminogen activator and its inhibitors PAI-1 and PAI-2 in primary cutaneous melanoma

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Background. *We investigated the differences in urokinase plasminogen activator (uPA) and its inhibitors type1 and 2 (PAI-1/2) concentrations in clinically suspected nevi, primary cutaneous melanoma and normal skin and correlations with histopathological prognostic factors of primary melanoma.*
Patients and methods*. Fifty-one patients were enrolled. The tissue concentrations of uPA, PAI-1 and PAI-2 were quantified by enzyme-linked immunosorbent assay (ELISA).*
Results. *Mean uPA and PAI-1 concentrations in melanomas were higher than in normal surrounding skin (uPA: 1.08; vs. 0.48 ng/mgp; PAI-1: 14.07 vs. 2.07 ng/mgp; $p < 0.001$). uPA and PAI-1 concentrations were higher in melanomas than in nevi, and higher in nevi than in normal surrounding skin (uPA: $p > 0.05$; PAI-1: $p = 0.02$). PAI-2 concentration was higher in normal surrounding skin than in nevi and melanomas ($p > 0.05$). Melanoma uPA, PAI-1 and PAI-2 concentrations correlated significantly with normal skin ($r = 0.73, 0.54, 0.38$ respectively). PAI-1 was significantly lower in melanomas of Breslow thickness ≤ 0.75 mm, Clark invasion of 0+I, without microscopic ulceration, without vascular invasion ($p < 0.01$) than in melanomas of Breslow thickness > 0.75 mm, Clark invasion > II, with ulceration and vascular invasion.*
Conclusions. *Determination of uPA and PAI-1 can provide significant additional prognostic information for melanoma patients.*

Key words: skin neoplasms - melanoma; urokinase plasminogen activator; plasminogen activator inhibitor 1; plasminogen activator inhibitor 2; prognosis

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Introduction

Malignant melanoma is one of the most aggressive human tumours. The prognosis of melanoma as well as other cancers is mainly dependent on its ability to invade and metastasise. Prognostic markers such as Breslow tumor thickness, Clark level of invasion, ulceration and vascular invasion are used for defining melanoma patients at risk and fol-

lowing adjuvant therapy. The clinical importance of other factors (clinical, biochemical-molecular) has not been established yet.[1]

Cancer invasion and metastasis are multistep events involving local invasion of the extra cellular matrix, angiogenesis, invasion of the blood vessel wall, survival of malignant cells in the vascular system, extravasation, and establishment of a secondary growth. During most of these steps, extra cellular matrix and basement membrane have to be degraded.[2] The breakdown of these barriers is catalysed by the proteolytic enzymes, which are released from the invading tumour. Four different proteases are mainly involved: metalloproteinases (collagenases, stromelysin, gelatinases), cysteine proteinases (cathepsin B, H, L), aspartyl proteases (cathepsin D), serine proteases (plasminogen activation system).[3]

The two known plasminogen activators (PAs) are tissue type (tPA) and urokinase type plasminogen activator (uPA). Proteolytic activity of tPA is important for the degradation of intravascular blood clots, while uPA contributes to extracellular proteolysis in a wide variety of physiological and pathological processes.[2-4] uPA has many activities. It converts inactive plasminogen to plasmin, which degrades most substrates in the extracellular matrix (proteoglycans, laminin, fibronectin, vitronectin), and activates other proteases (procollagenases, uPA). uPA is activated also by kallikrein, trypsin, cathepsin B, L, thermolysin and nerve growth factor.[3,4] Beside these degradative functions uPA exerts other activities that may enable it to play a role in invasion and metastasis. These include stimulation of cellular proliferation, enhancement of cellular migration, alteration of cellular adhesive properties and activation of specific growth factors.[3-5] Active uPA binds to a membrane-bound receptor known as u-PAR. uPA activity is controlled by two inhibitors, plasminogen activator inhibitor type - 1 (PAI-1) and type - 2 (PAI-2). In addition to inhibiting uPA, PAI-1 modulates cellular adhesion and migration by its attachment to extracellular protein vitronectin. PAI-2 is important in inhibition of apoptosis.[3,4] A strong impact of these proteolytic factors on prognosis of the cancer disease has been observed in a variety of malignancies. The strongest and most consistent evidence of a prognostic role exists with breast cancer. Elevated concentrations of uPA, PAI-1 and uPAR are associated with poor prognosis, high levels of PAI-2, on the other hand, correlate with good outcome.[2,5] uPA is prognostic also in gastric, colorectal, oesophageal, renal, endometrial, and ovarian cancer.[2,4,5] It is well known, that uPA, PAI-1 and PAI-2 expression in human melanoma cell lines correlated with a high metastatic capacity in nude mice.[6] However in human cutaneous and uveal melanoma uPA, PAI-1 and PAI-2 had not been detected in early stage of melanoma but appeared frequently in advanced primary melanoma and melanoma metastatic lesions.[7,8]

Our study was aimed to find out the differences of uPA, PAI-1 and PAI-2 concentrations in clinically suspected nevi, primary melanoma and normal skin concentrations and their correlation to the most important histopathological prognostic factors: Breslow thickness, Clark invasion, ulceration and vascular invasion.

Patients and methods

Patients

Fifty-one patients with clinical confirmed primary cutaneous melanoma (27 women: mean age 49.7; range 21-84 years and 24 men: mean age 56.5; range 17-83 years) were enrolled into a prospective study between 1998-2000. Inclusion criteria were: absence of metastases and macroscopically and histological complete surgical removal of the primary cutaneous melanoma (UICC pT1or T2N0M0, AJCC stage I and II).[9] The Medical Ethics

Committee at the Ministry of Health of the Republic of Slovenia approved the study protocol.

We totally excised melanoma lesions with safety edge of 1-2 cm. We excised 2 x 2 x 2 mm tissue specimens of the lesions and of the normal skin (at least 2 cm far away from the edge of tumours) for the quantification of uPA and PAI-1/2. They were snap-frozen in liquid nitrogen and stored at - 80°C.

The remaining tissue was fixed in 10% formalin and embedded in paraffin for histological examination. The histological diagnosis in 8 patients was dysplastic nevus and in 43 primary cutaneous malignant melanoma with clinical stage I (T1-2 N0 M0) less than 1.5 mm thick. The clinical and histopathological characteristics of primary tumours are shown in Table 1.

Tissue extraction and ELISA for uPA, PAI-1 and PAI-2

The uPA concentrations were determined in 41 pairs of triton extracts, and the PAI-1 and PAI-2 concentrations in 51 pairs of cytosols prepared from tumour and adjacent normal tissue samples (matched pairs) weighing 50 mg, obtained at surgery. The still frozen cut sections were dipped into liquid nitrogen and then pulverized in a microdismembrator (Braun - Melsungen, Melsungen, Germany).

For the triton extracts the still frozen pulver was dispensed with Tris buffered saline (TBS) (0.02 M Tris-HCl, 0.125 M NaCl, pH 8.5) containing 1% non-ionic detergent Triton X-100 (Sigma, St. Louis, Missouri, U.S.A.). The suspension was gently shaken for 3 hours at 4°C. For the cytosol the still frozen pulver was dispensed in a phosphate buffer (5 mM Na_2HPO_4, 1.7 mM KH_2PO_4, 1 mM monothioglycerol, 10% (vv-) glycerol, pH 7.4). Both, the tissue extracts and cytosol suspension were subjected to ultracentrifugation (100 000 g/45 min at 4°C) to separate tissue debris. Supernatants were collected, divided into aliquots and stored at - 70°C until use.

uPA, PAI-1 and PAI-2 concentrations were determined by commercially available ELISA kits (American Diagnostica, Inc., Greenwich, U.S.A.) for uPA, PAI-1 and PAI-2. Details of the kits are described elsewhere.[10] Levels of the uPA, PAI-1 and PAI-2 are expressed in ng/mg proteins. Protein content was determined with Bio Rad method.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows program. Differences of uPA, PAI-1 and PAI-2 concentrations in melanomas, nevi and normal skin were analysed by the Wilcoxon test. Spearman's

Table 1. Clinical and histopathological characteristics of the tumours

Characteristics	Number
Dysplastic nevus	8
Melanoma	43
Localization of primary lesion	
Head	4
Trunk	34
Extremities	13
Histopathological characteristics of melanomas	N = 43
Breslow	
≤ 0,75	28
> 0,75	15
Clark	
0+I	12
II + III	31
Ulceration	
Yes	7
No	36
Vascular invasion	
Yes	3
No	20
Undetermined	20
Histopathological type	
Lentigo maligna	2
Superficial spreading	35
Nodular	2
Unclassified	4

rank correlations were evaluated for the relations between uPA, PAI-1 and PAI-2 concentrations in melanomas and normal skin. Differences of uPA, PAI-1 and PAI-2 concentrations in melanomas and histomorphological variables among various groups of patients were analysed by the two-tailed t-test and the analysis of variance (ANOVA).

The p-values ≤ 0.05 were considered significant.

Results

uPA, PAI-1 and PAI-2 concentrations in melanomas, nevi and normal skin

Among 51 tumour specimens (43 melanomas, 8 dysplastic nevi) and normal skin, the concentration of u-PA was determined in 41 pairs of triton extracts (36 melanomas, 5 nevi), and of PAI-1 and PAI-2 in 51 pairs of cytosols (43 melanomas, 8 nevi) (Table 2). The mean uPA and PAI-1 concentrations in melanomas were significantly higher than in normal skin ($p < 0.0001$). The mean uPA concentration was higher in melanomas than in dysplastic nevi and higher in dysplastic nevi than in normal skin, however statistically insignificant ($p > 0.05$). Mean PAI-1 concentration was higher in melanomas than in dysplastic nevi, and higher in dysplastic nevi than in normal skin with significant results ($p = 0.02$). Mean PAI-2 concentration was not significantly higher in normal skin than in dysplastic nevi and melanomas ($p > 0.05$). There was a significant positive correlation ($r_s = 0.45$) between melanoma uPA and PAI-1 concentrations. Significant correlations between melanoma and normal skin concentrations for uPA, PAI-1 and PAI-2 were found ($r_s = 0.73; 0.54; 0.38$) (Figure 1).

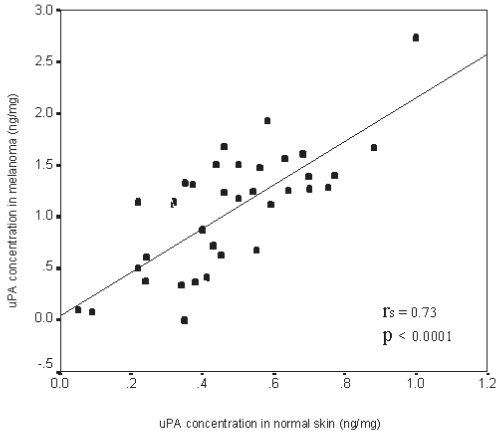

Figure 1. Correlation between melanoma and normal skin uPA concentrations in ng/mg proteins (n = 36, $r_s = 0,73$, $p < 0,0001$).

Table 2. Differences of uPA, PAI-1 and PAI-2 concentrations between melanomas, nevi and normal skin

	uPA (ng/mgp)	PAI-1 (ng/mgp)	PAI-2 (ng/mgp)
Melanoma	1,08 ± 0,58	14,07 ± 16,55***	9,21 ± 18,32
Dysplastic nevi	0,99 ± 0,58	4,84 ± 8,32****	13,44 ± 17,32
Normal skin around Melanoma	0,48 ± 0,21*	2.07 ± 1,83**	13,05 ± 19,72
Normal skin around Dysplastic nevi	0,51 ± 0,36	0,89 ± 0,91	28,8 ± 39,55

Levels are mean ± sd

*, ** $p < 0,0001$, statistically significant lower uPA and PAI-1 normal skin levels according to melanoma levels

***, **** $p = 0,021$ statistically significant higher PAI-1 melanoma levels according to nevi and higher nevi levels according to normal skin levels

Correlation between melanoma uPA, PAI-1 and PAI-2 concentrations and relevant prognostic factors

Melanoma uPA, PAI-1 and PAI-2 concentrations were compared to established histomorphological factors (Table 3). In contrast to uPA and PAI-2, PAI-1 concentrations were significantly lower in melanomas of Breslow tumour thickness ≤ 0.75 mm, Clark level of invasion 0+I, without microscopic ulceration on the tumour surface and absents vascular invasion of the tumours.

Much higher positive correlations (r_s = 0.67, 0.62 and 0.63 respectively; $p \leq 0.02$) between u-PA and PAI-1 concentrations were found in the group of the melanomas of Breslow thickness > 0.75 mm, with the level of Clark invasion III and present vascular invasion.

Discussion

In the present study using specific ELISA performed on tumour extracts of primary melanomas less than 1.5 mm thick, higher uPA and PAI-1 and lower PAI-2 concentrations than in nevi and normal skin were found. The correlation between uPA, PAI-1 and PAI-2 concentrations in melanomas and normal skin was found to be positive.

The prognostic value of uPA and PAI-1 in early stages primary malignant melanoma has not yet been investigated. However, a strong correlation between the metastases of the human melanoma cells in the nude mouse model as well as in the human cutaneous melanoma and expression of uPA and PAI-1 was found.[6] Dysplastic nevi are supposed to be an important risk factor for the development of the cutaneous melanoma. In 1979 Fräki et al. found out higher concentrations of plasminogen activators in primary melanomas and melanoma metastases comparing to extracts of nevi.[11] Recently De Vries et al reported that uPA, PAI-1, PAI-2 and uPAR appeared frequently in advanced primary cutaneous and uveal melanoma and melanoma metastasis lesions.[7,8,12] However uPA and PAI-1 accumulation was observed also in atypical nevocytes, whereas uPA proteolytic activity was detected only in melanomas.[13]

Table 3. Differences of mean concentrations of uPA, PAI-1 and PAI-2 in primary cutaneous melanomas with histomorphological prognostic factors

Variable	N	uPA±SD (ng/mgp)	p[a]	N	PAI-1±SD (ng/mgp)	p[a]	N	PAI-2±SD (ng/mgp)	p[a]
Breslow									
≤ 0,75 mm	22	1,01±0,54	n.s.	28	9,68±11,92		28	10,89±22,34	n.s.
> 0,75 mm	14	1,2±0,65		15	22,25±20,92	0,016	15	6,07±5,35	
Clark									
0+I	9	0,89±0,55		12	4,74±6,45		12	15,97±32,36	
II+III+IV	27	1,15±0,59	n.s.	31	17,67±17,89	0,001	31	6,59±7,78	n.s.
Ulceration									
Yes	7	1,38±0,74		7	27,76±23,27		7	3,2±2,68	n.s.
No	29	1,01±0,53	n.s.	36	11,41±13,82	0,015	36	10,38±19,82	
Vascular invasion									
Yes	2	1,99±1,04	n.s.	3	37,77±23,01		3	5,13 ±6,74	n.s.
No	15	1,02±0,55		20	9,5±12,74		20	11,48±25,62	
Undetermined	19	1,04±0,52		20	15,1±16,6	0,017	20	7,55±8,33	

[a]Analysis of variance, two-tailed t-test, $p \leq 0,05$; n.s. = not significant

Previously, uPA and PAI-1 have been claimed to be of independent prognostic value for disease free and overall survival in breast cancer patients.[14,15] In addition to breast cancer, components of plasminogen activation system also have a prognostic value in colorectal, gastric, oesophageal, bladder, endometrian and ovarian cancer.[2,5] Similarly Nekarda et al have found a stronger prognostic impact of PAI-1 than that of uPA in completely resected gastric cancer.[16]

The presence of the components of the PAs in malignant melanoma has earlier been studied using immunohistochemistry (IHC), in situ zymography and in situ hybridisation. Both, ELISA and IHC have their specific advantages. ELISA methods give an objective quantification of analyte levels, whereas IHC yields at best semi-quantitative information. ELISA and IHC may detect fractions of PA components with different efficiencies.[17,18] At present, ELISAs measuring the levels of uPA and PAI-1 performed consistently well, at least by their more extensively proven clinical value and unequivocal interpretation as demonstrated by the Quality Assurance Center in Nijmegen and from the European Organisation for Research and Treatment of Cancer (EORTC).[10]

Breslow tumour thickness, Clark level of invasion, ulceration and vascular invasion are the most important histological variables predicting melanoma outcome. The prognostic role of other possible markers like molecular and biochemical is not known yet. Our results prove the presence of the correlation of uPA and PAI-1 concentrations with prognostic value of Breslow thickness, Clark invasion, ulceration and vascular invasion also in early melanoma stage I. We observed that higher PAI-1 concentrations were associated with melanomas of Breslow > 0.75 mm, Clark II+III+IV, present ulceration and vascular invasion, which are prognostic adversely. Significant positive correlation between uPA and PAI-1 in melanomas with poor prognosis proves that also uPA has a prognostic impact. It indicates that their role in melanoma growth is co-dependent.

There are various speculative explanations of the role of excessive PAI -1 production in the tumour:[14,16,19] a) PAI-1 is important for reimplantation of circulating tumour cells at distant loci; b) since PAI-1 is present in endothelial cells and platelets, increased PAI-1 levels may reflect a high degree of angiogenesis, thus favouring tumour spread and metastasis; c) PAI-1 binds to adhesive glycoprotein vitronectin and influences cell adhesion and migration.

The prognostic role of PAI-2 is not well known yet. In breast cancer patients with high uPA concentrations, PAI-2 correlated with good prognosis.[20] In colorectal cancer, however, high PAI-2 concentrations were associated with aggressive disease.[21]

Our results prove that using ELISA it is possible to quantify the uPA, PAI-1 and PAI-2 concentration in very small specimens of early melanoma lesions.

Analogous to breast cancer, uPA and PAI-1 could become an additional prognostic factor for the progression of melanoma next to the established histological criteria. Furthermore, the fundamental role of uPA and PAI-1 in tumour invasion and metastasising indicates that these factors should be explored as targets for tumour biology - oriented therapies.[22]

To conclude, our results indicate that using ELISA uPA, PAI-1 and PAI-2 concentrations can be measured also in small samples of primary melanoma and that both uPA and PAI-1 might also be of prognostic importance in primary malignant melanoma. These findings need to be confirmed in further studies where relationship between uPA, PAI-1 and patient survival will be investigated.

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Breast cancer in the Czech Republic

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Background. *Malignant neoplasms present one of the most serious chapters of morbidity, mortality, and the overall perspective of the health status of Czech population. Malignant neoplasms have been registered in the Czech Republic since the end of the 1950s. Guarantor of the all-state registry is the Institute of Health Information and Statistics of the Czech Republic (IHIS CR), and conceptual and methodological steering is performed by the Council of the Czech Cancer Registry. The five most frequently diagnoses in Czech males and seven most frequently diagnoses in Czech females were followed during the last 20 years. The most frequent malignant neoplasm in Czech women is breast cancer.*

Conclusions. *The incidence of this cancer has increased by 75% during the studied period. During the year 2001, three pilot studies of preventive mammography screening were done in the country. One case of asymptomatic breast cancer in the study costs 80,000 Kč (in reality it was 120,000 Kč). These costs are markedly lower than the combined therapy of advanced stages of breast cancer.*

Key words: breast neoplasms; mammography; Czech Republic

Introduction

Malignant neoplasms (MN) present one of the most serious chapters of morbidity, mortality, and the overall perspective of the health status of Czech population. They can also be seen as an important measure of the health status of our population. Due to the extent of their occurrence and lethality, fatality rate, the incomplete knowledge of their etiopathogenesis, therapy, and prevention, they must be considered as one of the primary questions and tasks for the coming years. Neoplasms represent a challenge for health care and the whole society as well. MN are the second most common cause of death and constitute about 25% of all deaths in the Czech Republic.[1]

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Methodology

MN have been registered in the Czech Republic since the end of the 1950s. In 1976,

the cancer registry was established. Since 1991, the Cancer Registry of the Czech Republic has been a member of the International Association of Cancer Registries (IACR). It collaborates with the European Network of Cancer Registries and keeps in contact with registries in many countries.

In the early 1990s, the collection, supplementing, checking, and completion of data were gradually taken over by the 85 District Units of the Czech Cancer Registry, which are aggregated into 8 Regional Units. Guarantor of the all-state registry is the Institute of Health Information and Statistics of the Czech Republic (IHIS CR), and conceptual and methodological steering is performed by the Council of the Czech Cancer Registry.

The basic source of information contained in the Registry is the mandatory form »Report on neoplasm« (NZIS 022 2) filled in by the physician who diagnoses the disease. The notification is returned within 3 months to the District Unit of the Registry where it is checked, supplemented by additional data, and included in the database. The Registry is also complemented on the basis of check-up reports and by comparison with the database of deaths in the Czech Statistical Office (CSO).

Registration is performed according to the Decree of the Ministry of Health and Social Affairs (MSHA) of the CSR no.3/1989 in Bulletin of MHSA CSR (reg. in Law Collection, part 19/1988) - »Dispensary care for patients with precanceroses and cancer and mandatory notification of neoplasms«, applying methodology NZIS (the National Health Information System) no.515/1987 - »Cancer Registry«, following the »Instruction on data entries and returns« 56/1997 in the NZIS methodology »Handbooks for regional and district units« and other appropriate methodological instructions.

Data for the publication »Neoplasms« are usually processed with a two-year delay, which is necessary for the completion of the Registry with missing patients and missing data.[2]

Trends of registered cases of cancer

Trends of incidence of registered cancer cases (ICD - 10, dg. C00 - C097 and dg. D00 - D09) are shown in Figure 1. The relative indicators (cases per 100 000 males or females) are computed with reference to the mid-year population and also to world standard and European standard populations, the same for both genders, as published in the WHO Yearbook.

The incidence of all registered cancer cases in males in the Czech Republic grew by 40.1% during the period 1985 - 1998 (1985 - 414.8 cases per 100 000 males; 1998 - 583.6 cases per 100 000 males), whereas in females, it grew by 50.1% during the same period (1985 - 363.7 cases per 100 000 females; 1998 - 548.7 cases per 100 000 females). In the period 1985 - 1998, the growing incidence trend is seen in both sexes also at the world and European levels:

- by 27.8% - males world rates (1985 - 324.8 per 100 000 males; 1998 - 415.1 per 100 000 males)
- by 38.7% - females world rates (229.4 - 318.2)
- by 42.8% - males European rates (427.5 - 610.7)
- by 39.2% - females European rates (319.7 - 444.9)

In Czech females compared to the world and European rates, the highest incidence was observed in the followed period. The incidence of all registered cancer cases in Czech males is lower compared to the European rates, but higher than the incidence in the world standard. But the incidence growth is steeper in both sexes in the Czech Republic compared to the world and European rates.[2,3]

Trends of registered cancer cases in the Czech Republic - selected diagnosis (per 100 000 inhabitants)

Trends of registered cases of selected diagnosis for males and females separately during the studied period of the last 20 years (1980 - 1999) in Czech Republic are shown in Figures 2 and 3. The incidence of all registered cancer cases in males in the Czech Republic grew from 378.4 cases per 100 000 males (1980) to 570.5 cases per 100 000 males. The growth index 1999/1980 is 150.8. The growth was faster in the nineties than in the eighties (index 1990/1980 is 120.5; index 1999/1990 is 125.1). The incidence in Czech females was permanently lower than in males (1980 - 322.3; 1999 - 537.9), but the difference was systematically falling down, with the index M/F of 117.4 in 1980; 111.7 in 1990; and 106.1 in 1999. The incidence in females was growing faster than in males.

According to the selected diagnosis in Czech males, MN of the lung (C 33 + C 34) with 97.6 cases per 100 000 males was the most frequent cancer in the year 1980. MN of the stomach (C16) ranked second, with 32.4 cases per 100 000 males. The incidence of MN of the lung slightly increased in the eighties (99.6) and decreased during the nineties (88.9). The second most frequent cancer for males in 1999 was MN of the prostate (53.8 cases per 100 000 males). The incidence increased by 128% during the followed period. A considerable increase (120%) is seen in colon cancer (from 19.8 to 43.6). The incidence of MN of the rectum has grown by 49% (24.9 to 37.1). A remarkable decrease from 32.4 to 20.4 (37%) is seen in stomach cancer. The above-mentioned five selected diagnoses included 52.4% of all notified diagnoses in 1980, while in 1999, it was only 42.9%.[3]

The selected seven most frequent diagnoses in females in the Czech Republic were followed during the period 1980 - 1999. In 1980 and in 1999, the proportion of these diagnoses to all registered cancer cases was 54.6%, and 43.8%, respectively. The most frequent cancer in 1980 was breast cancer (C 50) (51.5 cases per 100 000 females) and it kept that position also in 1999 (89.9 per 100 000 females). During the followed period of 20 years, its incidence grew by 75%. The cancer of the colon ranked second in 1999 and its incidence grew by 76.4% during the last 20 years. A remarkable increase in Czech females represents MN of the lung; it grew by 111.3% (from 10.6 to 22.4). In this same period, the incidence of MN of the lung decreased in Czech males by 10%. In females, a systematic decrease of 34% in stomach cancer incidence was observed in the followed period. A stable incidence (about 20 per 100 000) during the 20-year period was seen in MN of the cervix uteri. The incidence of the cancer of the rectum increased by 34% and the incidence of the cancer of the corpus uteri by 35%.[3]

Breast cancer

The most frequent and most serious MN in women is breast cancer. MN of the breast has been registered since 1953 in the Czech Republic (in absolute numbers, there were 1,700 cases per year). In 1980, the incidence of breast cancer was 51.5 per 100 000 women (2,739 cases), and in 1999, it was already 89.8 per 100 000 women (4,740 cases in absolute numbers), which is 2.5% more cases than the year before.[2,7]

In 1999, the breast cancer incidence in females was for the first time higher than that of the lung cancer in males (breast cancer incidence - 89.8; lung cancer incidence - 88.9). The incidence of breast cancer increased by 75% during last 20 years (as mentioned above).[3]

During the last ten years, the absolute number of deaths from breast cancer gradually increased by 3.4%, while the fatality rate

decreased. Compared to 1989, it decreased by more than 10% and its present value is approximately 41%.

The number of MN in an unspecified stage, or more properly, with no stage identification in the notification, increased in cases of MN of the breast. This phenomenon was mostly seen in the 1990s. In cases where the stage was notified, the proportion of stages I and II was definitely growing, while the proportion of stages III and moderately also IV had a decreasing tendency. The cumulative 5-year survival rate in cases diagnosed in the years 1989-1993 increased in women by almost 10% compared to the cases diagnosed in the period 1980-1984.

Breast cancer incidence grows with age. During the last 5 years, the specific incidence of breast cancer increased more rapidly in the Czech Republic in the age groups of 55-59 years and 65-69 years (55-59: 1995 - 164.7 per 100 000; 1999 - 189.5; 65-69: 1995 - 218.7; 1999 - 248.7). It is important to mention that the specific incidence was markedly higher in all age groups over 50 years compared with the situation at the beginning of the 1990s.

On the basis of mandatory form »Report on neoplasms« it is possible to follow the changes in treatment modalities. Since the 1980s, the number of surgically treated breast cancer within 3 months from the diagnosis has been stabilized, ranging from 86 to 89 %. The proportion of radiotherapy is decreasing. In 1980, 76% of MN cases were treated by radiotherapy, in 1990, about 60%, and in 1999, 45%. On the other hand, the proportion of chemotherapy and hormonal therapy is increasing. In 1980 and 1999, respectively 11% and 46% of cases were treated by chemotherapy. As to the hormonal therapy, the proportion increased even more - from 8% of diagnosed breast cancer cases in 1980 to 49% of these cases in 1999.

The absolute number of deaths from breast cancer is under 2000 per year. Since the mid 1980s, the mortality rate has been ranging from 34 - 39 deaths per 100 000 women. The proportions of the mortality rate have been relatively stable in all age groups during the last 10 years. Breast cancer mortality increased only in the oldest age group (over 85 years old). This age group also had the highest specific mortality.[2,7]

Breast cancer incidence in the Czech Republic (even with its relatively steep growing tendency) is still lower in comparison with Western European countries. But it is higher compared to Slovakia, Hungary and Poland and similar to the incidence in Slovenia (see Table 1).

Table 1. Female breast cancer incidence per 100 000 in some selected European countries. Source: Database HFA 2000.

	1996	1997	1998	1999
Czech Republic	83,8	85,1	87,5	94,9
Slovenia	82,2	87,9	.	.
Slovakia	62,1	61,2	63,8	.
Hungary	35,0	41,7	43,0	97,5
Poland	48,8	.	.	.
Austria	110,1	110,8	109,3	.
Denmark	130,7	132,1	.	.
Finland	127,0	126,7	129,8	134,6
Norway	114,4	116,1	114,1	.
Netherlands	126,6	125,9	.	.
Sweden	130,6	130,1	138,2	140,9
United Kingdom	122,0	125,6	.	.

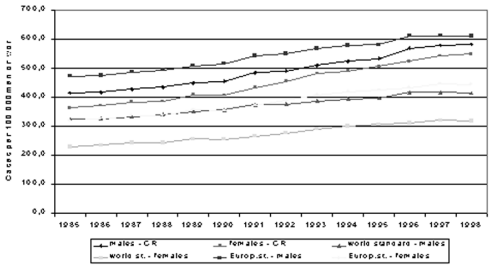

Figure 1. Trends of registered cancer cases (ICD - 10, dg. C00-C097 and dg. D00-D09). Source: UZIS CR[2]

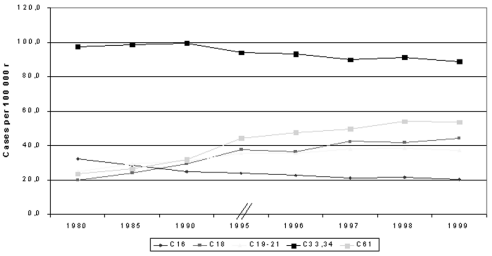

Figure 2. Trends of registered cancer cases - selected diagnoses (per 100 000 males) - males in the Czech Republic. Source: UZIS CR[4,5,6]
C16 - MN of stomach; C 18 - MN of colon; C 19-21 - MN of rectum; C 33, 34 - MN of lung; C 61- MN of prostate

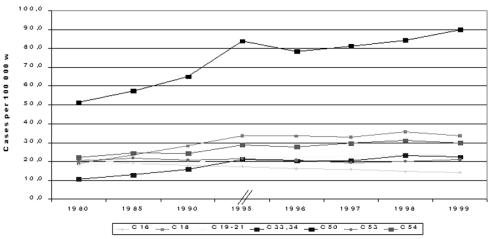

Figure 3. Trends of registered cancer cases selected diagnoses (per 100 000 females) - females in the Czech Republic. Source: UZIS CR[4-6]
C 16 - MN of stomach; C 18 - MN of colon; C 19-21 - MN of rectum; C 33, 34 - MN of lung; C 50 - MN of breast; C 53 - MN of cervix uteri; C 54 - MN of corpus uteri

Mammography - pilot study in the Czech Republic

The question of preventive mammography screening for all women of age 45 - 70 was discussed in the Czech Republic by the professionals several times. The main reason why it wasn't introduced was financial. For mammography examination women needed a recommendation either from a GP or a gynaecologist.

During the year 2001, three pilot studies were done in the country with the aim to make a detailed audit in a relatively short time and answer the questions by General Health Insurance Company before the introduction of payments for preventive screening. Two of the studies took place in Mamma Centrum in Prague and one in University Hospital in Hradec Králové. Each study included 1,500 women and the duration of each was 3 months.

The results of the first (that took place in Mamma Centrum in Prague from November 2000 to January 2001) are the following: Eleven cases of breast cancer were found among 1,500 examined women (9 of the women were without any symptom). Medical diagnoses were made within 2 hours from the examination in 98.5% of women. The 9 women who were diagnosed, but showed no symptoms, obviously benefited from the screening in the pilot study.

No doubt that preventive mammography is not a cheap method. Mamma Centrum obtained altogether 750,000 Kč to cover the pilot study; it means 500 Kč per one examined woman (1 EURO was approximately 31 Kč at that time). The real costs also included the clinical examination of a patient, registration, necessary ultrasonography for 1/4 of women, audit, taking of anamnesis, and the work of health professionals were at least 1.5 times higher.

One case of asymptomatic breast cancer in the study cost 80,000 Kč (in reality it was 120,000 Kč). These costs are markedly lower than the combined therapy of advanced stages of breast cancer. The economical profitability of the screening was proved. Preventive mammography screening was ratified in spring 2002 by the Decree of the Ministry of Health of the Czech Republic. The screening should start in November 2002 and is targeted to women aged 44 - 70 years once every 2 years.[8]

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Tumor blood flow modifying effects of electrochemotherapy: a potential vascular targeted mechanism

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Background. *The aim of this study was to determine the tumor blood flow modifying, and potential vascular targeted effect of electrochemotherapy with bleomycin or cisplatin.*
Materials and methods. *Electrochemotherapy was performed by application of short intense electric pulses to the tumors after systemic administration of bleomycin or cisplatin. Evaluated were antitumor effectiveness of electrochemotherapy by tumor measurement, tumor blood flow modifying effect by Patent blue staining technique, and sensitivity of endothelial and tumor cells to the drugs and electrochemotherapy by clonogenicity assay.*
Results. *Electrochemotherapy was effective in treatment of SA-1 tumors in A/J mice resulting in substantial tumor growth delay and also tumor cures. Tumor blood flow reduction following electrochemotherapy correlated well with its antitumor effectiveness. Virtually complete shut down of the tumor blood flow was observed already at 24 h after electrochemotherapy with bleomycin whereas only 50% reduction was observed after electrochemotherapy with cisplatin. Sensitivity of human endothelial HMEC-1 cells to electrochemotherapy suggests a vascular targeted effect for electrochemotherapy in vivo with bleomycin as well as with cisplatin.*
Conclusion. *These results show that, in addition to direct electroporation of tumor cells, other vascular targeted mechanisms are involved in electrochemotherapy with bleomycin or cisplatin, potentially mediated by tumor blood flow reduction, and enhanced tumor cell death as a result of endothelial damage by electrochemotherapy.*

Key words: sarcoma experimental - drug therapy - blood supply; bleomycin; cisplatin; electroporation; drug delivery systems

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Introduction

Enhanced delivery of chemotherapeutic drugs into tumor cells by electroporation is termed electrochemotherapy.[1] A local increase in plasma membrane permeability, after exposure of tumor nodules to electric pulses (electroporation), results in increased

uptake of chemotherapeutic drugs into the tumor cells. Electrochemotherapy has been shown to be successful for drugs such as bleomycin and cisplatin, which normally exhibit impeded transport through the plasma membrane. The increased antitumor effectiveness of bleomycin and cisplatin combined with electroporation has already been demonstrated in experimental and clinical studies although the underlying mechanisms remain to be clarified. [1-4]

In addition to increased drug delivery into the cells, application of electric pulses to the tumors was found to exert tumor blood flow modifying effect.[5,6] Electric pulses, as used in preclinical and clinical studies were found to reduce tumor blood flow. Transient reduction in tumor blood flow down to 30% of control was found, but recovered to almost pre-treatment level within 24 hours.[5]

Application of electric pulses to solid tumors would not be expected to selectively electroporate tumor cells alone. All cells in all areas where electric field exceeds the critical threshold level would be electroporated.[1,7] Therefore endothelial cells are also potential targets for electroporation. Since the initial concentration of the drug is the highest in tumor blood vessels, during electroporation, electrochemotherapy is probably effective on endothelial cells in the tumor blood vessels. This may lead to severe damage to the vasculature of the tumors and consequently induce a secondary cascade of tumor cell death, *e.g.* by abrogating oxygen supply to the cells. This phenomenon, described as vascular targeted therapy, has been exploited in several studies.[8]

The aim of this study was to elucidate tumor blood flow modifying and vascular targeted effects of electrochemotherapy with bleomycin or cisplatin by measuring tumor perfusion, and cells survival of endothelial cells in relation to their antitumor effectiveness.

Materials and methods

Animals, tumors and cell lines

A/J mice of both sexes, purchased from the Institute Rudjer Bošković, Zagreb, Croatia, were used. Subcutaneous murine fibrosarcoma SA-1 tumors (The Jackson Laboratory, Bar Harbour, ME) were implanted, by injecting 0.1 ml NaCl (0.9%) containing 5 x 10^5 viable tumor cells under the skin on the rear dorsum. Six to 8 days after implantation, when tumors reached approximately 40 mm^3 in volume (6 mm in diameter) mice were randomly divided into experimental groups, consisting of at least 6 mice. Treatment protocols were approved by the Ministry of Agriculture, Forestry and Food of the Republic of Slovenia No. 323-02-237/01.

Human dermal microvascular endothelial cells (HMEC-1) cells were generously provided by Dr. F.J. Candal (Center for Disease Control, Atlanta, USA). Cells were grown as monolayer in D-MEM supplemented with 10% fetal calf serum (FCS, Sigma, USA) in a humidified incubator at atmospheric oxygen supplemented with 5% CO_2 at 37°C. They were routinely subcultured twice per week.

Electrochemotherapy protocol

Bleomycin (Bleomycin, Mack, Germany) was dissolved in phosphate buffered saline and the dose of 5mg/kg in 0.2 ml volume was injected intravenously. Bleomycin solution was prepared freshly for daily injections.

cis-Diamminedichloroplatinum (II) (Cisplatin) was obtained from Bristol Myers Squibb (Austria) as a crystalline powder and a stock solution prepared in sterile H_2O at a concentration of 1 mg/ml. The final cisplatin solution was freshly prepared in 0.9% NaCl each day. Cisplatin at a dose of 4 mg/kg in 0.2 ml volume was injected intravenously.

Electric pulses were delivered by two flat, parallel stainless steel electrodes 8 mm apart (two stainless steel strips: length 35 mm, width 7 mm with rounded corners), which

were placed percutaneously at the opposite margins of the tumor. Good contact between the electrodes and the skin was assured by means of conductive gel (Parker Laboratories, New York, USA). Eight square-wave pulses of 1040 V amplitude (amplitude to distance ratio 1300 V/cm), with a pulse width of 100 μs and repetition frequency of 1 Hz were generated by electroporator Jouan GHT 1287 (Saint Herblaine, France). In the electrochemotherapy protocol, tumors were exposed to electric pulses 3 minutes after bleomycin or cisplatin injection. Treatments were performed without anesthesia and were well tolerated by the animals.

Tumor growth was followed by measuring three mutually orthogonal tumor diameters (e_1, e_2 and e_3) using a vernier caliper on each consecutive day following treatment. Tumor volumes were calculated by the formula Π x e_1 x e_2 x e_3 /6. From the calculated volumes the arithmetic mean and SE were calculated for each experimental group. Tumor growth delay was calculated for each individual tumor by subtracting the doubling time of each tumor from the mean doubling time of the control group and then averaged for each experimental group.

Assessment of tumor staining by Patent blue

Patent blue (Byk Gulden, Switzerland) was used to estimate tumor perfusion. Patent blue (1.25%), diluted in 0.2 ml 0.9% NaCl, was injected into tail vein of animals after tumor treatment. The dye was distributed evenly through the blood at approximately 1 minute, thereafter animals were sacrificed and tumors were carefully dissected. Tumors were cut along their largest diameter and the stained versus non-stained tissue per cross-section was immediately estimated visually by two persons. The mean of both estimations was used as an indicator of tumor perfusion. The results of individual experiments were pooled and presented as arithmetic mean and SE for each experimental group.

Cytotoxicity assay for SA-1 and HMEC-1 cells treated by electrochemotherapy

The sensitivity of the SA-1 and HMEC-1 cells to combined treatment with bleomycin or cisplatin and electric pulses (electrochemotherapy) was determined by *in vitro* colony forming assay. The cells (2.2 x 10^7 cells/ml) were mixed with bleomycin or cisplatin. One half of the mixture was exposed to 8 electric pulses (electric field intensity 1400 V/cm, pulse duration 100 μs, frequency 1 Hz) and the other half served as a control for bleomycin or cisplatin treatment alone. The bleomycin concentrations used ranged from 0.1 nM to 100 μM and the cisplatin concentrations from 16.7 to 670 μM. The cells were incubated with each drug for 5 min. The survival of cells treated with electrochemotherapy was normalized to electric pulses treatment alone. The IC_{50} values (drug concentration that reduced cell survival to 50% of control) were determined for each treatment group.

Statistical analysis

The significance of differences between the mean values of the groups was evaluated by modified t-test (Newman Keuls test) after a one way analysis of variance was performed and fulfilled. Sigma Stat statistical package (SPSS, USA) was used for statistical analysis. P levels less than 0.05 were taken as statistically significant.

Results

Antitumor effectiveness

Electrochemotherapy with either bleomycin or cisplatin was effective in inducing cytotoxicity in subcutaneous SA-1 tumors (Table 1). Treatment of tumors with electric pulses alone had a minor effect on tumor growth, resulting in only 1.3 days tumor growth delay. Treatment of mice with bleomycin or cisplatin alone had also minor effects on tumor

Table 1. Antitumor effectiveness of electrochemotherapy on SA-1 tumors in mice (* P<0.05)

Therapy	n	Tumor doubling time (Days, AM±SE)	Tumor growth delay (Days, AM±SE)	Cures
Control	20	1.8 ± 0.05		0 %
Electric pulses	17	3.1 ± 0.2*	1.3 ± 0.2	0 %
Bleomycin (5 mg/kg)	20	1.9 ± 0.1	0.1 ± 0.1	0 %
Electrochemotherapy with bleomycin	17	34.5 ± 2.9*	32.7 ± 2.9	70 %
Cisplatin (4 mg/kg)	10	3.7 ± 0.4*	1.9 ± 0.4	0 %
Electrochemotherapy with cisplatin	10	12.1 ± 1.6*	10.3 ± 1.6	0 %

growth; bleomycin having none, whereas cisplatin inducing 1.9 days tumor growth delay. When using bleomycin in electrochemotherapy, a highly significant growth delay of 32.7 days was achieved and 70% of the animals were cured (tumor free 100 days after the treatment). The animals tolerated the treatment well without scaring of the treatment area. Electrochemotherapy with cisplatin also resulted in good antitumor effect with reduction in tumor size at three days after the treatment, regrowth after 8 days, however no tumor cures were achieved. Tumor growth delay was 10.3 days, which was highly significant compared to the antitumor effectiveness of either single modality.

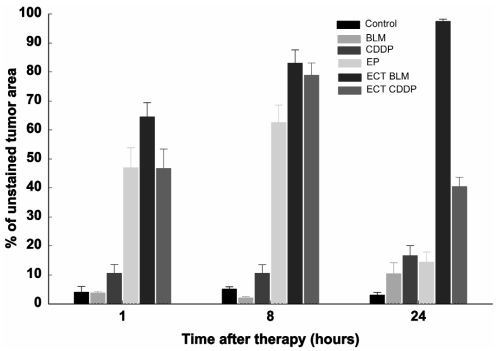

Figure 1. Changes in tumor blood flow at 1, 8 or 24 h after electrochemotherapy (ECT) with bleomycin (BLM) or cisplatin (CDDP), measured by Patent blue staining. Eight electric pulses (EP) were applied to the tumor (amplitude to distance ratio 1300 V/cm, pulse width 100 Ķs, repetition frequency 1 Hz) 3 minutes after intravenous injection of 5 mg/kg of bleomycin or 4 mg/kg of cisplatin. Mean values ± SE of the mean of at least 6 mice per point.

Tumor blood flow changes

Electrochemotherapy, either with bleomycin or cisplatin, induced substantial reduction of tumor blood flow. Untreated SA-1 tumors showed very low incidence of necrosis with approx. 90% of the tumor area stained with Patent blue. When electric pulses were applied to a tumor reduction in tumor staining was observed (Figure 1). By 1 hour after the application of electric pulses the percentage of unstained tumor section had increased to 45% and after 8 hours further increased to 65%, however tumor blood flow recovered almost completely within 24 hours after this treatment. Treatment with bleomycin alone did not induce changes in tumor blood flow. However, electrochemotherapy with bleomycin demonstrated substantial increase in unstained tumor area at 8 hours after treatment, and virtually complete shut down of tumor perfusion at 24 hours after therapy compared to electric pulses alone (Figure 1).

Treatment with cisplatin alone had minimal tumor blood flow modifying effect. However, electrochemotherapy with cisplatin demonstrated greatly increased unstained tumor area at 8 hours after treatment which remained significantly higher at 24 hours after the treatment compared to treatment with electric pulses alone (Figure 1).

Cytotoxicity of electrochemotherapy to tumor and endothelial cells

The sensitivity of SA-1tumor cells and human endothelial cells HMEC-1 to bleomycin and

cisplatin as well as to electrochemotherapy was evaluated by *in vitro* colony forming assay (Table 2). Endothelial cells were more sensitive to bleomycin than tumor cells. The potentiation of bleomycin cytotoxicity by electroporation was ~5000-fold for endothelial cells and ~2400-fold for tumor cells. Electrochemotherapy with cisplatin was less effective on endothelial as on tumor cells, but potentiation of cisplatin cytotoxicity by electroporation was bigger for endothelial cells (~10-fold), as for tumor cells (~8-fold).

Discussion

This study shows tumor blood flow modifying and vascular targeted effect of electrochemotherapy with bleomycin as well as with cisplatin. The sensitivity of endothelial cells to electrochemotherapy with either, bleomycin or cisplatin correlates well with the enhanced reduction of tumor blood flow induced by electrochemotherapy in vivo and its antitumor effectiveness.

As many preclinical and clinical studies have shown, electrochemotherapy either with bleomycin or cisplatin leads to high percentage of tumor cures, on many tumor types tested so far.[1,3,4,9,10] Electroporation was shown to significantly increase drug accumulation in the tumor cells.[1,11] In electrochemotherapy treated tumors more than twice the amount of platinum was determined in whole tumors, as well as bound to DNA compared with cisplatin treatment alone.[11] In view of our previous study observing that electrochemotherapy with cisplatin induced more than 20-fold increase in cell kill compared with cisplatin treatment alone, we proposed that, in addition to direct electroporation of tumor cells, other mechanisms may be involved in antitumor effectiveness of electrochemotherapy.[11]

Table 2. Cytotoxicity of electrochemotherapy to human endothelial HMEC-1 and mouse tumor SA-1 cells *in vitro*

Cell line / Group	HMEC-1 (IC_{50}; μM)	SA-1 (IC_{50}; μM)
Bleomycin	20.0	60.0
Electrochemotherapy with bleomycin	0.004	0.025
Cisplatin	380.0	166.0
Electrochemotherapy with cisplatin	40.0	20.0

The direct blood flow modifying effect of electric pulses applied to the tumors has now been established. Application of electric pulses reduces blood flow selectively at the site of its application, *i.e.* within the tumor site, without modifying flow in normal tissues.[5] Recently, a new method by staining of tumors with Patent blue was evaluated, giving data on tumor blood flow, in support of that found using the ^{86}RbCl extraction technique.[12] Since the two methods correlated well, Patent blue staining technique was preferred in this study, because of its simplicity. The present study confirms the results of our previous study that application of electric pulses to the tumors induces transient reduction in tumor blood flow.

Tumor blood flow modifying effect of electrochemotherapy was greater than after application of electric pulses alone. This effect was especially dramatic in electrochemotherapy with bleomycin, but in lesser extent after electrochemotherapy with cisplatin. Tumor blood flow after electrochemotherapy with bleomycin was completely shut down already at 24 hours after therapy, indicating that tumor vasculature was irreversibly damaged.[12] Since HMEC-1 endothelial cells were more sensitive to electrochemotherapy with bleomycin *in vitro* than SA-1 tumor cells, this vascular shut down may be ascribed in large part to the death of endothelial cells. In contrast, endothelial cells were less sensitive to electrochemotherapy with cisplatin *in vitro*, which was also reflected in less severe tumor blood flow changes induced by this therapy with flow partly restored after 24 hours.[13]

In summary, several mechanisms are involved in antitumor effectiveness of electrochemotherapy. Electroporation of the tumors increases delivery of cytotoxic drugs into the tumor cells, potentiating their cytotoxicity. Additionally, the current study demonstrates that nonselective electroporation of solid tumors enables cytotoxic action of electrochemotherapy to endothelial cells and enhanced tumor cytotoxicity by a vascular targeted mechanism.

Acknowledgment

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Prof. Božena Ravnihar, MD, PhD (1914-2002)

Professor Božena Ravnihar-Nataša, a partisan doctor, Nestor of Slovenian oncology, and Professor Emeritus at the Medical Faculty of the University of Ljubljana reached the end of her road. Her career was rich and fruitful and can hardly be unfolded in few words. Allow me to make us all remember of some momentous facts of her life.

She was born on March 18, 1914 in Ljubljana. She attended elementary and secondary school in Ljubljana and, after graduation from secondary school, she chose to study medicine. She started her study in Ljubljana, continued it in Prague and graduated at the Medical Faculty of Belgrade on 26 June 1940.

She joined the resistance on 28 May 1942 and was throughout the war principal head of partisan hospitals. After the war, she continued her work at the Sanitation Unit under military authority.

She was awarded with Order of Courage, Order of Partisan Star and Order of Merit for her great deeds during the Second World War. She also won the 1941 Partisan Memorial Reward.

In 1946, she was appointed Head of Laboratories at the Institute of Oncology in Ljubljana by the then Ministry of Health. She was improving her knowledge and skills at the oncology institutions abroad, in Stockholm, Copenhagen and Paris. Having obtained a fellowship from World Health Organization (WHO) she completed residency in radiotherapy and oncology in the States and also passed Board Exam there. Coming back from the States, she devoted herself to the work in Pathohistology Laboratory and was in addition to that also nominated Head of Radiotherapy Department.

In November 1950, she was elected a Teaching Assistant at the Medical Faculty of Ljubljana, in 1955 Assistant Professor, in 1961 Associate Professor of Radiotherapy and Oncology, and in 1971 Full Professor of Radiotherapy and Oncology. She was chairing the Chair of Oncology and Radiotherapy at the Medical Faculty of Ljubljana from 1964 to 1982.

On 19 June 1984, she was elected Professor Emeritus at the Medical Faculty of Ljubljana.

In 1961, she was nominated at the post of Medical Director of the Institute of Oncology

and, in January 1964, at the post of Director of the Institute of Oncology. She held that position until 18 March 1982. She retired two years later, on 18 March 1984. However, she continued to be active, creative and productive also after her retirement.

Scientific and medical achievements of Professor Ravnihar are impressively many: she wrote more than 300 papers, in which she dealt with almost every area of oncology. Her scientific articles touch upon clinical issues of cancer, particularly focusing on radiotherapy, epidemiology, and anticancer activity. She also introduced a number of innovations in cancer treatment, such as treatment of lung cancer by the irradiation with betatron. Already in 1965, she published, in cooperation with her colleagues, an article on concomitant treatment of lung carcinoma, combining radiotherapy and chemotherapy, on the treatment of head and neck cancer with tele- and brachytherapy. She designed the irradiation methods and developed evaluation methodology for assessing treatment results. Her achievements in epidemiology are well-grounded and systematic; she was the principal investigator of numerous international research projects on lung cancer and on breast cancer. An important contribution to epidemiology is her article »Epidemiologic Aspects of Cancer«, in which she presented the epidemiologic methods to be applied in programming the cancer detection and its quality control. In her works, she also discussed the issues of organized anticancer campaign.

Her research results in individual fields of anticancer activity, like prevention, detection, diagnostics and therapy, rehabilitation and epidemiology paved the way for setting up oncology centers in Slovenia as well as in Europe; she was actively involved in anticancer campaigns also on the international level through World Health Organisation (WHO) and International Union Against Cancer (UICC). She was initiator as well as founder and many years Head of the Cancer Registry of Slovenia, which was among the first population-based registry centers in Europe.

She was most eager in her endeavors to construct a new Institute or at least to add new buildings to the existing ones and to establish a functional comprehensive cancer center. In part, she almost fulfilled these set goals in the 1970s by the construction of Building TRT (teleradiotherapy). Regrettably, death came too early and prevented her to see her dreams of a new building coming true.

She drew up guidelines and directives how to organize, beside medical care, also research work at the Institute, and at the very beginning of her directorship, the Institute of Oncology was also given the status of a research institution by the decree issued by Ministry of Science and Technology.

She was very successful also in teaching. She designed the curriculum of the subject »Radiotherapy and Oncology« to be lectured at the Chair of Radiotherapy and Oncology of the Medical Faculty of Ljubljana and elaborated it with respect to multidisciplinarity and team work. We now continue this approach and develop it further. She was chairing the Chair of Radiotherapy and Oncology from 1964 to 1982. She was initiator of the program on physical and biological fundamentals of radiotherapy and also worked on its implementation before it was launched at the Institute of Nuclear Sciences in Vinča (Serbia). She also designed and developed the first program for specialization in radiotherapy, which was at that time considered as a pioneering achievement also on the European level. In former Yugoslavia, she was one of the principal strategists in creating the policy against cancer. She chaired numerous committees and boards. In the 1970s, she was President of Cancerology Association of Yugoslavia. Her roles as mentor and counsellor are also of invaluable significance; she was mentor or counsellor to almost every col-

league of the then growing generation of oncologists in Yugoslavia, not only at the Institute of Oncology in Ljubljana or in Slovenia

Due to her merits, the Institute of Oncology is at present a large and up-to-date cancer center in Slovenia, a central medical, research and university institution for cancer treatment. She was the first editor-in-chief of the medical review »Radiologia Iugoslava« that started to appear in 1964 and, having acquired a strong international reputation, she was also invited to a number of editorial boards of medical journals abroad. Moreover, many local and international experts associations appointed her as member of honor or awarded her with orders of merit.

Though the saying goes »Nemo propheta in sua patria«, her productive and creative work was nevertheless highly appreciated by local community. Numerous medals awarded to her by the state and local public prizes bear witness of that. In 1974, she won the highest reward by the federal state, AVNOJ prize, in 1978 she was awarded with the Order of the Republic with Golden Laureate, she was appointed Member of Honor of the Cancerology Section of the Republic of Slovenia, of the Cancerology Association of Yugoslavia, of the Association of Medical Societies of Yugoslavia, and of the Slovenian Medical Association.

While unfolding her rich and productive life story, I may have left aside more than I have told about her; however, these few fragments of her life witness of the noble nature of Professor Božena Ravnihar who set off on a journey through life as partisan doctor and continued it as oncologist, Professor at the Medical Faculty of Ljubljana, initiator of anticancer campaigns and many years' Director General of the Institute of Oncology in Ljubljana - yet, first of all, she was compassionate and humane, having empathy for everyone of us, for the problems we had. She always found a moment or a word of support for us when we were down, and never spared with blame or praise when we deserved it. Our Institute was her family. In the hearts of all of us, she was our Mum.

Professor Božena Ravnihar accomplished her mission. But she will stay among us as a legend. We shall keep her in our minds and hearts; anyhow, legends never die.

Zvonimir Rudolf

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Primarna tuberkuloza dojke. Prikaz primera

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Izhodišča. Diagnostično razlikovanje primarne tuberkuloze dojke od ostalih benignih in malignih obolenj je s sodobnimi slikovnimi metodami težavno. V mnogih primerih so mamografske in ultrazvočne značilnosti tuberkuloznih sprememb v dojki podobne spremembam pri raku dojke.
Prikaz primera. Prikazujemo primer bolnice, ki ni imela anamnestičnih podatkov o tuberkulozi in smo ji tuberkulozo dojke diagnosticirali med operacijo.
Zaključki. Pri bolnicah s primarno tuberkulozo dojke lahko postavimo napačno diagnozo. To je pogosteje pri bolnicah, ki anamnestično nimajo podatkov o tuberkulozi, ko so slikovno diagnostični izvidi zavajujoči in ko sumimo na rak dojke. V takih primerih diagnosticiramo bolezen po kirurški odstranitvi bolezenskih sprememb v dojki in s histološkin pregledom.

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Primerjava debeline dojke, izpostavljenosti sevanju in kakovosti slik pri uporabi polstranskih mamografskih projekcij pod kotoma 45° in 60°

Obad Kovačević D, Brnić Z, Hebrang A

Izhodišča. Pri standardnem presejalnem testu z mamografijo uporabljamo dvoje projekcij: kraniokavdalno in mediolateralno polstransko. Pri mediolateralni polstranski projekciji je kot centralnega žarka od 30° do 60°.
Bolniki in metode. Primerjali smo debelino komprimirane dojke, zmnožek časa in električnega toka, izpostavljenost sevanju in kakovost slik pri dveh različnih mamografskih poševnih projekcijah: pod kotoma 45° in 60°. Preiskave smo naredili pri 33 ženskah, pri katerih smo zaradi diagnostičnih zahtev poleg slikanja pod kotom 45° naredili tudi slikanje pod kotom 60°.
Rezultati. Srednja vrednost debeline komprimirane dojke je bila pri slikanju pod kotom 60° statistično značilno nižja kot pod kotom 45° (47,8 *vs.* 50,7 mm, $p<0.01$); pravtako sta bili tudi statistično značilno nižji srednji vrednosti zmnoška časa in eletričnega toka ter izpostavljenosti sevanju (42,6 *vs.* 46,7 mAs, $p<0.01$; 0,67 *vs.* 0,78 mGy, $p<0.01$). Našli smo tudi razliko v kakovosti slik, ki pa ni bila statistično značilno boljša.
Zaključki. Z uporabo polstranske mamografske projekcije pod kotom 60°smo dosegli vsaj enako kakovost mamografskih slik ob nižji sevalni dozi, kar je zelo pomembno, saj je mlečna žleza v dojki zelo radiosenzitivna.

Radiol Oncol 2003; 37(1): 9-12.

Scintigrafsko ugotavljanje peptične razjede s sukralfatom, označenim z radioizotopom

Naumovski J, Simova N, Janevik-Ivanovska E, Kovkarova E, Georgievska- Kuzmanovska S

Izhodišča. Sukralfat uporabljamo za zdravljenje ulkusne bolezni. Po peroralni aplikaciji se močno veže na poškodovano sluznico in na ta način zaščiti sluznico pred nadaljnjo poškodbo s kislino in pepsinom. Če sukralfat označimo z radioizotopom, ki je sevalec gama žarkov, lahko z gama kamero zaznamo morebitno poškodbo sluznice. Tako je bil namen študije potrditi primerno neinvazivno metodo za ugotavljanje razjede sluznice zgornjega gastrointestinalnega trakta. V preliminarni študiji smo ocenili pomen scintigrafije s sukralfatom, ki smo ga označili z radioizotopom, pri ugotavljanju peptične razjede.

Bolniki in metode. Pri 35 bolnikih, ki so bili predhodno endoskopsko pregledani, smo naredili scintigrafijo s Tc-99m-DTPA sukralfatom. Bolniki so bili razdeljeni v 2 skupini: 20 jih je imelo endoskopsko potrjeno peptično razjedo, kontrolna skupina 15 bolnikov pa ni imela bolezni v zgornjem gastrointestinalnem traktu.

Rezultati. Pri uporabi nove klinične metode smo ugotovili, da je imela scintigrafija 75 % senzitivnosti in 100 % specifičnosti ter 85,7 % natančnosti.

Zaključki. Scintigrafija s Tc-99m-DTPA sukralfatom lahko predstavlja dodatno dopolnjujočo metodo pri rutinskem ugotavljanju sluzničnih razjed.

Radiol Oncol 2003; 37(1): 13-6.

Zanesljivost ultrazvočne preiskave v diagnostiki malih plevralnih izlivov

Kocijančič I

Izhodišča. Namen raziskave je bil opredeliti zanesljivost ultrazvočne preiskave plevralnega prostora v radiološki diagnostiki malih plevralnih izlivov.

Bolniki in metode. Pri bolnikih, ki so bili zaradi različnih vzrokov napoteni na ultrazvočne preiskave trebuha in/ali plevralnega prostora, sem iskal ultrazvočne značilnosti plevralnih izlivov. Med januarjem 1997 in januarjem 2000 sem v raziskavo vključil 69 bolnikov. Pri 52 bolnikih sem našel izliv, ki ni presegal debeline 15 mm; ostali so predstavljali kontrolno skupino. Takoj zatem smo vsem naredili rentgenske posnetke prsnih organov stoje v postero-anterioriorni smeri in leže na boku v fazi izdiha.

Rezultati. Pozitivna napovedna vrednost ultrazvočne preiskave plevralnega prostora v diagnostiki malih plevralnih izlivov je 92% primerjalno z radiološkima preiskavama. Povprečna debelina plašča tekočine je bila ultrazvočno 9,2 mm in 7,6 mm na posnetkih leže na boku v fazi izdiha ($P<0.01$).

Zaključki. Ultrazvočna preiskava plevralnega prostora kaže visoko stopnjo zanesljivosti v diagnostiki malih plevralnih izlivov in lahko ustrezno nadomesti rentgenske posnetke leže na boku.

Radiol Oncol 2003; 37(1): 17-22.

Ocena analnega sfinktra z endoluminalnim ultrazvokom in manometrijo pri bolnikih z anstomozo ilealnega žepa

Sudoł-Szopińska I, Ciesielski A, Bielecki K, Baczuk L, Jakubowski W, Tarnowski W

Izhodišča. Namen študije je bil primerjati endoluminalno ultrazvočno preiskavo analnega sfinktra in manometrijo pri bolnikih z anastomozo ilealnega žepa (IPAA).
Bolniki in metode. Deset bolnikov starih med 23 in 50 let, ki so bili operirani zaradi ulceroznega kolitisa, smo pregledali z endoluminalnim analnim ultrazvokom in manometrijo.
Rezultati. Endoluminalna analna ultrazvočna preiskava je prikazala nenormalno sliko notranjega analnega sfinktra pri 9 bolnikih (90%); defekte zunanjega analnega sfinktra in puborektalne mišice pa pri 4 bolnikih (40%). Korelacijo med endoluminalno ultrazvočno in manometrično oceno vseh ocenjevanih mišic smo našli pri 5 bolnikih (50%); obe metodi sta pri oceni zunanjega analnega sfinktra korelirali pri 4 bolnikih (40%), korelacije pa nismo našli le pri enem bolniku. Obe metodi sta korelirali pri polovici bolnikov (50%) pri oceni notranjega analnega sfinktra, korelacijo obeh metod pri oceni zunanjega analnega sfinktra in puborektalne dinamične aktivnosti pa smo našli pri 9 bolnikih (90%).
Zaključki. Endoluminalna analna ultrazvočna preiskava in manometrija omogočata oceno morfologije in funkcije analnih sfinktrov pri večini bolnikov z IPAA. Metodi kažeta visoko korelacijo med ocenami funkcije zunanjega analnega sfinktra (9 bolnikov; 90%), medtem, ko pri notranjem analnem sfinktru manometrija pogosto (5 bolnikov; 50%) ne potrdi ultrazvočno ugotovljene hibe.

Radiol Oncol 2003; 37(1): 53-60.

Radiol Oncol 2003; 37(1): 23-7.

Maligni limfom testisov

Berkmen F

Izhodišča. Namen študije je bil analizirati bolnike z malignim limfomov testisov, oceniti pomen imunocitokemičnega barvanja pri potrjevanju histološke diagnoze in ugotoviti učinkovitost zdravljenja.
Bolniki in metode. Pregledali smo podatke o desetih bolnikih z malignim limfomom testisov in ugotavljali incidenco bolezni, histološke značilnosti, način zdravljenja in potek bolezni po zdravljenju.
Rezultati. Med leti 1984 in 1999 smo ugotovili 10 bolnikov z malignim limfomov testisov. Tumor se je pojavil bilateralno simultano pri 4 bolnikih, metahrono pri 2, pri 2 pa kot ponovitev bolezni. Preostali 4 bolniki so imeli unilateralni tumor. Nobeden ni imel povišanih tomorskih markerjev AFP in β-HCG, pravtako niso imeli predhodnega kriptohizma. 8 bolnikov je bilo mlajših od 50 let. 5 bolnikov je imelo difuzni ne-Hodgkinov limfom visoke malignostne stopnje, 3 srednje in 2 bolnika nizke. Vsi bolniki so bili začetno zdravljeni z radikalno orhiektomijo in glede na klinični stadij bolezni tudi s kemo- in radioterapijo. 5 od 10 bolnikov je še živih, brez znakov bolezni od 9 do 62 mesecev sledenja bolezni. Preostalih 5 bolnikov je umrlo v 3 do 42 mesecih.
Zaključki. Maligni limfom testisov je klinično podobna bolezen kot germinalni tumor testisov ter predstavlja približno 5% vseh tumorjev testisv in 1% vseh limfomov. Od germinalniega tumorja testisov se razlikuje v naslednjih točkah: (1) Maligni limfom testisov se običajno pojavlja v srednjih letih, (2) tumorska markerja AFP in β-HCG sta v mejah normale, (3) izjemno redko se pojavi pri kriptohizmu, (4) potrebno je zgodnje sistemsko zdravljenje, samo skrbno sledenje bolnikov po kirurškem zdravljenju ni priporočljivo, (5) prognoza je slaba. Potrebno je uporabiti imunohistokemično barvanje (LCA) za potrditev histološke diagnoze, kar omogoča načrtovanje ustreznega zdravljenja.

Radiol Oncol 2003; 37(1): 29-35.

Urokinazni plazminogenski aktivator in njegova inhibitorja PAI-1 in PAI-2 pri primarnem kožnem melanomu

Markovič J, Štabuc B

Izhodišča. Ugotavljali smo razlike v koncentracijah urokinaznega plazminogenskega aktivatorja (uPA) in njegovih inhibitorjev tipa 1 in 2 (PAI-1/2) v klinično sumljivih nevusih, primarnem kožnem melanomu in zdravi koži v okolici ter korelacije s histopatološkimi napovednimi dejavniki primarnega melanoma.

Bolniki in metode. Vključili smo 51 bolnikov. Tkivne koncentracije uPA, PAI-1 in PAI-2 smo merili z encimskoimunsko metodo (ELISA).

Rezultati. Povprečne koncentracije uPA in PAI-1 v melanomih so bile višje kot v zdravi koži (uPA: 1,08; vs. 0,48 ng/mgp; PAI-1: 14,07 vs. 2,07 ng/mgp; $p < 0,001$). Koncentracije uPA in PAI-1 so bile višje v melanomih kot v nevusih in višje v nevusih kot v zdravi koži ($p > 0,05$). Koncentracija PAI-2 je bila višja v zdravi koži kot v nevusih in melanomih ($p > 0,05$). Koncentracije uPA, PAI-1 in PAI-2 v melanomih so statistično značilno korelirale s koncentracijami v zdravi koži ($r = 0,73; 0,54; 0,38$). Koncentracije PAI-1 so bile statistično značilno nižje v melanomih debeline po Breslowu ≤ 0,75 mm, invazije po Clarku 0+I, z odsotno mikroskopsko ulceracijo, z odsotno vaskularno invazijo ($p < 0,01$) kot v melanomih debeline po Breslowu > 0,75 mm, invazije po Clarku > II, s prisotno mikroskopsko ulceracijo, s prisotno vaskularno invazijo.

Zaključki. Z določitvijo uPA in PAI-1 lahko dobimo pomemben dodaten podatek o prognozi bolnikov z melanomom.

Radiol Oncol 2003; 37(1): 37-42.

Rak dojke na Češkem

Hodačová L

Izhodišča. Na Češkem so maligne novotvorbe eden od najštevilnejših vzrokov obolevnosti in smrtnosti prebivalstva kot tudi pokazateljev njihovega zdravstvenega stanja. Od konca leta 1950 jih registrira vsedržavni Inštitut za zdravstveno informatiko in statistiko, s katerim sodeluje Svet registra raka Češke, ki registracijo načrtuje in vodi. Zadnjih 20 let posebno skrbno spremljajo 5 najbolj pogostih malignih obolenj pri moških in 7 pri ženskah. Pri ženskah je najpogostejše maligno obolenje rak dojke.

Zaključki. Rak dojke je v opazovanih letih narasel za 75%. V letu 2001 so izvedli v celotni državi 3 pilotske raziskave s preventivnim mamografskim presejalnim testom. Odkritje enega primera bolnice z asimptomatskim rakom dojke je stalo od 80.000 do 120.000 čeških kron, kar je znatno manj kot stane zdravljenje bolnice z napredovalim rakom dojke.

Radiol Oncol 2003; 37(1): 43-8.

Učinki elektrokemoterapije na pretok krvi v tumorjih in njeni možni mehanizmi delovanja ciljani na žilje tumorja

Serša G, Čemažar M, Miklavčič D

Izhodišča. Namen naše raziskave je bil določiti vplive elektrokemoterapije s cisplatinom ali bleomicinom na pretok krvi v tumorjih in določiti njene možne mehanizme delovanja ciljane na žilje tumorja.

Materiali in metode. Elektrokemoterapija je kombinirano zdravljenje sistemskega vbrizganja bleomicina in cisplatina nato pa sledi lokalna aplikacija električnih pulzov na tumor. V študiji smo ovrednotili protitumorski učinek elektrokemoterapije z merjenjem velikosti tumorjev, učinek na pretok krvi v tumorjih z barvanjem tumorjev s Patentnim modrilom ter občutljivost endotelnih celic na citostatika in elektrokemoterapijo z merjenjem preživetja celic.

Rezultati. Elektrokemoterapija je imela učinkovito protitumorsko delovanje, povzročila je velik zaostanek v rasti tumorjev, nekateri tumorji so bili celo pozdravljeni. Zmanjšanje pretoka krvi v tumorjih je sovpadalo s protitumorsko učinkovitostjo elektrokemoterapije. Zaznali smo skoraj popoln zastoj pretoka krvi v tumorjih že po 24 urah po elektrokemoterapiji z bleomicinom, medtem ko je elektrokemoterapija s cisplatinom povzročila samo 50% zmanjšanje pretoka krvi v tumorjih. Občutljivost humanih endotelnih celic HMEC-1 na elektrokemoterapijo nakazuje ciljano delovanje te terapije na žilje tumorja in vivo.

Zaključki. Podatki kažejo, da je v protitumorskem delovanju elektrokemoterapije udeleženih več mehanizmov. Poleg povečanega dostavljanja kemoterapevtikov v tumorske celice z elektroporacijo, elektrokemoterapija tudi zmanjša prekrvavitev tumorjev. Ta mehanizem je verjetno posredovan s smrtjo endotelnih celic, kar prav tako posredno povzroča smrt tumorskih celic.

Notices

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

Biomedicine

April 2-4, 2003

The »5th International Conference on Simulations in Biomedicine« will be offered in Ljubljana, Slovenia.

Contact Ms. Gabriella Cossutta, Conference Secretariat, Biomedicine 2003, Wessex Institute of Technology, Ashurst Lodge, Ashurst, Southampton, SO40 7AA, UK; or call +44 238 029 3232; or fax +44 238 029 2853; or e-mail gcossutta@wessex.ac.uk; or see http://www.wessex.ac.uk/conferences/2003/biomed03

Breast cancer

April 9-11, 2003

The ESO course »Evidence Based Management of Breast Cancer« will take place in Sarajevo, Bosnia and Herzegovina.

Contact Institute of Oncology, Clinical Center University of Sarajevo, Bolnicka 25, 71 000 Sarajevo Bosnia & Herzegovina; or fax +387 33 213 519; or e-mail onkokcus@bih.net.ba

Melanoma

May 2-5, 2003

The1st Mediterranean Melanoma Meeting will take place in Greece.

Contact Secretariat, Panos Travel Ltd., 4 Filellinon str., Athens - 10557, Greece; or call +30 10 3230380; or fax +30 10 3245049.

Gastric cancer

May 4-7, 2003

The 5th International Gastric Cancer Congress will be offered in Roma, Italy.

Contact Alfredo Garofalo, ARC - IGCC Scientific Secretariat, Via A. Borelli, 5, Roma - 00161, Italy; or call +39 6 55180577.

Radiation oncology

May 4-8, 2003

The ESTRO teaching course »Radiation Oncology: a Molecular Approach« will take place in Tenerife, Spain.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiotherapy

May 6-10, 2003

The ESTRO teaching course »Dose Determination in Radiotherapy: Beam Characterisation, Dose calculation and Dose Verification« will be held in Barcelona, Spain.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Brachytherapy

May 15-17, 2003

The Annual Brachytherapy Meeting GEC-ESTRO will take place in Luebeck, Germany.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Cancer epidemiology

May 18-22, 2003

The International Course on Advances in Cancer Epidemiology will take place in Rovigo, Italy.

Contact Secretariat, Olaf Kelm, International Agency for Research on Cancer (IARC), 150, cours Albert Thomas, Lyon - 69008, France; or call +33 4 72 73 81 54; fax +33 4 72 73 83 20.

Lung Cancer

May 22-24, 2003

The international conference on lung cancer »Lug Cancer, Standards and New Trends« will take place in Vilnius, Lithuania.

Contact Secretariat, Institute of Oncology, Vilnius University, Santariškiu 1, 2021 Vilnius, Lithuania; or phone +370 5 278 67 00 / 03; or fax +370 5 272 01 64; or e-mail sekretoriatas@loc.lt

Radiotherapy

May 25-29, 2003

The ESTRO teaching course »Physics for Clinical Radiotherapy« will be offered in St. Petersburg, Russia.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiology

May 28-31, 2003

The 83rd Congress of the German Radiologists will take place in Weisbaden, Germany.

Contact Secretariat, German Radiologists, Dt Roentgengesellschaft eV, Postfach 1336, D-61283 Bad Homburg, Germany; or fax +49 6172 488 587.

Clinical oncology

May 31 - June 3, 2003

The »39th ASCO Annual Meeting« will take place in Chicago, Illinois, USA.

Call ASCO Member Services at +1 888 282 2552 or +1 703 299 0158; or e-mail info@asco.org; or see http://www.asco.org

Radiobiology

June 1-3, 2003

The 2nd ESTRO workshop on biology in radiation oncology will be offered in Berg en Dal / Nijmegen, the Netherlands.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiotherapy

June 8-12, 2003

The ESTRO teaching course »Imaging for Target Volume Determination in Radiotherapy« will be held in Nice, France.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Allergology and clinical immunology

June 7-11, 2003

The »22nd Congress of the European Academy of Allergology and Clinical Immunology« will take place in Paris, France.

Contact Congrex Sweden AB, Attn: EAACI 2003, Linnegatan 89A, P.O. Box 5619, SE-114 86 Stockholm, Sweden, or call +46 8 459 66 00; or fax +46 8 661 91 25; or e-mail eaaci2003@congrex.se; or see http://www.eaaci.org

Paediatric radiation oncology

June 18-20, 2003

The »First International Congress of Pediatric Radiation Oncology« will take place in Lyon, France.

Contact Thomas Garmier, Package Organisation, 140, Cours Chalemagne, 69002 Lyon, France; or call +33 4 72 77 45 50; or fax +33 4 72 77 45 77; or e-mail package@package.fr

Radiotherapy

June 22-26, 2003

The ESTRO teaching course »IMRT and other Conformal Techniques in Practice« will be held in Amsterdam, the Netherlands.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Small Cell Lung Cancer

June 25-28, 2003

The »4th IASLC Workshop on Small Cell Lug Cancer« will take place in Helsingor, Denmark.

Contact Dr. Heine H. Hansen, The Finsen Center, 5072, The National University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; or phone +45 3545 4090; or fax +45 3535 6906; or e-mail 4th-sclc@iaslc.org

Oncology

August 3-8, 2003

The »12th World Conference on Tobacco or Health« will be offered in Helsinki, Finland.

Contact Ms. Aira Raudesoja, CongCreator CC Ltd., P.O. Box 762, FIN-00101 Helsinki, Finland; or call +358 9 454 2190; or fax +358 9 4542 1930; or e-mail secretariat@congcreator.com

Lung cancer

August 10-14, 2003

The »10th World Conference of the International Association for the Study of Lung Cancer« will be offered in Vancouver, Canada.

Contact 10th World Conference of Lung Cancer, c/o International Conference Services, 604-850 West Hastings, Vancouver BC Canada V6C 1E1, or call +1 604 681 2153; or fax +1 604 681 1049; or e-mail conference@2003worldlungcancer.org

Prostate cancer

August 31 - September 2, 2003

The ESTRO teaching course »Brachytherapy for prostate Cancer« will take place in Kiel, Germany.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiotherapy

August 31 - September 4, 2003

The ESTRO teaching course »Physics for Clinical Radiotherapy« will be held in Leuven, Belgium.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Cancer immunology and immunotherapy

September 8-13, 2003

The European cancer immunology and immunotherapy summer school will be offered in Ionian Village, West Coast of the Peloponese, Greece.

Contact Dr. M. Papamichail, Center for Immunology, St. Savas Cancer Hospital, 171, Alexandras Ave, Athens 115 22, Greece; or call +30-210-6409 624/5; or fax +30-210-6409 516; or e-mail papmail@netor.gr

Radiotherapy

September 13-18, 2003

The 7th Biennial ESTRO Meeting on Physics for Clinical Radiotherapy / ESTRO Meeting on Radiation Technology for Clinical Radiotherapy will take place in Geneva, Switzerland.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Oncology

September 21-25, 2003

The ESTRO 22 / ECCO 12 Meeting will take place in Copenhagen, Denmark.

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

Radiobiology

October 12-16, 2003

The ESTRO teaching course »Basic Clinical Radiobiology« will be offered in Santorini, Greece.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http://www.estro.be

Radiation therapy

October 19-23, 2003

ASTRO Annual meeting will be held in Salt Lake City, Utah, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; or see http://www.astro.org

Radiation oncology

November 9-14, 2003

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

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http:// www.estro.be

Radiation oncology

March, 2004

The ISRO international teaching course on »Radiation Oncology in the 21st Century« will take place in Cape Town, South Africa.

See http://www.isro.be

Surgical oncology

March 31 - April 3, 2004

The 12th ESSO Congress will be held in Budapest, Hungary.

See http://www.fecs.be/conferences/esso2004

Oncology

April 15-17, 2004

The European Oncology Nursing Society EONS Spring Convention will be held in Edinburg, UK.

See http://www.fecs.be/conferences/eons4

Brachytherapy

May 13-15, 2004

The Annual Brachytherapy Meeting GEC-ESTRO will take place in Barcelona, Spain.

Contact ESTRO office, Avenue E. Mounier, 83/12, B-1200 Brussels, Belgium; or call +32 775 93 40; or fax +32 2 779 54 94; or e-mail info@estro.be; or see http:// www.estro.be

Oncology

July 3-6, 2004

The 18th EACR (European Association for Cancer Research) Congress will be held in Innsbruck, Austria.

See http://www.fecs.be/conferences/eacr18

Paediatric oncology

September, 2004

The International Society of Paediatric Oncology - SIOP Annual Meeting will be held in Oslo, Norway.

See http://www.siop.nl

Lung cancer

September 23-25, 2004

The »9th Central European Lung Cancer Conference« will be offered in Gdansk, Poland.

Contact Conference Secretariat, »9th Central European Lung Cancer Conference«, Via Medica, ul. Swietokrzyska 73, 80 180, Gdansk, Poland; or call/fax +48 58 349 2270; or e-mail celcc@amg.gda.pl; or see www.lungcancer.pl

Radiation therapy

October 3-7, 2004

ASTRO Annual meeting will be held in Atlanta, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; or see http:// www.astro.org

Therapeutic radiology and oncology

October 24-28, 2004

The 23rd ESTRO Meeting will be held in Amsterdam, the Netherlands.

Contact ESTRO 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. estro.be

Medical oncology

October 29 - November 2, 2004

The 28th ESMO Congress will be held in Vienna, Austria.

See http://www.esmo.org

Radiation oncology

November 25-28, 2004

The ISRO international teaching course on »Practical Radiation and Molecular Biology with Mayor Emphasis on Clinical Application« will take place in Chiangmai Thailand.

See http://www.isro.be

Radiation oncology

March, 2005

The ISRO international teaching course on »Palliative Care in Cancer Treatment« will take place in Dar es Salaam, Tanzania.

See http://www.isro.be

Radiation oncology

September - October, 2005

The ISRO international teaching course on »Rational Developments from developing to developed Contries« will take place in Lombok, Indonesia.

See http://www.isro.be

Oncology

October 30 - November 3, 2005

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

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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – A Report for the First Quarter of 2003

The members of the "Docent Dr. L. Cholewa Foundation for Cancer Research and Education" found themselves at a need to reflect their past activities following the untimely death of Professor Vinko Kambič, one of its founding members, one of the most prominent figures in medicine and public life in general in Slovenia in the last decades, a leading world expert in otology, and a member of the Slovenian Academy of Sciences and Arts.

The "Docent Dr. L. Cholewa Foundation for Cancer Research and Education" started its activity approximately ten years ago with the intention to support all the interested experts in cancer research and other activities associated with oncology, in order to enhance the success of their work with the final goal of transmitting the latest diagnostic and therapy methods to the everyday research and clinical life and environment in Slovenia. Especially the latest is regarded as the most direct benefit for the ever increasing number of patients with various types of cancer in Slovenia, since the incidence rates of many cancers have kept raising in the recent years in this country. It was Professor Kambič's view that research is a difficult, complicated and demanding intellectual activity, and that natural inquisitiveness and curiosity, persistence and acquired knowledge usually are not enough. High quality research also demands a lot of money and many excellent ideas cannot be carried into effect for the simple lack of it. In many developed countries with extensive research capabilities, especially in medicine, the researchers can often count on financial assistance in the form of grants and stipends, provided by an ever growing number of funds and foundations. These institutions play an important role in material support of many scientists involved in cancer research, cancer education and in many of the related fields.

At the suggestion of Professor Kambič the fledgling Foundation was named after Dr. Josip Cholewa ten years ago, one of the first researchers in cancer on the territory of Slovenia and the founder of the "Banovinski Inštitut za raziskovanje in zdravljenje novotvorb", that later became the Institute of Oncology in Ljubljana, Slovenia. It is worth noting that Dr. Cholewa already in the early twenties of the 20th century, as a Head Physician in Brežice General Hospital, established a laboratory for cancer research. His research was based on a timeless principle of intersectorial approach to prevention, detection and treatment of cancer, where doctors with various specializations collaborate and constantly exchange news and views.

Professor Kambič was active in the "Docent Dr. L Cholewa Foundation for Cancer Research and Education" in the capacity of the President of the Supervisory Board and as a President of the Commission for grant allocation. His expert knowledge, experience, honesty and intuition represented major assets for the Foundation, and his relentless activity made the Foundation a known entity in Slovenia and abroad.

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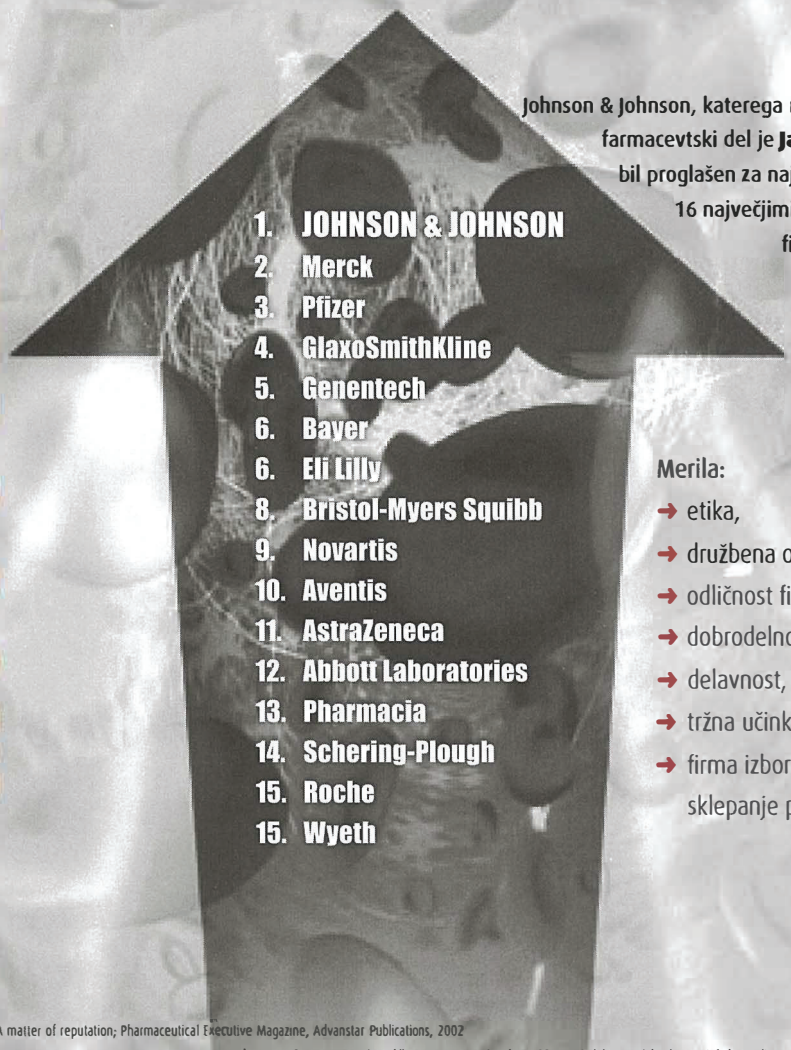

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Bolniki s kronično ledvično odpovedjo na hemodializi: Zdravilo injicirajte i.v. Ciljna koncentracija Hb: 10-12 g/dl pri odraslih in 9,5-11 g/dl pri otrocih. Odmerek povečajte, če se koncentracija Hb ne poveča za najmanj 1 g/dl na mesec. Faza korekcije: 50 i.e./kg trikrat na teden, i.v. Odmerek prilagajamo postopno, za 25 i.e./kg, trikrat na teden. Faza vzdrževalnega zdravljenja v vzdržujemo ciljno koncentracijo Hb. Odrasli bolniki z zmanjšanim ledvičnim delovanjem, ki se še ne zdravijo z dializo Faza korekcije: 50 i.e./kg trikrat na teden, i.v. Odmerek prilagajamo postopno, za 25 i.e./kg, trikrat na teden. Faza vzdrževalnega zdravljenja: vzdržujemo koncentracijo Hb 10 - 12 g/dl.
Odrasli bolniki z rakom, ki se zdravijo s kemoterapijo: Začetni odmerek je 150 i.e./kg, 3-krat na teden, s.c. Odmerek prilagodimo na osnovi spremembe koncentracije Hb in št. retikulocitov.
Kontraindikacije: Nenadzorovana arterijska hipertenzija, preobčutljivost za katero od sestavin zdravila, kontraindikacije v povezavi s programom avtologonega zbiranja krvi. Subkutano injiciranje pri bolnikih s kronično odpovedjo ledvic. Bolniki, pri katerih se med zdravljenjem z epoetinom pojavi čista aplazija eritrocitne vrste, bolniki s hudo koronarno, cerebrovaskularno, karotidno ali periferno arterijsko boleznijo, po nedavno prebolelem miokardnem infarktu ali cerebrovaskularnem inzultu pri katerih je predviden večji neurgenten ortopedski kirurški poseg in niso vključeni v program avtologonega zbiranja krvi, bolniki, ki iz kateregakoli razloga ne morejo prejemati ustrezne tromboprofilakse.
Neželeni učinki: Predvsem na začetku zdravljenja se lahko pojavijo gripi podobni simptomi. Poročali so o nespecifičnem kožnem izpuščaju in trombocitozi, ki je zelo redka. Najpogosteje se pojavi od odmerka odvisno zvišanje krvnega tlaka ali poslabšanje že obstoječe hipertenzije. Lahko se pojavi hipertenzivna kriza s simptomi, podobnimi encefalopatiji in generalizirani tonično-klonični krči. Pojavijo se lahko tromboze fistul. Pri bolnikih s kronično ledvično odpovedjo so po več mesecih ali letih zdravljenja z Eprex-om ali drugimi eritropoetini, v zelo redkih primerih poročali o eritroblastopeniji.
Posebna navodila za shranjevanje: Shranjujte zaščiteno pred svetlobo, pri temperaturi od 2° do 8 °C. Zdravila ne zamrzujte ali stresajte.

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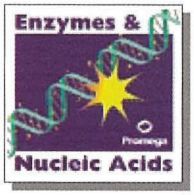

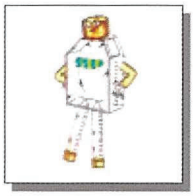

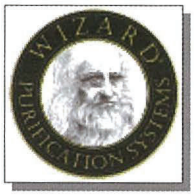

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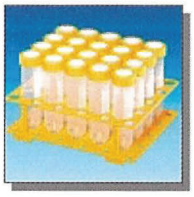

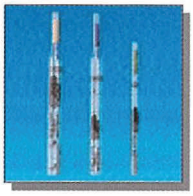

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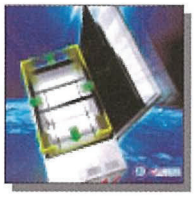

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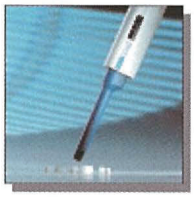

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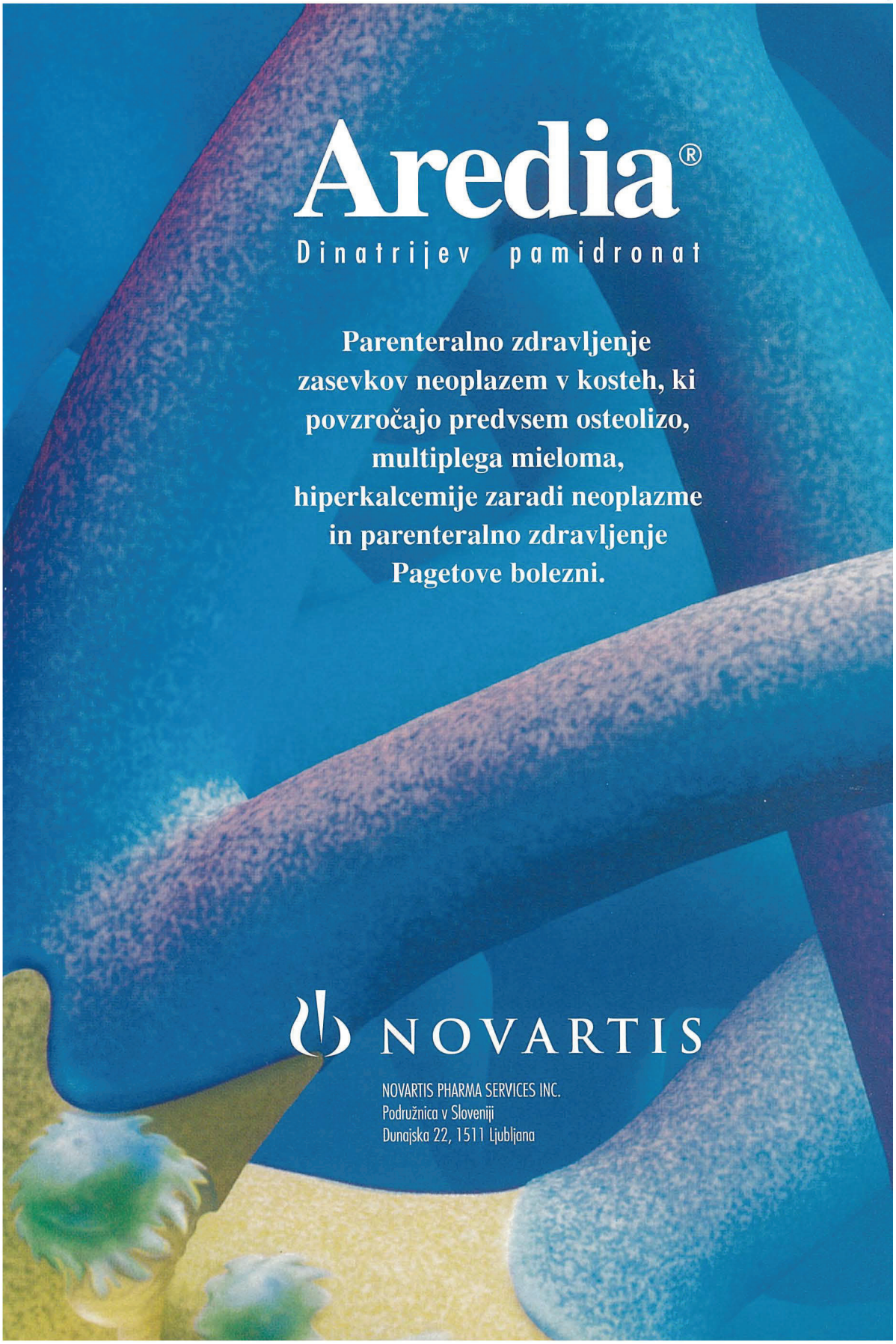
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