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CONTENTS

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

Radiol Oncol 2000; 34(4): 319-24.

Magnetic resonance cholangiography in patients with bile duct obstruction

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Background. *The aim of this study was to assess the diagnostic value of magnetic resonance cholangiography (MRC). This is a new non-invasive imaging technique for the evaluation of bile duct obstruction.*
Patients and method. *MRC was performed on patients with bile duct obstruction at 1.0 T U. Over a period of 26 months, 44 patients, 23 males and 21 females, mean age 51years, were examined. The basis were T2-weighted sequences through the liver to accentuate the fluid fill bile duct, and fast spin echo sequences. Usually, the thickness of the slices was 4 mm. Two spatial planes were performed, coronal and axial, with the breath held and released, and with maximum intensity projection (MIP) reconstruction. In our case, with Machine 1.0T, we compared the results of ultrasound and CT with MRC in the patients with bile duct obstruction before surgical intervention or drainage procedure.*
Results. *We examined 44 patients with jaundice by MRC and with the 100% accuracy identified the level of the obstruction. Clinical applications of MRC were evaluated on the basis of personal experience, and data literature. The main indication for MRC study was the evaluation of common bile duct obstruction without using contrast medium and biliary intervention.*
Conclusions. *MR technique has been dictated by image performance and sequence availability. Our experience and results confirmed that MRI is more accurate than US and CT in patients with bile duct obstruction.*

Key words: cholestasis-diagnosis; magnetic resonance imaging; bile ducts neoplasms; cholelithiasis,

Introduction

Current non-invasive imaging techniques, such as ultrasound (US) and computerized tomography (CT), have a limited potential in diagnosing biliary duct disorders. As a result, many patients with suspected biliary duct disorders undergo more invasive diagnostic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC).

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Those procedures have low, yet significant morbidity and mortality.[1] Magnetic resonance cholangiography (MRC) techniques can be an alternative to non- invasive methods of imaging of the biliary duct.[2] The techniques developed over the past 5 years have a diagnostic performance comparable to diagnostic ERCP and are being utilized clinically in the management of the biliary and pancreatic disease.[3,4] The interpretation involves the review of typically maximum intensity projection (MIP) after the processing of the volume data to allow a 3 D visualization of the biliary anatomy. An alternative approach which utilizes a projection technique allowing rapid assessment of the biliary and pancreatic duct systems without the need for post processing has been proposed.[5] RARE (Rapid Acquisition with Relaxation Enhancement) technique requires a long effective echo time of 750 - 1000 ms with the imaging contrast obtained by fluid alone, the so-called MR hydrography.[6]

Patients and methods

The MRC technique is based on heavily T2 weighted images which yields a remarkable increase in contrast between stationary fluids (bile) and background (hepatic parenchyma, abdominal fat). As a result, the bile presents a very high signal intensity compared with low signal intensity background. At our Institute, MRC examinations were performed by 1.0T super conductive magnet with body coil. We used T2 weighted images, fat suppressed (FS), turbo spin echo (TSE) axial sequences. Imaging parameters modified during the past two years experiences were as follows: TR - 3500ms, TE - 99ms. Images were acquired on the coronal plane with 4 mm partition thickness, with the breath held. The imaging volume was positioned to the bile duct using axial sequences as scout view. FOV was 380 mm. Image matrix size was 256 x 256. We used MIP reconstruction techniques (scan time 4min 43 sec). No patient preparation and sedation are required.

In 26 months, 44 patients were examined. The MRC was performed in the patients with bile duct obstruction. Our group of 44 patients included 23 males and 21 females, mean age 51.

Analysis

In each case, the investigators evaluated MRC (Figure 1) irrespective of the presence or absence of obstruction, the level and suspected cause of obstruction. Later, MRC findings were compared with the findings of US and CT that were made for all our patients before MRC.

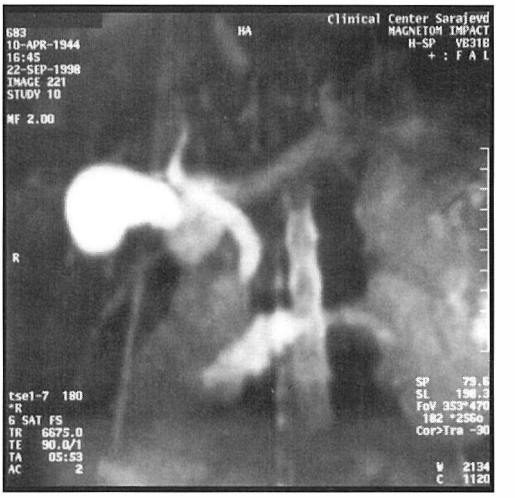

Figure 1. Normal anatomy on MIP reconstructed magnetic resonance cholangiography (MRC) images.

Results

In 44 patients, biliary obstruction represents the main indication for MRC study because of the potential of this technique to assess the presence, site and cause of the obstruction. All our patients had US and CT examination before MRC (Table 1).

Table 1. The MRC in biliary obstruction compare with US/CT

Finding	US/CT	MRC
Benign and malignant biliary strictures	4	6
Choledocholithiasis	6	8
Choledochoduodenal anastomosis with stones	0	2
Hilar lymphadenopathy, Tu hepatis	4	5
Cholangiocarcinoma	6	8
Pancreatic head carcinoma	14	15
Biliary tree dilatation - icterus	10	0
Total	44	44

In 6 patients, MRC revealed benign or malignant biliary stricture (Figure 2), in 8 choledocholithiasis (Figure 3), in 3 choledocholithiasis with choledochoduodenal anastomosis (Figure 4), in 5 hilar lymphadenopathy

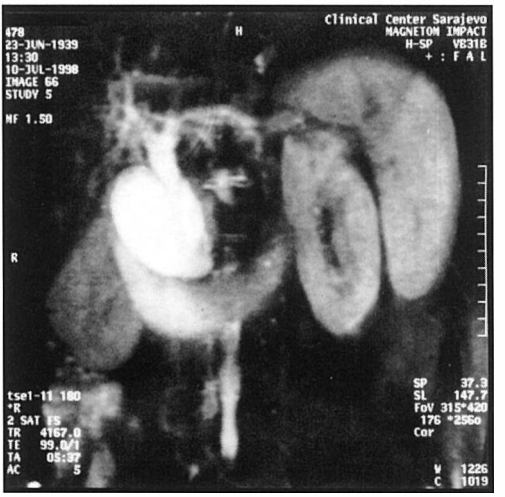

Figure 2. Common bile duct (CBD) is dilated with distal malignant stenosis.

and tumor hepatis (Figure 5), in 8 cholangiocarcinoma (Figures 6a and 6b.), and in 15 pancreatic head carcinoma (Figures 7a and 7 b).

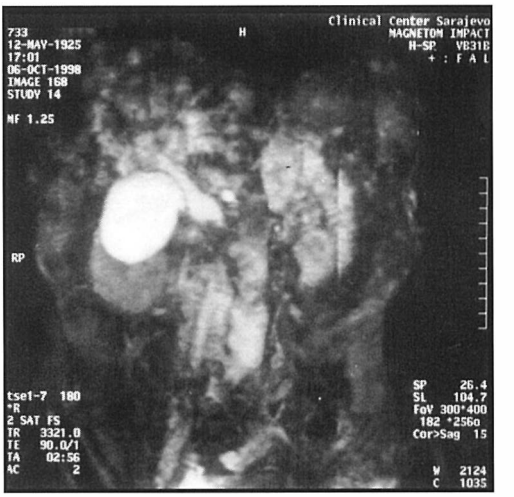

Figure 3. Maximum intensity projection (MIP) reconstructed MRC complete obstruction CBD with marked dilatation of the intrahepatic ducts and filling defects at the distal level of calculus.

Discussion

Biliary obstruction represents the main indication for MRC. The potential of this technique is to identify the presence, site, and cause of the obstruction. The accuracy in detecting the presence of the obstruction

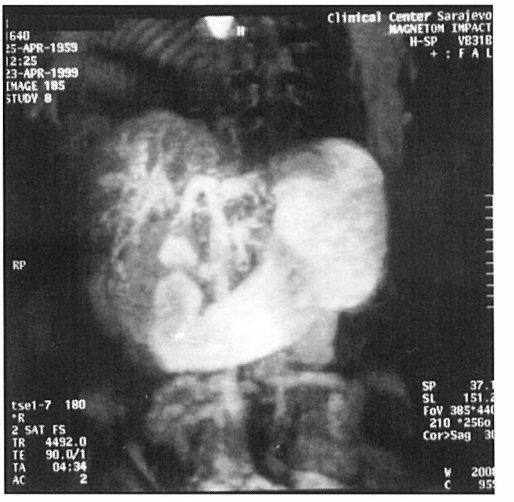

Figure 4. MIP reconstructed MRC complete obstruction CBD at the level of choledochoduodenal anastomosis, with remaining calculus.

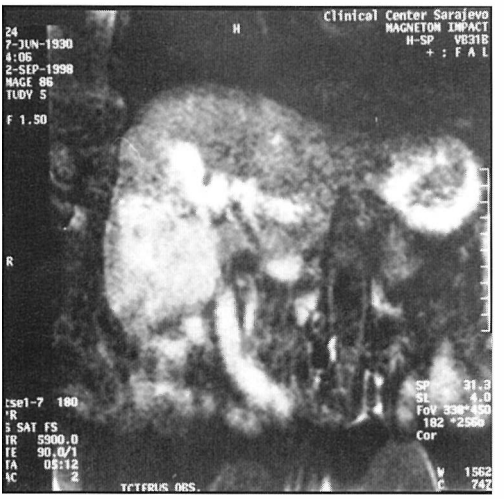

Figure 5. Liver tumor with the subsequent obstruction and intrahepatic biliary dilatation.

ranges between 91 - 100 % whereas the level of the obstruction can be correctly evaluated in 85 - 100 % of cases.[7,8]

We examined 44 patients with jaundice and determined the level and cause of obstruction by MRC with 100 % and 86 % accuracy. The typical cholangiographic appearance of pancreatic head carcinoma is represented by a sudden obstruction at the level of the head of the pancreas with a double duct sign due to biliary and pancreatic duct dilatation and evidence of mass effect. Usually, the obstruction, due to pancreatic cancer, is seen as "mouse tail" pattern or with a sudden reduction of the caliber of bile duct. In case of pancreatitis, the bile duct stenosis has a tapered aspect.[9]

The role of imaging modalities in cholangiocarcinoma is to identify the lesion, its stage, and, if unresectable, to plan the adequate palliative treatment. Cholangiocarcinoma may be presented as a stricture, involving CBD (30 - 36%), the common hepatic duct (15 - 30%), the biliary bifurcation with the typical aspect of mass lesion, or as a nodular process with intrahepatic solid mass.

MRC can provide a dilated map of the biliary tree above the stricture. Conventional MR images are needed for correct lesion identification and staging. In this case, T1weighted image, after contrast medium injection, can be very helpful for a correct identification of the lesion and of its relation with surrounding organs, even in the case of stenosing lesion.[9] The evaluation of the strictures by MRC usually depends on the morphology and

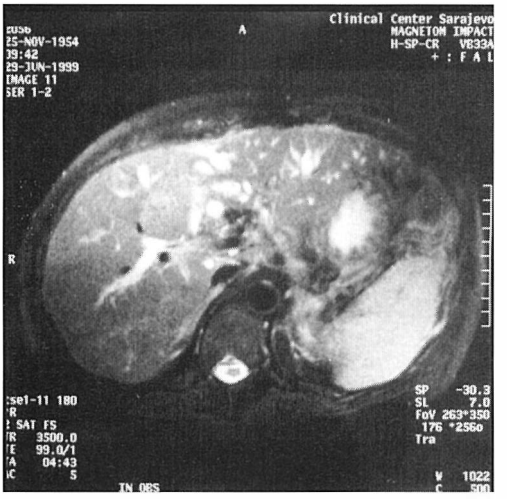

Figure 6a. Hilar cholangiocarcinoma with the marked dilatation of the intrahepatic duct; T2 weighted turbo spin echo (TSE).

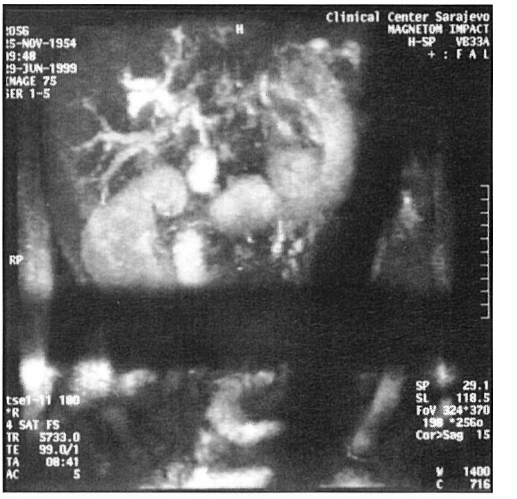

Figure 6b. Hilar cholangiocarcinoma with the marked dilatation of the intrahepatic duct; MIP reconstruction.

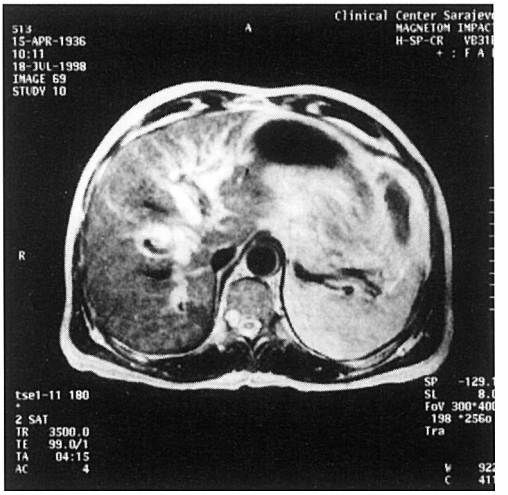

Figure 7a. Dilated bile duct - malignant obstruction due to pancreatic head carcinoma; axial T2 weighted.

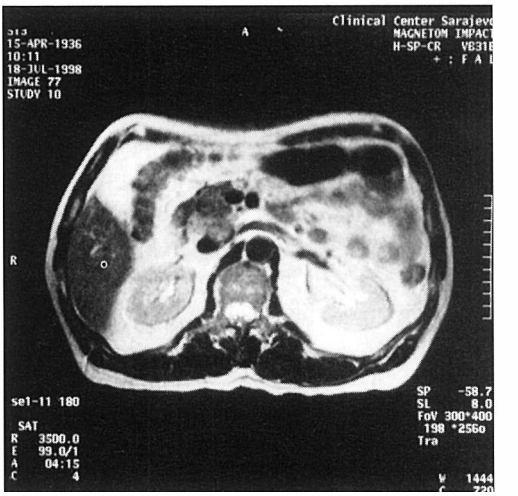

Figure 7b. Dilated bile duct - malignant obstruction due to pancreatic head carcinoma.

length of strictures. MRC in malignant strictures has to be considered as a part of complete abdominal evaluation, together with conventional MR images. Therefore, the role of MR images is to diagnose the obstruction, to define its cause, and to provide any additional information for CT and ERCP and that would require a change of the treatment plan.[9] In the study of 79 patients with biliary obstruction, the sensitivity and specificity of the MR diagnose of malignant obstruction were 86 and 98%, respectively.[10] Choledocholithiasis, irrespective of calcium content, almost always presents with low signal intensity on MR images.[10] Therefore, the stone is identified as round or oval "filling defect" within the CBD, surrounded by the high signal intensity bile. The diagnostic accuracy of MRC in the choledocholithiasis is very high, ranging between 89 and 97%.[11-14]

Nevertheless, different pitfalls can be observed which require a correct identification in order to avoid false diagnosis. They are represented by (a) artefacts on MIP reconstructed images, (b) CBD completely filled with stones, (c) pneumobilia, and (d) differential diagnosis between air bubbles and small stones. Secondary biliary involvement can be caused by hilar lymphadenopathies, or hepatic metastases with the occlusion of segmental or subsegmental branches. In these cases MRC, can show the intrahepatic duct dilatation and the level of the intrahepatic hilar or subhilar occlusion. MRC displays the biliary map with the evaluation of dilated segments that may require percutaneous drainage.[9]

The role of MRC in the diagnostic algorithm of the patients with biliary - enteric anastomosis is to avoid unnecessary invasive imaging modalities.[14,15] In the patients with hepaticojejuno-stomy, only PTC may be performed while MRC can also serve as a screening method for patients requiring treatment or as further evaluation with PTC or ERCP. MRC may also be used as a guide for a subsequent interventional procedure. Only 3 patients who had previously undergone biliary surgery and choledochoduodenostomy were included into our study.

Conclusion

The dilatation of the biliary tree due to tumor, stones or stricture was depicted with

excellent contrast resolution. It is know from literature that MRC technique has been dictated, to some extent, by the image performance and sequences availability. MRC can provide non-invasive comparable diagnostic information for the diagnostic ERCP of biliary disorders and may allow selective use of therapeutic ERCP. Sometimes MRC, together with conventional MR images, may replace CT and ERCP in pre-surgical evaluation of patients.

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Radiol Oncol 2000; 34(4): 325-9.

Duplex-Doppler ultrasound evaluation of intrapancreatic blood flow in patients with insulin-dependent diabetes mellitus

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Background. *The purpose of the study was to assess the value of pulse-wave and color-Doppler ultrasound (CDUS) in estimation of the pancreatic blood flow, and to test the hypothesis that accelerated atherosclerosis in insulin-dependent diabetes mellitus (IDDM) causes an increased vascular resistance.*

Patients and methods. *Gastroduodenal arteries in 40 patients with IDDM and 30 healthy volunteers were insonated, and resistance index (RI) and pulsatility index (PI) were assessed. The statistical significance of the difference between Doppler indices among examined groups, as well as the correlation with the age, sex and duration of the disease were tested.*

Results. *In the control group, median RI was 0.71 and median PI was 1.46. In IDDM patients group median RI was 0.74 and median PI was 1.54. The differences between these Doppler indices were not significant, with a p=0.82 for RI, and p=0.74 for PI. Also, no significant correlation was observed between RI and PI and the duration of the disease.*

Conclusions. *CDUS is simple noninvasive imaging modality for the estimation of blood flow in the gastroduodenal artery, which, in our work, did not prove to be of particular value in the assessment of pancreatic flow in IDDM patients.*

Key words: diabetes mellitus, insulin-dependent; pancreas-blood supply- ultrasonography; Doppler, duplex

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Introduction

Pulse-wave color-Doppler flow imaging enables examination of blood flow in almost all vessels, with the superb ability to position sample volume in as small vessel as is gastroduodenal artery. The flow spectrum of the superior mesenteric artery (SMA) before a meal is typical for high-resistant bed, with short protodiastolic reverse flow and small diastolic run-off. After a meal, the spectra in SMA and in celiac axis are similar, triphasic,

without diastolic reverse flow.[1-3] The persistence of flow in diastole is the consequence of low distal vascular impedance of the receiving hepatic circulation. As the blood reaches the more distal branches of smaller size, the "systolic window" is being filled. The spectrum of the gastroduodenal artery reflects its slow flow with parabolic velocity profile.[2] In such a small vessel, vascular resistance is critical for the whole intraluminal range of velocities; hence, small changes in vascular resistance sensitively influence Doppler indexes. The atherosclerotic process, that is by its nature vessel-obstructing, is undoubtedly accelerated in the patients with insulin-dependent diabetes mellitus (IDDM) in comparison to non-diabetic patients. We wished to examine its consequences in the pancreas expecting an increased vascular resistance.

The purposes of our work were: (a) to evaluate usefulness of pulse-wave and color-Doppler in the assessment of flow in the gastroduodenal artery and its branches; (b) to determine RI and PI values in the group of IDDM patients and in control group of healthy volunteers; (c) to compare Doppler indices between these groups and (d) to determine the correlation between the duration of IDDM and age with Doppler indices.

Patients and methods

In the period from January 1996 to June 1997, 70 persons, 40 patients with IDDM and 30 healthy controls, were examined. The age ranged from 18 to 44 years (mean 30.3±7.2), and male/female ratio was 32/38.

Forty patients (17 males/23 females), aged from 18 to 44 years (mean 31.1±7.6), had IDDM of mean duration of 10.6±8.4 years. All patients were hospitalized because of the necessity for the regulation of glicaemia and were under medical control for at least seven days. Inclusion criteria were: the absence of endogenous insulin secretion on the basis of insulin and C-peptide level follow-up, the absence of other diseases of pancreas, the absence of heart diseases, and the blood pressure before the examination below 140/90 mm Hg.

In the control group, 30 healthy volunteers, predominantly medical staff, with an equal number of males and females, were observed. The inclusion criteria were absence of the diabetes mellitus and glicaemia below 6.7 mmol/L (capillary blood), the absence of any other pancreatic disease as well as of heart diseases in medical history, and the blood pressure values below 140/90 mm Hg before the examination.

The aims of the study and the nature of the method applied were explained to the patients and they agreed to be examined.

All examinations were performed with Acuson 128 XP/4 ultrasonic unit, equipped with curved array 3.5 MHz probe (assigned by manufacturer as C3) for general purposes, with footprint size of 66 mm. The frequency of color Doppler velocity mode was 3.5 MHz, and color Doppler energy mode (power-Doppler) 2.5 MHz.

The examination began with B-mode morphological analysis. The identification of pancreatic contours and measurement of the head, body and tail were performed for orientation of pancreatic status. In a fifth of patients, difficulties occurred with insonation of pancreatic head, although we had instructed the examinees to adhere to recommended preparative diet. Color-Doppler or power-Doppler was used to identify the gastroduodenal artery in the head of pancreas, or cephalad to it. The sample-volume was then positioned in the site of the strongest color signal while the patient was holding his breathe back. Spectral analysis was performed. The color signal was sometimes so weak and inconstant that it could hardly be traced, especially with restless patients unable to hold their breath; those spectra were received blindly from the estimated

area. The sample volume was set at the length of 2 mm. Semiquantitative spectral analysis was performed. RI and PI were determined as a mean value of three measurements. Each examination took about 30 minutes.

"Goodness-of-fit test" (Kolmogornov-Smirnov) was used to evaluate whether the distribution of variables was normal. Mann-Whitney U-test was used to assess the significance of difference of observed variables, and correlation was assessed with Spearman's method.

Results

In the group of IDDM patients with the mean duration of disease of 10.6±8.4 years, the distribution of Doppler indices were as follows: median for RI was 0.74 with quartiles (25th percentiles) at 0.64 and 0.78; median for PI was 1.54 with quartiles at 1.26 and 1.88.

In the group of healthy controls, median for RI was 0.71 with quartiles at 0.64 and 0.77; median for PI was 1.46 with quartiles at 1.40 and 1.80.

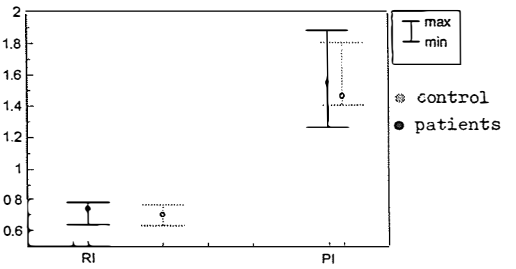

Figure 1. Doppler indexes RI and PI in IDDM patients and healthy controls.
n.s.= statistically nonsignificant difference

Figure 1 shows distribution of Doppler indices in the patients and control group.

Mann-Whitney U-test was used to compare RI and PI values in IDDM patient group and controls. There was no significant difference between these Doppler indices, with p=0.82 for RI, and p=0.74 for PI. Median for RI was slightly lower in the control group than in the patients group, and the quartiles were almost identical. Median for PI values in IDDM group was higher than in the controls, with a slightly larger interquartile range as well, but the difference did not reach the statistical significance.

There was no significant difference of RI and PI values between males and females when examined as a common group (patients + controls). For RI was p=0.21 and for PI was p=0.44.

No significant sexual difference of Doppler indices was observed in control group either for RI (p=0.40) or for PI (p=0.74). Similarly, RI and PI values did not differ significantly between males and females in IDDM patients (p=0.41 and 0.15, respectively).

Spearman's rang-correlation method disclosed the absence of significant correlation between Doppler indices and the age in the patients and controls observed as a unique group as well as in the IDDM patients, but the correlation was significant for RI in healthy controls (r=0.37, p=0.04) (Table 1).

Table 1. Correlation between age and Doppler indices

	Patients + Controls	Patients	Controls
RI	r=0.13	r=0.06	r=0.37
	p=0.27	p=0.72	p=0.04
PI	r=0.14	r=0.12	r=0.17
	p=0.25	p=0.48	p=0.36

Non-significant correlation was observed between Doppler indices and the duration of the disease in the IDDM patients group (Table 2).

Table 2. Correlation between duration of IDDM and Doppler indices in patients

RI	r = -0.08	p = 0.63
PI	r = -0.05	p = 0.76

Discussion

Pulse-wave and color-Doppler is a useful method in noninvasive assessment of blood flow. It adds a new dimension to "classic" gray-scale ultrasound enabling, in addition to morphological estimation, also functional one.[1] The flow spectrum of celiac axis is similar to that of the superior mesenteric artery after a meal, both having a significant diastolic flow as a result of low resistance. The spectral waveforms of the gastroduodenal artery reflect higher resistance, while amplitudes are lower and spectral "window" absent because of small diameter and tortuosity of the vessel.[2-4]

Nghiem *et al.* used pulse-wave and color-Doppler in the assessment of blood flow in the transplanted pancreas in 7 patients. Their RI values ranged from 0.7 to 0.9, and PI from 1.1 to 1.4.[5] Our values of Doppler indices do not differ significantly either from those by Nghiem et al, or those of observed groups, *i.e.* of diabetic patients (RI=0,74,PI=1,54) and control group (RI=0,71,PI=1,46).

Lang *et al.* refer to their preliminary experiences with color Doppler ultrasound after combined kidney/pancreas transplantation. In normal pancreatic grafts, median RI was 0.61 (range 0.55-0.70). When rejection process occurred, RI exceeded 0.80. Other cases of pancreatic dysfunction were not associated with the change of RI.[6]

Our results did not support our preliminary hypothesis that the diabetics will have increased vascular resistance in pancreas because of accelerated process of atherosclerosis that is inherent to the disease itself.

No significant differences in Doppler indexes' values were observed between males and females (we proved significant difference of size of the pancreas between males and females within the same population).

Significant correlation of Doppler indices and age was observed only for RI in the group of healthy examinees. The influence of age, hypertension and morphologic changes of small arteries related to diabetes on vascular resistance is not easy to explain fundamentally, and this is surely a serious limitation to the clinical value of Doppler methods in diabetic patients.

Measurements of RI and PI reflect the intrapancreatic blood flow only approximately, estimating vascular resistance as a decisive factor of circulation in the gland. As these indices are not exact predictors, a precise estimation of volume flow rate would give more valuable results. It is, however, questionable whether the differences of volume flow would be significant, the more so the measurement of flow is linked to difficulties of precise measurement of vessel diameter and velocity simultaneously, and at the same point of the vessel. Small errors of measured variables will result in a significant inaccuracy of blood flow rates.[7]

Finally, we can conclude that duplex-Doppler flow imaging does depict blood flow in the gastroduodenal artery, and may noninvasively contribute to the estimation of pancreatic circulation. However, in our work, the differences between normal subjects and IDDM patients, as well as the correlations between the indices and age, sex and duration of the disease, have not reached a statistical significance, although resistance in diabetics proved to be slightly higher than in controls.

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Renal vascular resistance in patients with chronic renal failure

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Background. *Duplex Doppler sonography has the potential to provide physiological information concerning renal arterial blood flow and resistance. The purpose of the study is to evaluate duplex Doppler sonography for assessing renal vascular resistance (RVR) in patients with chronic renal failure.*

Materials and methods. *Resistive indices (RIs) and pulsatility indices (PIs) were measured in the intrarenal arteries of 30 patients with chronic renal failure and 20 control subjects. RIs and PIs of control subjects were compared to those of the patients with chronic renal failure and correlated with the laboratory and clinical findings.*

Results. *In the control subjects, the mean RI was 0.59±0.03 (±SD) and mean PI was 1.00±0.11. In the patients with chronic renal failure, the mean RI was 0.71±0.11 and mean PI was 1.69±0.21. Elevated RIs and PIs were associated with the progression of renal failure. Statistically significant ($p<0.001$) correlations were observed between both, RI and PI, and the serum creatinine level, creatinine clearance rate, and systolic and diastolic blood pressure measurements.*

Conclusion. *Doppler indices reflect an increased RVR in the patients with chronic renal failure and correlate with the laboratory and clinical parameters, whereas RI and PI measurements offer no advantages over these parameters to predict the disease progress.*

Key words: kidney failure, chronic; renal artery-ultrasonography; vascular resistance

Introduction

Sonography is routinely performed to evaluate the patient with suspected or known renal disease. Although gray-scale sonography can provide important anatomic information, it lacks the ability to provide significant physiological data. Duplex Doppler sonography has the potential to provide physiological information concerning renal arterial blood flow and resistance.[1-3] Doppler study of small intrarenal vessels, although not difficult, requires a proper technique to obtain useful measurements.[3,4] Most investigators have concentrated on the study of distal intrarenal vessels, which are not actually seen during the examination but are detected by sampling the Doppler spectrum at the corticomedullary

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junction or along the borders of the medullary pyramids.[5] A study by Knapp (1995) of 120 subjects found the resistive index (RI) measurements to be most consistent at the level of the interlobar-arcuate arteries.[4]

Most investigators have used RI to characterize the intrarenal Doppler wave form.[5-8] These easily calculated parameter is defined as RI=(Peak Systolic Shift-Minimum Diastolic Shift)/Peak Systolic Shift. Increases in downstream resistance result in a relative reduction of diastolic flow compared with the systolic flow and elevation of the RI. Hence, RI can be used as an estimate of renal arterial resistance.[4] Several studies have investigated normal intrarenal RI values; the majority suggest 0.70 as a reasonable upper limit for the normal RI.[4,9,10] Conditions other than intrinsic renal disease can also affect the RI. A significant hypotension, markedly decreased heart rate, and perinephric or subcapsular fluid collection can elevate the RI.[11-13] In this study, the authors hypothesize that Doppler sonographic indices that are measured in intrarenal arteries will reveal the changes of RVR in patients with renal failure.

Patients and methods

Patients

The investigated group comprised 30 patients (mean age 51.4 years) with chronic renal failure (glomerular or tubulointerstitial diseases, nephroangiosclerosis). The criteria for diagnosing chronic renal failure were: (1) Azotemia for > 3 months, (GFR- glomerular filtration rate is about 20 to 35 percent of normal); (2) Prolonged symptoms or signs of uremia; (3) Symptoms or signs of renal osteodystrophy; (4) Kidneys reduced in size bilaterally.

The patients with chronic renal failure have glomerular disease (N=9) (primary glomerular disease (N=7), such as focal segmental glomerulosclerosis, membranous glomerulo nephropathy, membranoproliferative glomerulonephritis and multisystem diseases (N=2), such as systemic lupus erythematosus), tubulointerstitial disease (N=11) and nephroangiosclerosis (N=10).

The patients with a history of heart disease or diabetes mellitus, as well as all patients with conventional US findings of renal calculi, collecting system dilatation, or suspected expansive processes were excluded from the study.

The control subjects were 20 healthy volunteers, mean age 49.3 years. RIs and PIs of control subjects were compared with those of the patients with chronic renal failure.

Methods

Real-time and color duplex US examinations were performed using a color Doppler scanner (Radius CF, general Electric Medical Systems), with a 3.75 MHz curved-array transducer. Pulsed Doppler US studies of the segmental, interlobar and arcuate arteries were performed in both kidneys in each patient. The segmental, interlobar and arcuate arteries were distinguished with respect the position of the Doppler sample volume for the inner kidney zone (renal sinus), middle zone (corticocentral boundary) and outer zone (corticomedullary border). RI was measured according to the following formula (peak systolic frequency shift-minimum diastolic frequency shift)/ peak systolic frequency shift. The PI was measured with the formula: (peak systolic frequency shift-minimum diastolic frequency shift)/mean frequency shift during the whole cardiac cycle.

All control subjects and patients were examined in the supine and semioblique positions; they had to suspend respiration for 10 seconds so that a representative spectra could be obtained.

For all patients, laboratory findings for the presence of proteinuria and serum creatinine levels and creatinine clearance rates were available. Normal values for serum creatinine and creatinine clearance are 62-124 mikro-

mol/L (Jaffe method) and 1.2-2.4 ml/sec, respectively.[14] In healthy adults, urinary protein excretion, as measured in the 24-hour urine specimen, is up to 150 mg. Mild protein excretion is referred to as low-grade proteinuria when urinary protein excretion is less than 1 to 2g/24 h, whereas the excretion of 3.5g/24 h or more is defined as nephrotic range proteinuria.[15]

Doppler sonographic indices were correlated with systolic and diastolic blood pressure values, which had been measured prior to US examination. The interval between US examination and blood or urine sampling for laboratory examination was less than 5 days in all cases. All laboratory examinations were performed in the same laboratory.

Results

Mean RI in the control subjects and in the patients with chronic renal failure was 0.59±0.03 (±SD) and 0.71±0.11, ($p<0.01$), respectively. Mean PI in the controls and in the patients with chronic renal failure was 1.00±0.11 and 1.69±0.21, ($p<0.01$), respectively. The patients with chronic renal failure were classified by RI values into two groups. Group I included 15 patients with normal RI, mean age 43.7 years. Group II was composed of 15 patients with elevated RI (more than 0.70), mean age 63.4 years. Of the 30 patients with chronic renal failure (50%), 12 of whom were found to be hypertensive (blood pressure>140/90mmHg), an elevated RI was noted in 15 patients. Mean values of systolic and diastolic blood pressure were 160±15mmHg and 105±13mmHg, respectively. An RI <0.70 was observed in the remaining 15 patients of the 30 (50%), of whom 12 were normotensive. In hypertensive patients, mean RI and mean PI were 0.74±0.12 and 1.90±0.20, respectively. In the normotensive patients, mean RI and mean PI were 0.64±0.09 and 1.19±0.32, respectively. The statistical significance of RI and PI differences in normotensive and hypertensive patients with chronic renal failure was calculated to be $p<0.02$ and $p<0.04$, respectively.

In the patients of group I, who were younger (mean 43.7 years), glomerular disease was present in 60% (N=9) of patients, and tubulointerstitial diseases in 40% (N=6). In 86% of these patients, the creatinine clearance rate was higher than 0.25ml/sec, and in 10 patients, proteinuria was lower than 3g/l. In the patients of group II, who were older (mean 63.4 years), nephroangiosclerosis was present in 66.6% (N=10) of patients, and tubulointerstitial diseases in 33.3% (N=5) of patients. In 80% of the patients of group II, the creatinine clearance rate was lower than 0.25 ml/sec, and proteinuria was higher than 3g/l in 8 patients.

Discussion

Normal RI values have been established in native kidneys, and the cut off value of 0.70 or greater is generally considered to represent an abnormal RI.[16] The age was shown to be an important variable that affected RI values as well as arterial hypertension.[5] A highly significant correlation was found between the RI, the serum creatinine levels and creatinine clearance rates in patients with diabetic nephropathy and several other parenchymal diseases, particulary those affecting the tubulointerstitial and vascular compartments of the kidney.[5,16] Our results show that Doppler indices do accurately reflect an elevated RI, especially in the patients with the creatinine clearance rate of less than 0.25ml/s ($p<0.001$). RI has been found to correlate with renal function much better than PI.

Based on the results of our study, an elevated RI appears to reflect progression of renal failure, while hypertension without TOD (target organ damage) does not seem to affect RI.

Studies suggest that RI elevation is more likely to occur with a vascular or tubulointerstitial renal process, and is much less likely with the disease limited to the glomeruli.[3] Furthermore, RI is not a measure of renal function per se, but rather reflects renal vascular resistance. When an elevated renal arterial resistance accompanies abnormal renal function, RI is more closely related to renal function, especially in diabetes mellitus.[3,5,6,17] Conversely, some renal pathology causes a significant loss of renal function with little or no change in renal vascular resistance. In these instances, RI does not reflect the loss of renal function.[14] In patients with chronic renal disease, RI is closely related to certain haemodynamic and functional parameters.[10,17]

The drawback of the present study is a relatively small number of patients studied. Moreover, it was not designed in a longitudinal fashion as each patient was examined only once by duplex Doppler US. Furthermore, it is not surprising that the disease with a destructive and deformative effect on the renal parenchyma increases RI. Therefore, measuring RI and PI alone cannot alter the patient's outcome. However, a good correlation between RI and renal functional parameters on the one hand and the development of arterial hypertension in the patients with chronic renal failure, on the other, that was observed in our study, may eventually prove that duplex Doppler US could be used as an additional parameter in the assessment of severity of chronic renal failure.

In conclusion, color duplex Doppler US in intrarenal arteries proved to be useful in the assessment of increased RI in chronic renal failure patients. Elevated RI and PI heralded the progression of renal failure. Doppler indices correlated significantly with renal function tests. However, additional longitudinally designed studies on a larger patient group will be necessary to evaluate in full the clinical usefulness of duplex Doppler US in patients with chronic renal failure.

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Bone marrow protection by amifostine in Re-186-HEDP treatment: first results obtained in a rabbit animal model

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Background. *In the last few years various reports dealt with radioprotective effects of amifostine (Ethyol®, USB, Philadelphia, PA). Since amifostine is markedly accumulated in bone marrow it looks worthwhile to study the radioprotective effects of amifostine on bone marrow in patients treated with Re-186-HEDP. As a first step animal studies were performed using New Zealand White rabbits.*

Materials and methods. *A total of 18 rabbits received 300 MBq Tc-99m-HDP for whole-body scintigraphy. Thereafter, 9 animals were treated with 200 mg/kg body weight amifostine, and 9 rabbits served as controls receiving physiological saline solution. Then, these 18 rabbits received 400 MBq Re-186-HEDP i.v. Two rabbits served as untreated controls and received neither Tc-99m-HDP nor Re-186-HEDP. Blood samples were taken at the beginning and in two-week-intervals for the duration of two months in all 20 animals. Laboratory findings were determined for white and red blood cells, for platelet count and for hemoglobin. Two months after therapy all animals were sacrificed, and both femora were removed surgically for histopathological examination of bone marrow.*

Results. *In controls as well as in amifostine-treated animals, the red blood cell count and the hemoglobin were almost constant at all times of observation. In 9 control rabbits the mean platelet count was 265.22±127.41 Mrd/l prior to Re-186-HEDP-therapy. Two weeks after therapy the mean platelet count was reduced to 211.22±52.8 Mrd/l. Prior to Re-186-HEDP-therapy the mean platelet count of amifostine-treated rabbits was not significantly different ($p>0.05$) from control rabbits. Two weeks after injection of the radionuclide the mean platelet count decreased to 180.67±37.43 Mrd/l in the amifostine group. There was no significant difference between rabbits of the control group and amifostine-treated animals ($p>0.05$). Thus, amifostine was not able to prevent a transient thrombocytopenia. Two weeks after therapy only a slight decrease of the white blood cell count was recognized in controls. In contrast, amifostine-treated rabbits showed a considerable decrease of the white blood cell count two weeks after therapy with a mean value of 3.39±0.91 Mrd/l. This difference was statistically significant ($p<0.0002$).*

Discussion. *The insufficient radioprotection of amifostine concerning the platelet count was probably due to pharmacocinetics of amifostine. Since the generation of free radicals in the bone marrow caused by Re-186-HEDP lasts several times longer than the radioprotective effect of amifostine given as one single dose prior to the application of Re-186-HEDP. However, the observed decline of white blood cells due to amifostine application is yet unknown.*

Conclusion. *In order to use amifostine as a suitable agent for radioprotection multiple doses of amifostine might be applied, i.e. two shots per day for the duration of 3 to 4 days after the application of Re-186-HEDP. The observed leucopenia should be studied in further animal studies.*

Key words: Radiation-protection agents; bone marrow; amifostine; erythrocyte count; platelet count, hemoglobin; Re-186-HEDP; bone metastases

Introduction

Patients with prostate cancer will develop bone metastases in nearly 70 %,[1] which may result in pathological fractures as well as in severe bone pain.[2,3] The application of β⁻-emitting osteotropic radionuclides, *i.e.* Sr-89-chloride, Sm-153-EDTMP, and Re-186-HEDP is one therapeutic approach in palliative treatment of painful, multilocular bone metastases.[4-10] Since bone metastases show a preferential uptake of bone-seeking radionuclides, *i.e.* Re-186-HEDP, this therapy is rather specific, while non-affected tissue is spared from the effects of the β⁻-irradiation.[11] In 75% of the patients pain relief occurs within one to two weeks after the application of Re-186-HEDP and lasts for about 1-6 months.[3,10,12] However, Re-186-HEDP delivers a substantial dose to the bone marrow, thus, a potential bone marrow suppression is still the most important dose-limiting factor.[3,10-13] This radiobiological side-effect is mainly confined to a decline of the platelet count, called thrombocytopenia.[14,15] Therefore, one inclusion criteria for patients undergoing rhenium-therapy is a platelet count of at least 150 Mrd/l prior to therapy, and in clinical routine a blood count is performed directly prior to the application of the bone-seeking radionuclide.[16] However, some patients do not fulfill this inclusion criteria at the day of admission and therefore, rhenium-therapy can not be performed as planned. Thus, the reduction of radiobiological side-effects is of major interest in patients treated for painful bone metastases. On the other hand, therapy with standard activities of 1200 MBq Re-186-HEDP is still a palliative treatment which does not influence the prognosis of the underlying disease at all. However, a reduction of side-effects of Re-186-HEDP might improve tolerability of rhenium-therapy. Thus, in the future, Re-186-HEDP might be applied not only as palliative but also as curative means in patients with multilocular bone metastases.

In the last few years various reports dealt with radioprotective effects of the phosphorylated aminothiol amifostine (Ethyol®, USB, Philadelphia, PA).[17-29] Since amifostine markedly accumulates in salivary glands the application of amifostine has been successfully used both in external radiotherapy in patients with head and neck tumors[30] and high-dose radioiodine therapy in patients with differentiated thyroid cancer.[26-29,31-34] Since amifostine is also markedly accumulated in bone marrow[25,35-38] it looks worthwhile to study the radioprotection of bone marrow in order to avoid/reduce bone marrow toxicity in patients treated with Re-186-HEDP, and thus, to increase the tolerability of rhenium-therapy. As a first step animal studies were performed.

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Material and method

Animal studies

In order to investigate the radioprotective effects of amifostine an animal model was established using New Zealand White rabbits. A total of 20 animals aged between two and three months and weighing 2.1 to 3.1 kg with a mean weight of 2.86±0.11 kg were used. As a first step, 18 rabbits received 300 MBq Tc-99m-HDP as intravenous injection by a vein flow placed in the ear. For bone scintigraphy 2 hrs p.i., all rabbits were positioned in prone position directly onto a low-energy high-resolution collimator of a large field of view gamma camera (Diacam, Siemens, Erlangen, Germany). For anesthesia, 50 mg/kg Ketanest® (Ketaminhydrochlorid,

Parke-Davis, Berlin, Germany) and 4 mg/kg Rompun® (Xylazinhydrochlorid, BayerVital, Leverkusen, Germany) were administered in a mixed syringe as intramuscular injection in the upper leg directly prior to image acquisition. Images were acquired over 20 min each and stored digitally in a 256x256 matrix. Directly after bone scintigraphy 9 animals were treated with 200 mg/kg Amifostine® (Amifostine, USB, Philadelphia,PA) as slow intravenous infusion over 5 min. Nine rabbits served as controls receiving a corresponding volume of physiological saline solution. Then, these 18 rabbits received 400 MBq Re-186-HEDP dissolved in less than 0.6 ml. Whole-body scintigraphy was performed at 24 hrs or 48 hrs p.i. in order to evaluate the distribution of the Re-186-HEDP applied. Again, 50 mg/kg Ketanest® (Ketaminhydrochlorid, Parke-Davis, Berlin, Germany) and 4 mg/kg Rompun® (Xylazinhydrochlorid, BayerVital, Leverkusen, Germany) were administered for anesthesia in a mixed syringe as intramuscular injection in the upper leg. Rabbits were positioned as described above directly onto a low-energy high-resolution collimator of a large field of view gamma camera (Diacam, Siemens, Erlangen, Germany). Images were acquired over 20 min each and were stored digitally in a 256x256 matrix.

Two rabbits served as untreated controls and received neither Tc-99m-HDP nor Re-186-HEDP. Blood samples were taken at the beginning and in two-week-intervals for the duration of two months in all 20 animals. Laboratory findings were determined for white and red blood cells, for platelet count and for hemoglobin. Two months after therapy all animals were sacrificed, and both femora were removed surgically for histopathological examination of bone marrow.

Histopathological examination

The bone marrow was stained in conventional manner with Hematoxilin/Eosin, Giemsa, and Berlin blue. An experienced pathologist performed histopathological examinations in a blind manner. Evaluation criteria were the cellularity of the bone marrow, the number and differentiation of the erthropoesis, granulopoesis and thrombocytopoesis, the evaluation of bone marrow vessels, and the quantity of bone marrow's iron content.

Evaluation

Blood samples were directly transferred to the central laboratory and determined the same day in order to avoid an artificial decline of platelets. Hemoglobin was measured in g/dl. White blood cell count, red blood cell count, and platelet count were measured in Mrd/l, respectively.

Whole-body scintigramms acquired after injection of Tc-99m-HDP or Re-186-HEDP were.evaluated by visual inspection.

Statistics

Data are given as mean ± one standard deviation. Two-tailed Student's t-test for paired data was used to evaluate statistical differences between animal subsets. $P<0.05$ was considered to be significant.[39]

Results

Animal model

The animal model chosen was easy to handle. Due to the size of the ear veins both the injection of the radiopharmaceuticals and the drawing of blood samples were easy to perform. Moreover, the chosen anesthesia consisting of a mixture of Ketanest® and Rompun® was safe and allowed image acquisition without any movement artifacts.

Red blood cells

Details of the red blood cell count for all groups of rabbits are given in Table 1. In con-

trols, the red blood cell count was almost constant at all times of observation. Prior to therapy a mean red blood cell count of 6.07(0.84 Mrd/l was measured in this group. At two, four, six and eight weeks after therapy the red blood cell count was 6.07±0.39, 6.61±0.42, 6.59±0.63 and 6.18±0.58 Mrd/l, respectively. Corresponding results were observed for animals of the amifostine-treated group. Prior to therapy a mean red blood cell count of 6.29±0.51 Mrd/l was measured in these animals. Two, four, six and eight weeks after therapy the mean red blood cell count amounted to 6.25±0.46, 6.12±0.41, 5.82±0.34 and 6.19±0.4 Mrd/l, respectively. Thus, amifostine-treated animals showed almost unchanged red blood cell counts during Re-186-HEDP-therapy.

Two completely untreated animals showed an almost constant red blood cell count during all times of observation. In these two animals a mean red blood cell count of 6.0±0.13 Mrd/l was measured at first time of observation and amounted to 6.25±0.13, 6.7±0.04, 6.07±0.86 and 5.98±0.23 in two-week-intervals up to eight weeks after beginning of the study.

Hemoglobin

Details of values for hemoglobin are given in Table 1. In animals of the control group mean hemoglobin was 12.53±1.14 g/dl prior to therapy and amounted to 12.84±0.9, 14.32±0.75, 14.09±1.01 and 13.71±0.72 g/dl two, four, six and eight weeks after therapy, respectively. Thus, animals pretreated with physiological saline solution only showed near unchanged hemoglobin at all times of observation. Laboratory findings of hemoglobin determined prior and in two-week intervals showed corresponding results for amifostine-treated animals. In these rabbits mean hemoglobin amounted to 13.41±0.96 g/dl prior to therapy and was 13.23±0.94, 13.64±0.52, 12.74±0.54 and 13.87±0.86 g/dl at two, four, six and eight weeks after therapy, respectively.

Moreover, unchanged values for hemoglobin were observed in both untreated animals with hemoglobin amounting to 12.75±0.49 g/dl at the beginning and amounting to 13.4±0.99, 14.6±0.99, 13.25±0.92 and 13.2±0.57 g/dl at two-week-intervals.

Table 1. Mean values and standard deviation of the red and white blood cell count, the platelet count and the hemoglobin prior to and 2, 4, 6 and 8 weeks after Re-186-HEDP treatment in the control group, the amifostine-treated group and in the untreated rabbits

		Time with respect to Re-186-HEDP i.v				
		Before	2 weeks after	4 weeks after	6 weeks after	8 weeks after
RBC [Mrd/l]	Controls	6.07±0.53	6.07±0.39	6.61±0.42	6.59±0.63	6.18±0.6
	Amifostine	6.29±0.51	6.25±0.46	6.12±0.41	5.82±0.34	6.19±0.4
	Untreated	6.00±0.13	6.25±0.13	6.70±0.04	6.07±0.86	5.98±0.2
Hgb [g/dl]	Controls	12.50±1.11	12.84±0.90	14.32±0.75	14.09±1.01	13.71±0.72
	Amifostine	13.40±1.12	13.23±0.94	13.64±0.52	12.74±0.54	13.87±0.86
	Untreated	12.80±0.54	13.40±0.99	14.60±0.99	13.25±0.92	13.20±0.57
Platelets [Mrd/l]	Controls	265.2±127.4	211.2±52.8	359.7±93.3	338.8±90.5	359.0±86.7
	Amifostine	286.2±73.2	180.7±37.43	214.8±122.0	267±89.6	251.4±102.9
	Untreated	378.0±161.2	315.5±129.4	379.5±112.4	275.5±105.4	327.0±70.7
WBC [Mrd/l]	Controls	6.64±1.27	5.43±0.88	6.96±1.41	8.1±1.46	7.79±0.84
	Amifostine	5.73±2.1	3.39±0.91	4.61±1.48	5.29±1.24	5.76±1.34
	Untreated	6.6±1.41	6.15±0.21	6.75±1.63	9.2±4.53	9±2.55

Platelet count

Details of platelet count are given for all rabbits in Table 1. In 9 control rabbits mean platelet count was 265.22±127.41 Mrd/l prior to Re-186-HEDP-therapy. Two weeks after injection of the radionuclide mean platelet count was reduced to 211.22±52.8 Mrd/l. Four and six weeks after therapy mean platelet count increased to 359.67±93.26 and 338.78±90.46 Mrd/l, respectively. Prior to the sacrification mean platelet count of 359±86.72 Mrd/l was measured for all animals pre-treated with physiological saline solution only.

Prior to Re-186-HEDP-therapy the mean platelet count of amifostine-treated rabbits was not significantly different (p>0.05) from control rabbits amounting to 286.22±73.2 Mrd/l. Two weeks after injection of the radionuclide the mean platelet count of the amifostine group decreased to 180.67±37.43 Mrd/l. There was no significant difference between rabbits of the control group and amifostine-treated animals (p>0.05). Four, six and eight weeks after Re-186-HEDP-therapy the platelet count increased to 214.78±121.97, 267.67±89.6 and 251.44±102.89 Mrd/l, respectively. Moreover, there was no significant difference between animals treated with either physiological saline solution or amifostine.

Laboratory findings of two untreated animals revealed platelet count of 378±161.22 Mrd/l at the beginning and 315.5±129.4, 379.5±112.43, 275.5±105.36 and 237±70.71 Mrd/l at two-week-intervals follow-up.

White blood cells

Values of the white blood cell count are given in detail in Table 1. Prior to Re-186-HEDP-therapy mean white blood cell count of

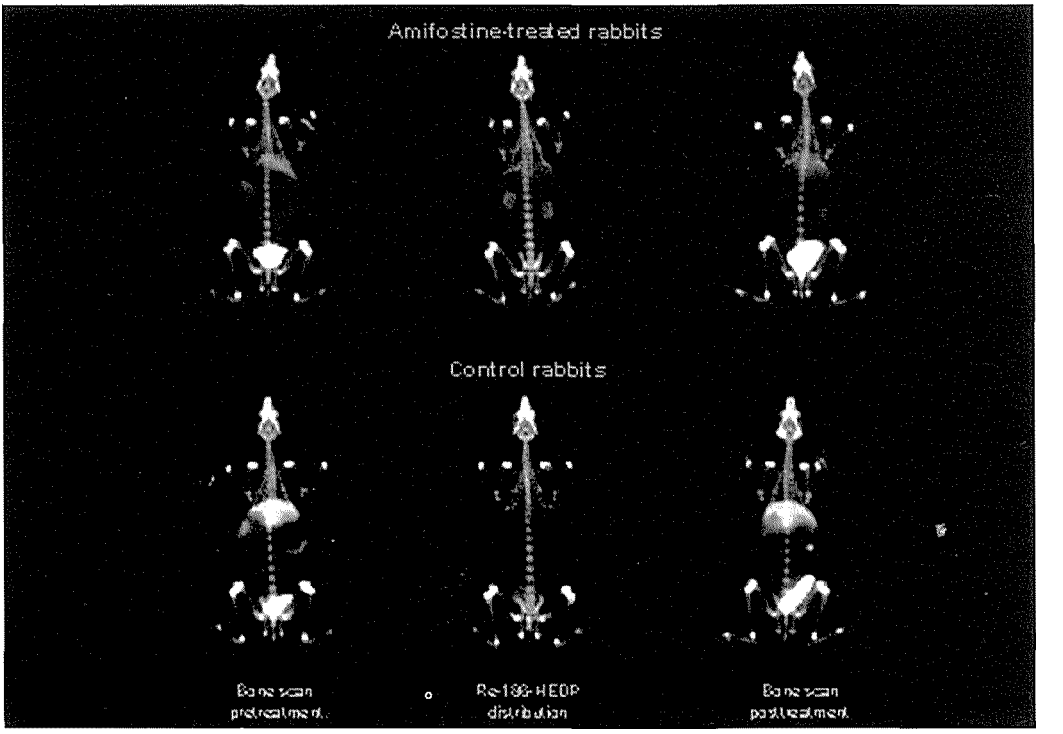

Figure 1. Whole body scintigraphy after injection of 300 MBq Tc-99m-HDP prior to (left column) and 2 months after Re-186-HEDP-therapy (right column) in a rabbit of the control group (lower row) and in an amifostine-treated animal (upper row). Distribution of Re-186-HEDP 48 hrs after i.v. application is displayed in the middle column.

6.64±1.27 Mrd/l was measured for rabbits of the control group. Two weeks after therapy a slight decrease of white blood cell count was recognized in this animal group with a mean value of 5.43±0.88 Mrd/l. Four, six, and eight weeks after therapy white blood cell count increased to mean values of 6.96±1.41, 8.1±1.46 and 7.97±0.84 Mrd/l, respectively. Amifostine-treated animals revealed mean white blood cell count of 5.73±2.1 Mrd/l prior to the injection of the radionuclide. In contrast to the control group, amifostine-treated rabbits showed a considerable decrease of white blood cell count two weeks after therapy with a mean value of 3.39±0.91 Mrd/l. This difference was statistically significant ($p<0.0002$). In follow-up studies the white blood cell count removed to 4.61±1.48, 5.29±1.24 and 5.76±1.34 Mrd/l at four, six and eight weeks after therapy, respectively.

In two completely untreated animals white blood cell count remained almost unchanged with values of 6.6±1.41, 6.15±0.21, 6.75±1.63, 9.2±4.53 and 9±2.55 Mrd/l at the beginning and in two-week intervals, respectively.

Scintigraphic findings

Left column of Figure 1 shows examples of whole-body scintigraphy 2 hrs after injection of Tc-99m-HDP of one animal of the control group (lower row) and one animal of the amifostine-treated group (upper row). Prior to Re-186-HEDP-therapy there was no difference between the control animals and the amifostine-treated animals concerning the distribution of Tc-99m-HDP. Examples of whole-body scintigraphy 48 hrs after injection of Re-186-HEDP are displayed in the middle column of Figure 1. The visual evaluation of the scintigramms showed a distribution of Re-186-HEDP comparable to bone scans in both groups of rabbits. Examples of bone scintigraphy at 8 weeks after Re-186-HEDP-therapy are shown in the right column of Figure 1. There was no visual difference of the distribution of Tc-99m-HDP in either control animals or amifostine-treated animals. Moreover, there was no visual difference between the distribution of the Tc-99m-HDP prior to and eight weeks after therapy with Re-186-HEDP.

Histopathological findings

Eight weeks after Re-186-HEDP-therapy all 18 rabbits showed hyperemic bone marrow vessels as compared to untreated animals (Figure 2).

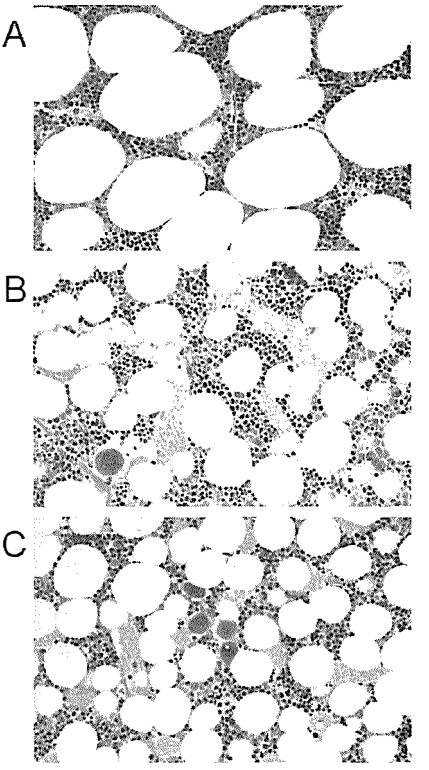

Figure 2. Histological examination of bone marrow in conventional Giemsa staining, magnification: 200fold. A: animal which received neither Tc-99m-HEDP nor Re-186-HEDP. B: animal of the control group. C: animal of the amifostine group. Note the comparable cellularity and differentiation of the different cell lines of B and C as compared to the bone marrow of the completely untreated animal (A). However, in contrast to the untreated animal the blood vessels of B and C are filled with red blood cells, and thus, appear hyperemic.

There was no difference between animals treated with or without amifostine concerning the cellularity of bone marrow, the number and differentiation of erythropoesis, granulopoesis and thrombocytopoesis, and the quantity of iron. Moreover, histopathological examination revealed no difference between animals treated with amifostine and those rabbits, which received physiological saline solution only.

Discussion

Prostate cancer is the second most common malignancy in men in Western Europe.[1] The incidence is 15-16 per 100.000 habitants per year with increasing tendency. As much as 80% of patients with prostate cancer will develop bone metastases.[1] In about one third of all patients osseous metastases are detected at primary staging. Moreover, the skeleton is the only single site of metastases in a reasonable amount of patients.[3] In case of multilocular, osseous metastases a complete remission of prostate cancer is nearly impossible.

Since osseous metastases are often associated with bone pain, effective pain relief is the primary goal when caring for patients with prostate cancer and multiple osseous metastases. Traditional therapeutic approach is the application of central or peripheral analgesics in combination with neuroleptics.[6] Moreover, a steroid medication, diphosphonates and hormonal drugs may complete analgesic effects. However, the therapy with opioids is limited in many patients due to side-effects, *i.e.* nausea, vomits and gastrointestinal symptoms and thus, often associated with a loss of patient's quality of life.[7]

Skeletal pain confined to a single site metastasis usually responds to external beam radiotherapy in 70-80 %.[6,40,41] In case of multilocular, osseous metastases external beam radiation is helpful to avoid pathologic fractures or compression of the spinal cord.[42] However, hemibody or whole-body irradiation for pain relief is often limited by bone marrow suppression, gastrointestinal symptoms and a radiation pneumonitis.[14,43] Therefore, an effective relief of pain with low side-effects and an improvement in patient's quality of life is warranted in these patients.

The application of β^-–emitting osteotropic radionuclides is a promising method to selectively irradiate osseous metastases by sparing normal tissues from short-range irradiation.[11,13] Due to the osteoblastic character of osseous metastases the radiopharmaceutical is predominantly accumulated in malignant transformed cells, which leads to a rather selective irradiation of bone metastases. Re-186-hydroxyethylidendiphosphonate (Re-186-HEDP) has recently been developed for palliative treatment of painful osseous metastases.[5] Re-186 has a therapeutic β^-–emission of 1,07 MeV associated with a γ^-–emission of 137 keV. Moreover, Re-186-HEDP and Tc-99m-HDP, which is commonly used for diagnostic bone scintigraphy, have an almost exactly similar bone distribution since both sorts of diphosphonates bridge to the hydroxyapatite of bone substance. Therefore, pretherapeutic and posttherapeutic scintigraphic imaging is possible which allows a control of Re-186-HEDP distribution as shown in Figure 1 (middle column). Re-186 has a short physical half-life of 3,8 days that allows a single application of activities of 1110 to 1850 MBq with high tumor doses as well as an easy handling of radioactive waste, *i.e.* urine. About 50% and70 % of the activity injected are excreted via the kidneys into the urine within the first 6 hours and 24 hours after application, respectively. Apart from the distribution in osseous structures Re-186-HEDP is not accumulated in any other structures of the body.

Pain relief is attained within two weeks after application of Re-186-HEDP and lasts for about 1-6 months. Response rates of Re-186-HEDP-therapy of 70-80 % have been

reported.[3,10,12] Especially in patients with oral medication of non-opioid analgesics, Re-186-HEDP-therapy led either to a reduction or to a stop of oral drug medication. Due to the short physical half-life, Re-186-HEDP treatment can be repeated after 4-6 months.

The main radiobiological side-effect of bone seeking radiotherapeuticals is their potential bone marrow toxicity.[11,13-15] Thrombocytopenia plays the major role in this bone marrow suppression. The decline of platelets presents with a nadir about two to three weeks after its application. Since patients with prostate cancer often show a bleeding tendency caused by the additional use of non-steroid anti-inflammatory drugs and by a tumor infiltration of the bladder frequent controls of platelet count are necessary in posttherapeutic follow-up. In clinical practice platelet counts are regularly defined in two-week intervals for the duration of two months after Re-186-HEDP-therapy. Since thrombocytopenia was proven to be the main side-effect a reduction of the platelet counts' decline would improve tolerability of Re-186-therapy. On the other hand, thrombocytopenia is the dose-limiting factor. Thus, by reducing the bone marrow toxicity of Re-186-HEDP higher activities of more than 1200 MBq might be injected as one single dose in the future. Thus, Re-186-HEDP might be applied not only as a palliative but also as curative means in patients with prostate cancer.

The pro-drug amifostine emerged as the most promising radioprotector synthesized and tested in a large study funded by the US army. In clinical trials amifostine was shown to protect salivary glands from irradiation damage in patients with thyroid cancer under high-dose radioiodine therapy.[26-29,31,32,44,45] Moreover, amifostine was proven helpful in patients with cancer of the head and neck treated with chemo-irradiation.[30,45,46] In these patients amifostine was able to significantly reduce side-effects, *i.e.* mucositis, xerostomia and thrombocytopenia as compared to a non-amifostine treated patient group. Moreover, either in patients with thyroid cancer nor in patients with head and neck cancer amifostine was shown not to protect tumor tissue, which is a prerequisite for its potential use in tumor therapy.[25,33,47]

When administered intravenously, amifostine is rapidly cleared from the plasma with an alpha half-life of as less than one minute and a beta half-life of less than 10 minutes.[48] In contrast to its brief systemic half-life, there is a prolonged retention of the drug and its metabolites in normal tissues.[36] In the first 30 minutes after amifostine administration, the drug uptake into normal tissues such as salivary glands, liver, kidney, heart and bone-marrow demonstrated an up to 100-fold greater difference as compared to tumor tissue.[36]

In this preclinical study the radioprotective effect of amifostine on bone marrow suppression under Re-186-HEDP-therapy was studied using a rabbit bone marrow model. Therefore, in a total of 18 rabbits, 400 MBq Re-186-HEDP were applied intravenously in order to evaluate the bone marrow suppression in rabbits pretreated either with amifostine or with physiological saline solution only. Neither red blood cell count nor hemoglobin was changed by Re-186-HEDP in controls and in rabbits pretreated with amifostine. Moreover, by histopathological examination there was no difference concerning the red blood cell line in all three groups of animals. This is in accordance with the observations of other investigators who reported no influence of Re-186-HEDP on hemoglobin and red blood cells.[16]

In contrast, a marked decline of the platelet count of about 20 % was observed two weeks after application of Re-186-HEDP in controls. This is again in accordance with the observation of other investigators.[7,11,13-16] Following whole-body exposure by external radiation, thrombocytopenia develops slowly over a period of approximately 30 days after doses of 200-400 cGy. After the application of a dose of 600-1000 cGy the production of

platelets is completely stopped, which leads to a decrease of the platelet count reflecting the life range of the platelets of approximately 9 days.[15] It was estimated that standard activities of 1200 MBq Re-186-HEDP deliver a radiation dose of about 75 cGy to the bone marrow leading to the marked platelet suppression.[8] In contrast to the investigations of de Klerk[15] who reported a nadir of decline of platelet count at week 4 after therapy in this rabbit animal model a marked reversible decline of platelets occurred as early as two weeks after therapy. Thus, in amifostine-treated animals peripheral platelet count showed a comparable decrease of about 37.1%. Thus, amifostine could **not** reduce the transient thrombocytopenia in animals treated with Re-186-HEDP. This is probably due to the pharmacocinetic properties of amifostine. First, amifostine was applied as a single dose prior to Re-186-HEDP. Second, while Re-186-HEDP has both a biological and a physical half-life of about three days, the biological half-life of amifostine within the bone marrow is probably less than 24 hrs. Thus, the generation of free radicals within the bone marrow caused by Re-186-HEDP lasts several times longer than the radioprotective effect of amifostine. This leads to the conclusion that in order to use amifostine as a suitable agent for radioprotection, multiple doses of amifostine might be applied, *e.g.* two single shots per day for the duration of 3 to 4 days after the application of Re-186-HEDP. However, concerning the thrombocytopoesis 8 weeks after therapy the pathologist described no difference between animals treated with Re-186-HEDP and totally untreated animals. Thus, in order to investigate the myelotoxic effect of Re-186-HEDP the sacrification of the animals might be performed earlier than 8 weeks after therapy, *e.g.* 2 weeks after therapy while the platelet count decrease exhibits its nadir.

As far as white blood cells are concerned amifostine-treated animals showed a significant reduction of leucocytes as compared to animals of the control group. There was no explanation for this side-effect of amifostine while nausea, vomiting and potentially hypotension are well-described side-effects after the administration of amifostine. However, a reduction of white blood cells is yet unknown. Moreover, there was no difference in the granulopoesis between all three groups of rabbits investigated as demonstrated by histopathology. Thus, in order to evaluate cytotoxic effects of amifostine or Re-186-HEDP on the genesis of white blood cells the sacrification of the rabbits might be performed earlier. However, the hyperemic blood vessels of all animals treated with RE-186-HEDP might be interpreted as a late reactive sign of bone marrow damage.

Conclusions

In this animal model amifostine given in one single dose was not able to avoid the transient thrombocytopenia in rabbits treated with Re-186-HEDP. However, in order to use amifostine as a suitable agent for radioprotection multiple doses of amifostine might be applied, *e.g.* two single shots per day for the duration of 3 to 4 days after the application of Re-186-HEDP. The observed leucopenia should be studied in further animal studies.

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Algorithm for percutaneous stenting in patients suffering from superior vena cava syndrome

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Background. *Superior vena cava syndrome (SVCS) has been considered an emergent, life-threatening condition for a long time. The rate of causes of the syndrome has changed substantially since its first description by W. Hunter in a patient suffering from saccular aneurysm of syphilitic aorta in 1757.*
Since the beginning of the era of radiotherapy, this was the main treatment modality for patients with SVCS. The emergent feature of the syndrome required immediate initiation of radiotherapy, often without the proper knowledge of the histopathological diagnosis of the SVCS underlying cause. The development of radiotherapy and chemotherapy in various types of cancer, and the development of supportive care in oncology and an understanding that SVCS is not an emergent life-threatening oncological condition evoked a need for treatment differentiation in SVCS patients.
Conclusions. *Percutaneous stenting became a very efficient method in the treatment of SVCS patients since 1986. The purpose of stenting is supportive and/or palliative. The algorithm for stenting use has been developed. Algorithm is based on 4 questions emerging from daily clinical practice. To get valid responses, certain diagnostic procedures and tools are recommended and required.*
1. Does the patient really suffer from SVCS?
2. What is the patient's general condition?
3. Is the stenting of SVCS contraindicated? (What is the origin of SVCS, what is the severity of SVCS?)
4. Is the histopathology of the process causing SVCS known? What is the histopathology of the process causing SVCS?
Responses to the questions above give reasons for the selection of a treatment modality. Rational usage of percutaneous implantable stents in properly chosen patients suffering from SVCS of malignant ethiology ensures efficient differentiation of treatment modalities in supportive and/or palliative care of SVCS patients.

Key words: superior vena cava syndrome-therapy; stents; palliative care, algorithm for stenting

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Introduction

Superior vena cava syndrome (SVCS) is a critical condition diagnosed frequently by the symptoms and signs at the present time. SVCS may be caused by obstruction of SVC by tumorous invasion of venous walls and lumen or by extrinsic pressure of tumor mass both can be accompanied by intravascular thrombosis.[1,2] SVCS was firstly reported and described by William Hunter in 1757.[3] In the 17th century however, the majority of SVCS was caused by inflammatory conditions such as saccular aneurysm of syphilitic aorta as in Hunter's first case. Bronchogenic carcinomas and malignant lymphomas are responsible for a vast majority of SVCS today.[4-11] Moreover, there is a relatively new group of causes of SVCS that can be described as iatrogenic.[11] Proportions of malignant and benign causes of SVCS in the long run are given in Table 1. Recently, a comprehensive overview of SVCS published causes has been given elsewhere.[11]

For a rather long period of time, SVCS has been suggested as a life threatening condition requiring an immediate treatment (usually radiotherapy) even without previous knowledge of tissue diagnosis.[8,18-24] The development of radiotherapy tactics used in the treatment of SVCS was described in previous papers.[8,18-20,24] Thus, radiotherapy became the main treatment modality for all (presumably) malignant cases of SVCS.[1,25,26]

Experimental animal SVCS models, research of human SVCS causes, supportive care implementation and its results, better understanding of symptoms and sings development, revision of overall survival results were keystones of a change in the opinion on SVCS.[4,27] Now, SVCS is not considered as an emergent, really life-threatening condition as originally thought of.[4,9,28] Except in rare cases of SVCS with brain edema and/or intrabronchial obstruction accompanied with significant dyspnoea, there is no reason to start with immediate treatment without proper tissue diagnosis of the SCVS cause. The use of supportive treatment methods can diminish and alleviate symptoms and signs of SVCS for a time long enough to allow safe tissue biopsy and to establish the histopathological diagnosis of the SVCS cause.[4,10,11,29]

The diagnosis is the most important for a more "specific" treatment of SVCS. Such treatment can ensure fast disappearance of symptoms and signs of SVCS and longer overall survival in certain cases in comparison with previously universally used radiotherapy.[30,31]

Methods of supportive treatment in patients suffering from SVCS changed substantially. Intravenous stents started to be used in supportive and/or palliative treatment of SVCS in 1986.[32] At present, several kinds of metallic stents are used.[33,47] If properly indicated, stent indwelling may faster alleviate and exterminate the significant SVCS symptoms and signs.[1,2,29]

The treatment with self-expandable or balloon-expandable stents is not suitable for all patients because there are contraindications in stent indwelling as well as in certain situations that can be debatable from the point of view of the achievable aim of treatment and cost-benefit ratio.[42-44,48,49]

For the rational use of stents in supportive and/or palliative treatment of SVCS, the algorithm for stents indwelling has been developed. It is based on 4 questions that can be answered after the following examinations.[28]

Question No. 1: Does the patient really suffer from SVCS?

Reason for the question No. 1

The question is necessary because several patients had been referred for SVCS treatment while they suffered from different diseases (like parotitis, dermatological diseases, allergic edema, status post tooth extraction).[10,50]

Response

Response can be given by personal medical history, basic physical exam and duplex sonography assessing the blood flow of big veins. If the flow curve from duplex sonography is not physiological, computerized tomography with contrast medium and/or phlebography are necessary to obtain a more correct diagnosis.

If the response is *"YES"*, go to the *Question No.2.*

If the response is *"NO"*, go to the *Treatment No.1.*

Treatment No 1

Give different treatments for the specific (different) diseases.

Question No. 2: What is the patient's general condition?

Reason for the question No. 2

The question is needed because patients in very poor general condition are incapable to undergo diagnostic procedures. Their death can be imminent. The stenting would be not ethical in this situation.

Response

Response can be given by an evaluation of the patient's condition by the examination of his or her subjective and objective status (basic physical examination) and according to certain validated models. E.g.: Escalante's model,[51] Karnofsky's scale etc. (Table 1).

If the response is *"POOR"*, go to the *Treatment No. 2.*

Table 1. Escalante's validated model for predicting imminent death

Progressive disease
Zubrod >/= 3
Triage Pulse >/= 110/min
Respiration >/= 28/min

If the response is *"GOOD"*, go to the *Question No. 3.*

Treatment No. 2

Palliative treatment at the hospice or at the palliative care unit for the symptomatic treatment (corticosteroids, diuretics, positioning, oxygen, antibiotics, etc.)

Question No. 3: Is the stenting of SVC contraindicated? (What is the origin of SVCS, what is the severity of SVCS?)

Reason for the question No. 3

Stenting is contraindicated in patients with excessive obliteration of the large veins or their extensive invasion by of cancer (SVC and both brachiocephalic veins).

Table 2. Kishi's scoring system for signs and symptoms of SVCS obstruction

Signs and symptoms	grade
Neurological symptoms	
Stupor, coma, or blackout	4
Blurry vision, headache, dizziness, or amnesia	3
Changes in mentation	2
Uneasiness	1
Laryngopharyngeal or thoracic symptoms	
Orthopnea or laryngeal edema	3
Stridor, hoarseness, dysphagia, glossal edema, or shortness of breath	2
Cough or pleural effusions	1
Nasal and facial signs or symptoms	
Lip edema, nasal stiffness, epistaxis, or rhinorhea	2
Facial swelling	1
Venous dilatation	
Neck vein or arm vein distension, upper extremity swelling, or upper body plethora	1

Response

Response can be given by phlebography with digital subtraction (DSA) and spiral computerized tomography with contrast medium. Clinically, a severity of SVCS can be evaluated by Kishi's[48] or Nicholson's[49] classifications (Table 2).

If the response is *"YES"*, go to the *Treatment No. 3.*

If the response is *"NO"*, go to the *Questions No. 4.*

Treatment No. 3

Supportive care with corticosteroids, diuretics, oxygen, positioning, anticoagulants, antibiotics; relevant histopathology (endoscopy and/or biopsy); anticancer palliative therapy may be applied (chemotherapy or radiotherapy, or consider bypass).

Question No. 4a: Is the histopathology of the process causing SCVS known?

Reason for the questions No. 4

73 - 97% of SVCSs are caused by cancer. (Table 3)

The question is raised by different treatments of different cancers.

Table 3. The rate of benign and malignant causes of SVCS during the time since its first observation

Year	Author	Causes	
		Benign	malignant
		(%)	(%)
1757	Hunter[3]	97	3
1934	Ehrlich[12]	54	46
1949	McIntire[13]	67	23
1954	Schechter[14]	40	60
1975	Lokich[8]	3	97
1987	Fincher[15]	13	87
1992	Baker[1]	10	90
1993	Escalante[2]	3	97
1994	Tayade[16]	13	87
1998	Kee[17]	27	73

If the response is *"NO"*, go to *Treatment No. 4A.*

If the response is *"YES"*, go to *Question No. 4B.*

Treatment No 4A

Supportive care: Percutaneous stenting and endoscopy and/or bioptic methods to obtain tissue sample.

Question No. 4B: What is the histopathology of the process causing SVCS?

SVCS can appear in patients suffering from malignant tumors in three situations:[10,44]

Group A: SVCS is the first sign of cancer (its histopathology is not known).

Group B: SVCS appears during a diagnostic process due to suspect for cancer (its histopathology can or cannot be known).

Group C: SVCS appears during the follow-up period (histopathology is usually known if cancer progression is revealed), in some cases, an oncological treatment is exhausted and cannot be repeated (group C1), in other cases, progressive disease is not proven - a cause of SVCS may be late sequels of the previous treatment (group C2).

According to our assessment of 151 patients with SVCS, the rates of patients in the groups are as follows: A - 25%, B - 65%, C - 10%.[10,50]

Chemosensitive cancers (groups A, B, C)

- Lymphomas
- Small cell lung cancer
- Germ cell tumors
- Etc

Rather chemoresistant cancers (groups A, B, C)

- Non small cell lung cancer
- Malignant melanoma

Progressive cancer - all oncological treatment is already exhausted (group C1)

- Further oncological treatment is not possible any more

The cause of SVCS is late sequel of previous oncological treatment (group C2)

- Radiation fibrosis of mediastinum

Treatment No. 4B

- Differentiated chemotherapy according to the diagnosis (as curative or palliative treatment of patients of groups A, B, and the rest of group C - see the group definitions)
- Percutaneous stenting or surgical methods (bypass) (both as a palliative treatment in patients of the groups C1 and C2 and as supportive care in patients of groups A and B and rest of group C), and
- Chemotherapy and/or radiotherapy (as curative or palliative treatment in patients of groups A, B, and the rest of group C)

In summary, endovascular treatment is a simple and safe procedure to restore the patency of SVC in patients with malignancies. In most cases, it should be indicated as the first-line treatment and performed as early as possible. With proper knowledge of the SVCS cases, the best results could be obtained, if stenting follows the correct treatment schedule.

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case report

Electrochemotherapy with cisplatin of breast cancer tumor nodules in a male patient

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Background. *The metastases of breast cancer in a male patient were treated with electrochemotherapy by intratumoral injection of cisplatin. Electrochemotherapy is chemotherapy with the subsequent local application of electric pulses to the tumor nodules in order to increase drug delivery into the cells.*

Case report. *Cutaneous metastases of breast cancer were treated with the intratumoral administration of cisplatin and by 8 electric pulses (1300 V/cm) applied a minute later to each cutaneous metastasis. The treatment resulted in complete response of two electrochemotherapy treated cutaneous metastases and partial response of the third metastasis. In cutaneous metastases treated with intratumoral administration of cisplatin without electric pulses, only partial response was obtained.*

Conclusion. *This study confirms that electrochemotherapy with cisplatin is effective in the treatment of breast cancer metastases, too, as it was already proved for electrochemotherapy with bleomycin.*

Key words: breast neoplasms, male - therapy - drug therapy; cisplatin; electroporation; drug delivery system, electrochemotherapy

Introduction

Electrochemotherapy is a treatment approach that utilizes the application of electric pulses to tumors in order to facilitate the accumulation of chemotherapeutic drugs in the cells.[1] In preclinical studies, it was demonstrated *in vitro* and *in vivo* that cytotoxicity and antitumor effectiveness of bleomycin and cisplatin is potentiated several fold by electrochemotherapy.[2]

These favorable preclinical data have been confirmed in the clinical studies on cancer patients with cutaneous and subcutaneous tumors treated by electrochemotherapy with bleomycin and with cisplatin.[3] Objective responses were obtained for the majority of the electrochemotherapy - treated lesions, whereas the lesions that were only exposed to electric pulses or only treated with bleomycin or cisplatin did not respond.

Electrochemotherapy with cisplatin, given

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intratumorally, was demonstrated to be effective on many different tumor types, but not on breast cancer metastases.[4,5] Therefore, the aim of this study was to determine whether electrochemotherapy with cisplatin would also be effective in the treatment of cutaneous metastases of breast cancer.

Case report

Patients' history

A male patient, born in 1932 (H.F. No.: 6804/90) has been treated for locally advanced right breast cancer since 1990. He received 4 cycles of chemotherapy, consisting of epidoxorubicin, cyclophosphamide and 5-FU and was also irradiated to the right mammary region. Clinically, complete remission was achieved, but it was never histologically proved. He was then treated with hormonal therapy with tamoxifen until the first progression of disease in July 1997 with lung metastases and locoregional progress in the right mammary region. After the progress, the patient was treated with the second and third line hormonal therapy with aminoglutethimide and anastrozole. Both treatments resulted in stagnation of lung and cutaneous metastases and lasted approximately 1 year. In July 1999, the second line chemotherapy with etoposide was started due to the progression of lung metastases. With chemotherapy, the stagnation of lung metastases was achieved only until November 1999 when the lung and cutaneous metastases in the right mammary region progressed again. We started to apply electrochemotherapy to the cutaneous metastases in right mammary region; the possibilities of standard treatment were tired out.

Electrochemotherapy protocol

Electrochemotherapy consisted of intratumoral administration of cisplatin and subsequent exposure of cutaneous breast cancer nodules to electric pulses. Cisplatin was administrated intratumorally, at a dose of 1 mg per 100 mm^3 of nodule. The time interval between the cisplatin administration and of electric pulses application was 1 minute. The nodules to be treated were sprayed with Xylocaine in order to avoid pain. Square wave electric pulses of 100 μs, 910 V amplitude (1300 V/cm), frequency 1 Hz were delivered through two parallel stainless steel electrodes (distance 7 mm, width 7 mm, length 14 mm, with rounded tips) with an electropulsator Jouan GHT 1287 (Jouan, France). Electric parameters were controlled by oscilloscope HM 205-3 (Hameg Instruments, Germany). Electric pulses were delivered in two trains of 4 pulses with one-second interval, in two perpendicular directions (4+4 configuration). A good contact between electrodes and the skin was assured by means of conductive gel. When several nodules were treated at the same time (in the same session), electric pulses were delivered one after the other at the intervals of at least 1 minute.

Follow up

During electrochemotherapy, the patient was monitored for the evaluation of acute treatment side effects. Immediately after the therapy, the patient remained in the outpatient clinic for two hours before he was released home. The patient was examined in two-week intervals for the evaluation of response to electrochemotherapy. Tumor nodules were measured with calliper and photographed before and after treatment.

According to WHO guidelines, the response to electrochemotherapy was assessed as complete response (CR), if nodules became impalpable, partial response (PR), if nodules decreased in size by more than 50%, no change (NC), if they decreased in size by less than 50% or increased in size by less than 25%, and progressive disease (PD), if they increased in size by more than 25%.

Results of the treatment

In November 1999, the patient agreed to enter the electrochemotherapy protocol. Three of 10 cutaneous metastases, one on the right shoulder and two in the right mammary region, were treated with electrochemotherapy. Two cutaneous metastases in right mammary region were treated with intratumoral administration of cisplatin without electric pulses. Five cutaneous metastases served as controls (Table 1).

Eight weeks later, CR was obtained in two metastases treated with electrochemotherapy, and PR was obtained in the third metastasis (Figure 1). In both metastases treated with intratumoral administration of cisplatin without electric pulses, partial response was obtained 8 weeks later (Figure 2). Three of control metastases progressed, and two of them were the same size.

Six months after the beginning of treatment, in May 2000, another progress of disease in the lung was found and the patient died due to lung metastases at the end of the same month. The two metastases in which CR was achieved with electrochemotherapy, remained in CR until the patient's death, whereas the third metastasis in which only PR was achieved has already progressed by that time.

Electrochemotherapy was well tolerated by the patient. There were no major local or general side effects. The intratumoral route of cisplatin was tolerable, the patient did not complain of the pain. The application of electric pulses induced muscle contractions beneath the site of treatment after each pulse, but they were released immediately after the pulse was discontinued. After the treatment, only erythema and slight oedema occurred at the treated area, but both disappeared in one day. There were no exulcerations of cutaneous nodules. After electrochemotherapy, the patient did not complain of fatigue or other kind of discomfort. The treatment with intratumoral cisplatin did not cause any local or systemic toxicity.

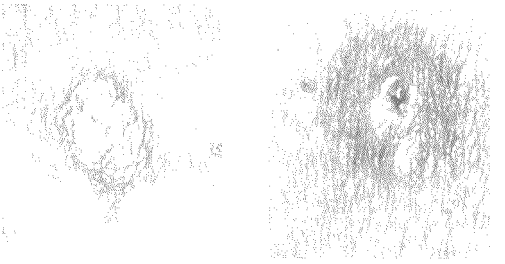
Discussion

This case report shows that electrochemotherapy is effective also in the treatment of cutaneous breast cancer nodules, because in two electrochemotherapy treated cutaneous nodules CR was obtained and, in the third nodule, PR was obtained.

Electrochemotherapy was already proved to be effective in the treatment of cutaneous and subcutaneous nodules of different histological types of tumors. Mostly used chemotherapeutic drugs were bleomycin and cisplatin. The results of numerous trials performed at five cancer centers demonstrated that electrochemotherapy with bleomycin is very effective in the treatment of cutaneous

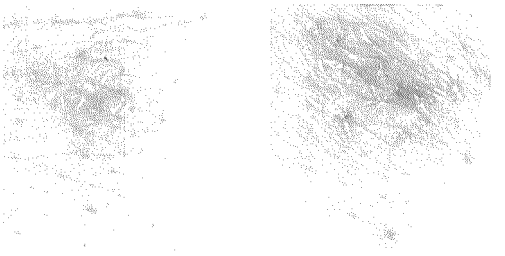
Table 1. Summary of tumor response

Treatment	Size of the treated nodules (mm^3) Before treatment	After 8 weeks	Response
Control nodules	417.8	2436.3	PD
	9.4	10.6	NC
	10.5	13.0	NC
	34.5	57.6	PD
	22.0	41.9	PD
Cisplatin	37.7	18.3	PR
	20.1	7.8	PR
Electrochemotherapy	37.7	0	CR
	30.2	0	CR
	13.9	3.1	PR



A B

Figure 1. Photomicrograph of tumor nodule before electrochemotherapy (A) and 8 weeks after it (B). The nodule (V = 37.7 mm^3) was injected with 0.377 mg of cisplatin and, after 1- minute, 8 electric pulses (1300 V/cm, 1 Hz, 100 (s) were applied to the nodule. Eight weeks after the treatment, the tumor nodule was in CR.



A B

Figure 2. Photomicrograph of tumor nodule before treatment with cisplatin (A) and 8 weeks after it (B). The nodule (V = 37.7 mm^3) was injected with 0.377 mg of cisplatin intratumorally. Eight weeks after the treatment, the tumor nodule was in PR.

and subcutaneous nodules of different tumors, including breast adenocarcinoma nodules.[6] In all of the nodules CR was obtained. Eight additional metastatic breast cancer nodules were treated with electrochemotherapy; but they couldn't be evaluated because the follow-up was too short.

The first clinical study of electrochemotherapy was performed at the Institute of Oncology, Ljubljana, by evaluating antitumor effectiveness of electrochemotherapy with intratumorally administered cisplatin. In all electrochemotherapy treated nodules of histological different tumors, CR was obtained.[4] Another clinical study on malignant melanoma patients showed that electrochemotherapy with intratumoral administration of cisplatin is effective, resulting in 68% of CR in the treated cutaneous tumor nodules.[5]

No clinical study on electrochemotherapy of cutaneous breast cancer nodules with cisplatin administered intratumorally has been done so far. Some preclinical studies were made on electrochemotherapy and intramuscular administration of bleomycin to breast cancer nodules in experimental animals.[7] Thirty-three of 38 electrochemotherapy treated nodules regressed at least partially within 2- 3 weeks, three of them were cured. In none of the control nodules treated only with bleomycin given intramuscularly neither partial response nor growth arrest were attained.

In conclusion, clinical studies of electrochemotherapy with cisplatin administrated intratumourally have demonstrated to be effective and safe in the treatment of different histological types of tumors. Our case report demonstrates it is effective in the treatment of breast cancer nodules, too. The clinical study on more breast cancer patients is going on.

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Synchronous and metachronous bilateral germ cell tumours of the testis

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Background. *We reported fourteen patients with bilateral testicular tumours, and discussed the need for contralateral testicular biopsy during orchiectomy to detect carcinoma in situ (CIS).*

Patients and methods. *Fourteen patients with bilateral testicular tumours were reviewed in order to establish the incidence, histologic findings, predisposing factors, interval between the development of two primaries, type of treatment administered and the overall outcome.*

Results. *Bilateral tumours were identified fourteen times between 1984 and 1996. The tumours occurred simultaneously in five patients, and a contralateral malignancy developed in the others after a time ranging between 6 and 107 months. The most frequent histologic diagnosis was seminoma and was confirmed in 10 cases. Four patients had a history of undescended testis. One patient also had persistent müllerian duct syndrome. All patients were initially treated with radical orchiectomy. According to their stage, all patients were treated with radiotherapy and/or chemotherapy. Four patients died in the period between 6 and 33 months after the diagnosis. The remaining 10 are still alive with, no evidence of disease.*

Conclusions. *The second tumour is diagnosed more often due to prolonged follow-up examinations; periodic self-examination by patients; ultrasonography of the testis; tumour markers AFP and beta-HCG and a contralateral testicular biopsy during orchiectomy. CIS of the contralateral testis evolves into invasive cancer in probably most of the patient germ cell tumours and usually cured by radiotherapy. Despite that, we do not advocate a routine biopsy of the contralateral testis in the patients with unilateral testicular tumour due to the following reasons: 1. CIS of the testis is the precursor of most malignant testicular germ cell tumours except for spermatocytic seminoma, Teratoma and Paediatric yolk sac tumours. 2. CIS is not diagnosed in about 95 % of all cases with testicular tumours. 3. CIS may be randomly distributed and a single biopsy may not detect it. 4. Testicular biopsy does not only devoid minor complications but also affects spermatogenesis. 5. Development of a germ cell tumour in general takes 3 and 5 years, a non-palpable testicular tumour can be localised by ultrasonography and ultrasound scanning occasionally identifies CIS based on irregular pattern secondary to the normal tubules. 6. Scar lesions in the testis after biopsy may render sonographic interpretation more difficult. 7. The natural history of CIS is unknown and the precise method of treatment is controversial. 8. There is no data that CIS has an impact on survival. 9. A careful follow-up is warranted to all germ cell tumour patients, including those with negative biopsies. So, a watchful waiting policy to the problem of the CIS should be the choice.*

Key words: testicular neoplasms-pathology; orchiectomy; carcinoma in situ - diagnosis; germinoma

Introduction

Testicular carcinomas are relatively rare tumours; however, they are the most common solid tumours occurring in males between the ages of 20 and 34 years. The incidence of testicular tumours is 2.1 to 2.3 per 100 000 males.[1]

The metachronous appearance of second tumours deserves a particular attention because it has been reported that once a patient has a malignant tumour of one testis, the risk of developing a tumour on the opposite side is much higher than that of the general population.[1] The increase of the bilateral testicular cancer may be due not only to higher survival rates obtained with cisplatin based chemotherapy but also to its early detection by the ultrasound of the testes.

The aim of the present paper was to analyse a group of patients with bilateral germ cell tumours of the testis and to discuss the need for a biopsy of the contralateral testis during orchiectomy for the first primary.

Patients and methods

From 1984 to 1996, 876 patients, 17 to 68 years of age, were treated for a testicular germ cell tumour in Ankara Oncology Education and Research Hospital. We reviewed the medical records of these patients to identify and study bilateral testis tumours (BTT) with respect to their incidence, histopathologic findings, predisposing factors, interval between the development of two primaries, type of treatment administered, and the overall outcome.

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Results

Bilateral invasion was identified in fourteen patients (1.6%). The tumours occurred simultaneously in five patients (0.57%). In nine cases, a contralateral malignancy developed after a time interval ranging between 6 and 107 months. The age of patients ranged from 21-58 years (median 34.5 years). Seminoma was the most frequent pathologic diagnosis (10/14 cases), followed by mixt tumours (2/14 cases: seminoma + embryonal carcinoma, seminoma + teratocarcinoma), and each one had embryonal carcinoma and teratocarcinoma (Figure 1). Four of fourteen patients (28.5%) had a history of undescended testis. One of these patients also had persistent Müllerian duct syndrome with bilateral abdominal testicular seminoma.[2]

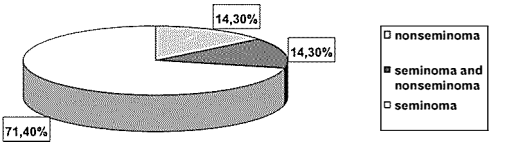

Figure 1. Histologic findings in consecutive bilateral testicular tumors.

Initially, all patients were treated with radical orchiectomy. In accordance with the staging system used in our hospital[3] the patients were classified as follows:

- stage I: four patients
- stage IIb: one patient
- stage IIc: five patients
- stage III: one patient
- stage IV: three patients

Four of ten seminoma patients in stages I and IIb, and seminoma + teratocarcinoma case in stage I, received radiotherapy. Of the remaining eight patients in stages between IIc and IV were treated with the reduced dose PVB chemotherapy protocol (cisplatin, vinblastine, bleomycin).[3] Three months after radiotherapy, the seminoma + teratocarcinoma case in stage I was also treated with

chemotherapy because the level of tumour marker AFP was noted to be high. Four patients died 6, 9, 20 and 33 months, respectively after the diagnosis of the second tumour. Three of four patients died due to central nervous system metastases, and the fourth died because of myocardial infarction. All other patients are still alive and the longest survival time is 8 years and 11 months.

Discussion

Although the average incidence of testicular tumours is in the range of 2.1 to 2.3 per 100.000 males, it seems to have increased in the last three decades. It remains the most common solid tumour in men between the ages of 20 and 34 years.[1,4,5]

In patients who survive one testicular malignancy, the risk of developing a contralateral testicular malignancy is 500 to 1000 times greater than in healthy male subjects. The risk is again increased by the factor 2 to 4 in cases of previous cryptorchidism.[6-8] The risk factors like cryptorchidism in unilateral malignancy were reported to range between 7 and 35% of the total number of patients with testicular cancer.[9,10]

In our series, the incidence of cryptorchidism is 2.7% (24 patients) and 28.5% of these (4 patients) had BTT. More recent studies document an increased incidence of BTT. The relative incidence of BTT reported in the literature from 1981 to 1995, can be calculated as 2.36%.[8,11-15] In the current study, BTT is 1.7% of the total incidence of testicular carcinomas.

In principle, bilateral tumours can occur synchronously or metachronously, i.e. at different times. Recent literature suggests that approximately two thirds of the metachronous testicular tumours occur within 5 years of the first diagnosis.[16] Our study disagrees with this maintaining that 33.3% of all metachronous tumours occurred within 5 year of the first diagnosis and that 66.6% were diagnosed after a period of more than 5 years (Figure 2). The incidence of synchronous BTT have been reported in the range of 16.6% to 31.5%.[16-18] Our incidence is 35.75%.

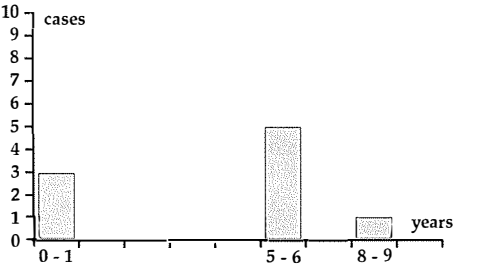

Figure 2. Time-interval until the diagnosis of the contralateral testicular tumour.

In Denmark, the incidence of carcinoma *in situ* (CIS) in the contralateral testis in patients with testicular malignancy has been reported to be 5% to 6%; however, 50% of these men had a history of cryptorchidism. Though the reports of sequentially diagnosed BTT are increasing in number, routine biopsy of the opposite testis remains controversial. CIS is a characteristic pattern within the seminiferous tubules. In typical cases, such tubules contain two types of cells: CIS germ cells and Sertoli cells, and CIS is the precursor of most types of malignant testicular tumours, except of teratoma, spermatocytic seminoma, paediatric yolk sac tumours and epidermoid cyst (monodermal teratoma).[19] Thus, CIS is found in only 5% of patients with the primary tumour of the testicle. Biopsy carries the risk of a transscrotal procedure in consecutive tumour and scar lesions in the testis may render sonographic interpretation more difficult.

A technique that seems to have a bright future is non-invasive CIS detection employing ejaculate examination for the presence of aneuploid cells in flow cytometry or detection of tumour cells in the ejaculate using a specific monoclonal antibody.[20] There is no doubt that an impalpable testicular tumour

can be localised by ultrasound, and ultrasound scanning occasionally identifies CIS based on irregular pattern secondary to the abnormal tubules.[5] Thus, no risk of implanting the carcinoma in the scrotal wall or altering the lymphatic drainage has been involved. Realistically, we do not recommend a routine biopsy of the contralateral testicle to detect CIS during radical orchiectomy, except in cryptorchidic patients, as cryptorchidism is an important indication for biopsy of the other testicle and as a tumour in the contralateral testicle occurs in around 50% of all these cases.

The management plan of the tumour in the contralateral testis depends upon the time interval between the development of the two tumours, extent of the therapy of the original tumour and the histologic type and stage of the second tumour. There is no standard therapy for patients with consecutive tumour, and each patient requires an individual therapeutic approach. The prognosis of patients depends on the same factors that affect the prognosis of unilateral testis tumours. In the absence of an identifiable disease, a policy of watchful waiting and for identifiable metastases cisplatin based chemotherapy should be treatment of choice.[20,21]

Treatment at each major site of urologic malignancy has characteristic side effects on sexuality and fertility. Bilateral orchiectomy have a negative effect not only on potency but also on sexual life because serum testosterone reaches castrate levels in mean of 3 hours.[22] An abnormally low level of testosterone may cause difficulty in achieving full erection, a loss of sexual desire, reduced ejaculate, a need for prolonged stimulation to reach orgasm and often a decrease in the intensity of pleasure produced during penile caressing and orgasm.[23,24] The rates of sexual dysfunction in our cases are shown in Table 1. The reduction of the testosterone levels secondary to an orchiectomy provokes a counter-regulatory effect with an intra-hypothalamic increase of adrenergic activity from which hot flushes result. Although these flushes are not dangerous, they can sometimes be extremely bothersome and, as a result, can potentially reduce the quality of life of patients.[24] Only one of our cases experienced hot flushes. Since in the case of post-menopausal hot flushes in women, sufficiently high-doses of oestrogen lead to complete disappearance of their complaint, a replacement of testosterone for bilaterally orchiectomised patient with BTT is however indicated.

Table 1. Sexual dysfunction in patients treated for bilateral testicular cancer

	Number of patients	Total (%)
No current sexual activity	1	10
Erectile dysfunction	4	40
Low sexual desire	8	80
Reduced ejaculate	10	100
Reduced orgasmic intensity	2	20

Conclusions

Second tumors are being increasingly diagnosed due to the following reasons: (1) Prolonged follow-up examinations; (2) Periodic self-examination by patients; (3) Ultrasonography of the testis; (4) Tumour markers AFP and beta-HCG; (5) A contralateral testicular biopsy at the time of orchiectomy.

CIS of the contralateral testis evolves into invasive cancer in probably most of the patients with germ cell tumours and cured by radiotherapy. Although CIS of the testis is the precursor of most malignant germ cell tumours we do not advocate routine biopsy of the contralateral testis with unilateral testicular tumour. It is estimated that only the typical form of seminoma could be diagnosed and CIS occurs in the testicle containing seminoma in more than 85% of the cases.[25,26]

The natural history of CIS is unknown and the precise method of treatment is controver-

sial. In a large study involving 87 institutions in Europe, the prevalence of TIN in the contralateral testis was found to be 4.9%. Testicular atrophy was reported to be an independent factor for prevalence in a multivariate analysis.[27] Since CIS is not randomly dispersed throughout the testis a single biopsy may not detect it.[28] There is a small but definite false-negative detection rate, and there are reported cases of the development of neoplasia despite the earlier negative biopsy for testicular intraepithelial neoplasia.[28]

A 3 mm surgical testicular biopsy has a diagnostic sensitivity close to 100%, it is not devoid of minor complications such as infection, superficial serous exudates, localised induration and pain. It has been suggested that biopsy of the contralateral testis affects spermatogenesis.[29] Thus, ultrasound scanning occasionally identifies CIS based on irregular pattern secondary to the normal tubules and scar lesions in the testis after biopsy may render sonographic interpretation more difficult. On the other hand, searching for more disease in the contralateral testis and facing treatment of CIS, since 95% of patients does not have CIS in the other testis, may impose unnecessary emotional stress in some patients.[27,30]

Radiotherapy can eradicate CIS and, thereby, prevent cancer development; but, to date, there is no data whether Leydig cell function is affected or not at even low doses (14 Gy).[31] Furthermore, close follow-up is warranted to all germ cell tumour patients, including those with negative biopsies. So, to our opinion, a watchful waiting policy to the problem of CIS in the contralateral testis should be the choice.

The treatment principles of secondary tumours should be similar to that for primary tumours. In order to prevent sexual dysfunction and hot flushes, administration of androgens may be mandatory in some cases. Thus, an artificial testicular implant can be performed if psychological resistance occurs.

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The relationship between DNA methylation and expression of three different DNA methyltransferases in ovarian cancer

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Background. *DNA methylation in mammals is required for embryonic development, X chromosome inactivation and imprinting. Previous studies have shown that methylation patterns become abnormal in malignant cells and may contribute to tumorigenesis. The aim of the study was to ascertain the relationship between overall DNA methylation and the expression of DNMT1, DNMT3A and DNMT3B in ovarian cancer samples.*

Materials and methods. *DNA digestion with either methylation sensitive HpaII, or methylation insensitive MspI restriction endonuclease and quantitative reverse transcription-PCR methods were used to analyse global methylation levels and expression levels of five ovarian cancer and three normal ovarian tissue samples.*

Results. *All five analysed cancer samples were hypomethylated. The differences of methylation levels between normal ovarian tissue and carcinoma samples were statistically significant ($P<0.05$). All five cancer samples showed overexpression of DNMT3A and DNMT3B, and only two ovarian tumour samples showed overexpression of DNMT1. There was no correlation between global demethylation and expression levels for the three different DNMTs.*

Conclusion. *Genome wide hypomethylation facilitates tumour development with predisposition of cells to structural and numerical chromosomal aberrations but the paradox of the global hypomethylation observed in cancer cells and the high levels of DNMTs that are present in these cells still remain to be resolved.*

Key words: ovarian neoplasms, DNA methylation; methyltransferases

Introduction

Investigations into the genetic aetiology of cancer have markedly advanced our understanding of the disease. A growing body of evidence supports the hypothesis that epigenetic events have a prominent role. Mammalian cells possess the capacity to modify epigenetically their genome via DNA methylation. Methylation occurs at the 5 position of the cytosine ring within the context of the

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CpG dinucleotide. CpG islands are short sequences rich in the CpG dinucleotides.[1]

Mammalian DNA methylation has been proposed as an important factor in maintaining genome stability.[2] Human cancer cells typically contain DNA with abnormal CpG dinucleotide methylation patterns. Most often, the cancer cell DNA induces increases in CpG dinucleotide methylation at specific CpG island sequences, accompanied by decreases in CpG dinucleotide methylation at most other sites.[3] There is a growing body of evidence that abnormal methylation of CpG islands in the promoters of tumour suppressor genes can contribute to cancer formation and progression by providing an alternative means to mutational inactivation.

DNA methylation results from a methyl transfer reaction performed by a *trans*-acting enzyme known as DNA methyltransferase (DNMT). Two distinct methyl transfer activities can be distinguished, based on the methylation status of the substrate.[4] The activity which uses hemi-methylated CpG dinucleotides as a substrate is referred to as maintenance methylation activity, whereas *de novo* DNA methylation activity refers to new addition of methyl groups at the sites that were previously unmethylated. Until recently, only one DNA methyltransferase (DNMT1) had been cloned from human cells. It is characteristic of DNMT1 that its relative *de novo* activity is 1-2 orders of magnitude lower than its maintenance activity.[4] Recently, two additional mammalian DNMT genes have been identified, that are referred to as DNMT3A and DNMT3B. These genes differ from DNMT1 in that the encoded polypeptides DNMT3α and DNMT3β have approximately equal ratios of *de novo* DNA methyltransferase activity: maintenance DNA methyltransferase activity.[5]

Ovarian carcinomas are a heterogeneous group of tumours of various cell types. Ovarian epithelial tumours are subdivided into benign (cystadenoma) and malignant (carcinomas) categories. These tumours also include a third category, called tumours of low malignant potential (LMP), which are intermediate between cystadenomas and carcinomas and, like benign tumours, are stable over time. Substantial progress has been made in our understanding of the molecular biology and genetics of ovarian epithelial tumours. Cheng *et al.* report that alterations in DNA methylation are early, but not initial events in ovarian tumourigenesis.[6] Certain global hypomethylation levels are associated with both tumours of low malignant potential and carcinomas, but not with cistadenomas.[7]

One of the proposed causes of changes in the methylation machinery in transformed cells is overexpression of one or more of the three known catalitically active DNMTs. In this study, the relationship between overall DNA methylation and the expression of DNMT1, DNMT3A and DNMT3B in ovarian cancer samples was investigated.

Material and methods

Five ovarian cancer samples and three normal ovarian tissue samples taken from total hysterectomies performed for prolaps or fibromyoma were analysed. All tissue samples were collected for therapeutic or diagnostic purposes according to ethical rules. Approximately 2g of the surgically removed tissue was frozen immediately in liquid nitrogen and stored at -80°C until DNA and RNA isolation. Total RNA was isolated by the Trzole reagent kit (Life Technologies) and residual DNA contamination was removed using a High Pure RNA isolation kit (Roche). Genomic DNA was isolated by the standard method of protinase K digestion and phenol-chloroform extraction.

The methylation status of total genomic DNA was established as previously described.[8] DNA was digested with either methylation-sensitive *HpaII*, or methylation insensi-

tive *MspI* restriction endonuclease. The digested DNA samples were separated on 1% agerose gel and blotted. Hybridization was performed with ^{32}P-labelled total DNA from human placenta. For each lane, the ratio r between the radioactivity present between the molecular weights of 1.8 kilobase (kb) and 2.9 kb and the totality of the smear was calculated. The value of R for *MspI* digestion was expected to be identical for all the DNA. It was 0.17 ± 0.01 for all eight samples. The ratio between R obtained for *MspI* and *HpaII* digestion was calculated for each DNA. This value (RD=relative demethylation) multiplied by 100, theoretically ranges from 0 (the most methylated) to 100 (the least methylated).

A real time fluorescent detection method was used to quantify the mRNA expression of DNMT1, DNMT3A and DNMT3B by RT-PCR.[9] Reverse transcription was performed using the Superscript II enzyme (Life Technologies) with 2µg of total RNA, 200 ng of oligo d(T) and 0.5 mM of each dNTP. Primers for PCR were chosen with the assistance of the computer program Primer Express (Parker-Elmer Applied Biosystem). The following primers were used: 1) DNMT1: 5'-TGGAGAGAA GCTCCCTCTGTTC-3' and 5'-CCGAGCTCAACCTGGTTATGTT-3'which yield a 119 bp fragment; 2) DNMT3A: CAAT-GACCTCTCCATCGTTCAAC-3' and 5'AGC-CGGCCAGTGCCCTCGTAG-3'; DNMT-3B: 5'-CCATGAAGGTTGGCG ACAA-3' and 5'-TGGCATCAATCATCACTGGATT-3' 4) histone H4, partially degenerated primers were used taking into account the published sequences for the different forms (Genebank released 104), 5'-ATYTAYGAGGAGACY-CGCG-3', 5'-CCATGG CKGTGACYGTCTT-3' which gave a 107 bp fragment.

The specific cDNA of interest and reference cDNA (histone H4) were PCR-amplified separately by PCR using a GeneAmp 5700 sequence detection system and a SYBR Green PCR kits (Parker Elmer Applied Biosystems). The detection method was based on the property of the SYBR Green dye, which fluoresces when bound to double stranded DNA. At each cycle, the amount of amplified product was measured by monitoring the green light emitted. PCR amplification was performed in MicroAmp Optical tubes (Parker Elmer Applied Biosystems) positioned in a 96 well support. The reaction mixture (25 µl) contained the reverse transcription product, 250 nM each primer, 200 µM each dATP, dCTP, and dGTP, 400 µM d UTP, 4mM MgCl2, 5 units of AmpliTaq Gold DNA polymerase, 1 unit of AmpErase uracil N-glycosylase and 1 x SYBR Green PCR buffer containing the SYBR Green dye. Thermal cycling consisted of 1 cycle at 50°C for 2 min and at 95°C for 10 min, followed by 40 cycles at 60°C for 1 min and at 95°C for 15 s.

Each assay included a standard curve and nontemplate control and the tested samples, all in duplicate. All the primer pairs used gave an efficiency of amplification higher than 95%. Two reverse transcriptions followed by at least two PCR amplifications were performed for each sample. For each sample (corresponding to 10 ng of total RNA), the cycle number at which the fluorescent signal crossed the threshold in the exponential phase of the PCR reaction was measured and compared to the standard curve. The standard curve was constructed with serial dilutions of reverse transcription products corresponding to 0.1, 1, 10 and 100 ng of total RNA from a reference cell line (MDA-MB-134). The expression of the tissue was compared to the standard curve and reported in equivalent quantity of total RNA from the reference cell line. Normalisation of RNA amounts was performed using histone H4 expression analysed with the same procedure. The expression ratios DNMT1/H4, DNMT3A/H4 and DNMT3B/H4 were calculated. This method did not give the absolute quantity of mRNA, nor did it allow a quantitative gene to gene comparison of the expression.

Results

The relative demethylation value (RD) was measured for control DNAs from three normal ovarian tissues. All three samples had similar RDs ranging from 37 to 39 with a mean RD at 37 ± 1. The RD values were much more variable for the five ovarian tumour tissues, ranging from 41 to 57, with a mean RD at 47 ± 6. Thus by comparison with controls, tumour sample DNAs were hypomethylated and there was no overlapping between the RDs for normal and tumour ovarian samples. The differences of global methylation levels between normal and tumour samples were statistically significant ($P<0.05$).

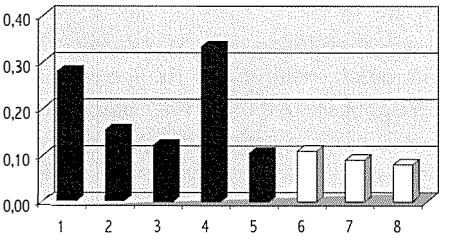

Figure 1. The relative expression levels of DNMT1 in five ovarian tumours (black) and normal ovarian samples (white). The expression levels were normalised with expression levels for the proliferation-associated gene H4.

Figure 1 shows the relative expression levels of DNMT1 in five individual ovarian tumours and three normal ovarian samples. We found overexpression in just two ovarian tumours when the proliferation-associated gene H4 was used for normalisation.

Figure 2 shows the relative expression levels of DNMT3A and DNMT3B in the same samples as described above when the proliferation associated gene H4 was used for normalisation. The expression levels of DNMT3A and DNMT3B for each tumour versus the mean expression level for each gene in the normal ovarian samples were calculated. We found overexpression of DNMT3A and DNMT3B in all five ovarian tumours. The

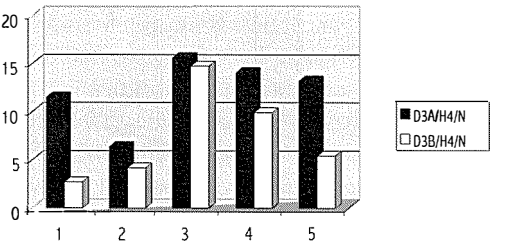

Figure 2. The relative expression levels of DNMT3A and DNMT3B normalised with expression levels for H4. The expression levels for each ovarian tumour were such that the mean expression level of three normal ovarian samples equals a value 1.

overexpression means that the expression for DNMT in tumour tissue is at least 2-fold higher than the mean expression level in 3 normal ovarian samples.

No relations were found between global DNA methylation and the expression of DNMT1, DNMT3A and DNMT3B.

Discussion

The phenotypic characteristics of every living cell are determined primarily by the nucleotide sequence of their respective genome. However, several epigenetic mechanisms may modulate genomic activity and further contribute to phenotypic variation. DNA methylation is the only known covalent epigenetic modification of mammalian DNA.[10] Patterns of methylation are heritable, undergo characteristic changes during embryological development and are tissue specific. The degree of DNA methylation is generally inversely correlated with transcription activity when it occurs within the promoter region of a gene.

A growing body of evidence suggests that alterations in DNA methylation play a major role in the development of human cancers.[11] Transformed cells of virtually all types often simultaneously have widespread loss of methylation from normal methylated sites, increased total activity of DNMT and more regional areas of hypermethylated DNA.[12]

In our study, all five ovarian cancer samples were hypomethylated in comparison with global methylation status of normal ovarian tissue. Qu *et al.* described hypomethylation in satellite 2 DNA of chromosome 1 and 16 of most ovarian carcinomas and LPM.[13] Cheng and co-workers compared the levels of DNA methylation in ovarian cystadenoma, LMP tumours and carcinomas.[6] They reported that mean global levels of DNA methylation showed significant differences among the three ovarian tumour subtypes. They also measured 5 mC levels in four samples of normal ovarian tissues. As in our study, the methylation levels of normal ovarian tissue samples were significantly higher than in tumours. All these findings are consistent with the hypothesis that the genome wide hypomethylation facilitates tumour development with a predisposition of cells to structural and numerical chromosomal aberrations.

The enzymatic methylation machinery itself is composed of three known catalitically active DNA methyltransferase, DNMT1, 3A and 3B. DNMT1 is targeted to replication foci and has a 10-40-fold preference for hemimethylated DNA substrates.[14] The newly identified DNMT3 enzymes are essential for embryonic development and are responsible for the wave of *de novo* methylation seen during embryogenesis which establishes the somatic methylation pattern for the organism.[5]

The exact nature of the methylation defect in cancer cells is not known; however, it has been noted by several groups that DNMT1 is overexpressed in tumour cells and it has been shown more recently that the DNMT3 family can be overexpressed, too. The degree of overexpression varies depending of the tumour type and the method of analysis. Not all tumours, however, overexpress the DNMTs, though overexpression may be necessary; in many cases, it is probably not sufficient to cause the methylation defects observed in cancer cells.[15] In our study, we found overexpression of DNMT3A and DNMT3B in all five ovarian cancers. The mean expression levels were 12-fold higher for DNMT3A and 7-fold higher for DNMT3B than the mean expression levels for normal ovarian tissue. For DNMT1, we found overexpression in just two cases.

The paradox that remains to be resolved is the global hypomethylation observed in cancer cells notwithstanding the high levels of DNMTs that are present in these cells. One possible explanation is that cancer cells also express high levels of a demethylase, which actively removes methyl groups from the DNA. We did not find any correlation between global hypomethylation and DNMT expression in ovarian tumours.

Abnormal hypermethylation recurrently associated with gene silencing has been reported for tumour suppressors genes Rb1 [16], VHL [17], and CDKN2/p16.[18] Hypomethylation of several oncogenes was also reported in tumours. In ovarian cancer, Cheng *et al.* found methylation of the *MyoD1* locus in five of ten ovarian carcinomas, but none of the five normal ovarian tissue samples showed methylation of these sites.[6] McCluskey *at al.* reported that p16 silencing is also important for the development of ovarian carcinoma.[7]

Identification of specific genetic targets for methylation changes in ovarian epithelial tumours may not only lead to a better understanding of the molecular mechanisms and determinants of their development, but may also facilitate the use and monitoring of methylation-targeting drugs in the treatment of ovarian cancer patients.

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Logit modeling of the Modulation Transfer Function (MTF) of metal/film portal detectors

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Background. *Logit analysis is used to fit measured Modulation Transfer Function (MTF) data of front-metal/film detectors at megavoltage energies. The detectors consist of double-emulsion portal film placed abutting front metal-plates of Copper or Lead ranging in thickness from 0.39 to 2.40 mm. The MTF data reported by other investigators is also analyzed and authenticates this type of modeling. The logit function predicts the MTF to within experimental uncertainty and the weighted linear regression analysis demonstrates that the fitting is successful with high correlation coefficient: -0.999 ≤ r ≤ -0.995. The logit function parameterizes the MTF with two regression parameters, a and b. These parameters exhibit a linear relationship with the front-plate mass thickness greater than the maximum range of electrons.*

Conclusions. *The logit fitting analysis allows the calculation of the MTF for metal-plates that can be used in the design of the front-end of electronic portal imaging devices.*

Key words: radiotherapy, high-energy; linear models; logit, MTF, megavoltage, portal detectors

Introduction

The modulation transfer function (MTF) is commonly used to describe the resolution capabilities of imaging systems, which often have a metal-plate component. Few MTF's of metal-plate/film or other types of portal detectors are found in the literature since measuring detector MTF's at therapy energies is a very task intensive process that is prone to large systematic errors. Fit modeling may be helpful in the determination of the metal of choice for these systems, as well as, the determination of the metal of choice for the front-end of electronic portal imaging devices (EPID's). Moreover, parameterization can help quantify the dependence of the MTF on physical quantities, such as metal-plate physical density.

MTF modeling of screen/film systems for diagnostic radiological purposes has been performed in the past with varying degrees of success, using exponential, Lorentzian and Gaussian functions.[1-4] It has been shown that the MTF of radiological phosphor screen/film

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detectors can be accurately modeled by the logistic or logit function with typically high correlation coefficients[5,6] (i.e., r = -0.998). Logit analysis is a straight-line transform method that can effectively parameterize the MTF and is relatively simple to implement. The MTF's of metal/film detectors at megavoltage energies have been measured,[7-9] however, there have not been any reports of the analytical representation or the fit modeling of the MTF for front-metal/film detectors at megavoltage energies. We perform logit analysis of MTF's obtained for front-metal/film detectors irradiated at megavoltage energies. To obtain a comprehensive set of fitting parameters, we use the MTF data we have measured for a large number of metal/-film combinations.[9] We also analyze the MTF data reported by other investigators[7] to authenticate this type of modeling.

Logit analysis

The logit analysis transforms sigmoidally shaped functions into straight-line functions[10] that can then be analyzed in terms of the "slope" and "intercept" regression parameters. Following the approach described by Bencomo and Fallone[6] for diagnostic screen/-film systems, we can fit the MTF of metal/film detectors by a function $MTF_L(f)$ given by:

$$MTF_L(f) = \frac{1}{1+e^{-(a+b\ln(f/f'))}} \qquad (1)$$

where f is spatial frequency and f' is a constant (typically 1, with units of f) to ensure correct dimensionality. The straight-line logit transform of Eq. 1 is:[10]

$$logit(MTF_L(f)) = \ln\left(\frac{MTF_L(f)}{1-MTF_L(f)}\right). \qquad (2)$$

When the logit of the measured $MTF(f)$ is plotted versus $ln(f/f')$ a straight line results, which is represented by $a + b \ln (f/f')$ where a and b are the "intercept" and "slope" of the line, respectively.

The constants a and b are regression parameters that were estimated using Berkson's calculated methods[10] which are summarized as:

$$b = s_{lx} / s_x^2 \quad , \qquad (3)$$

$$a = \bar{l} - b\bar{x} \qquad (4)$$

where

$$s_{lx} = \sum_{i=1}^{n} w_i'(l_i - \bar{l})(x_i - \bar{x}) \quad , \qquad (5)$$

$$s_x^2 = \sum_{i=1}^{n} w_i'(x_i - \bar{x})^2 \qquad (6)$$

and

$$l_i = \ln\{MTF(f_i)/[1 - MTF(f_i)]\} \qquad (7)$$

$$x_i = \ln(f_i) \quad , \qquad (8)$$

$$w_i' = w_i / \sum_{i=1}^{n} w_i \quad , \qquad (9)$$

$$w_i = MTF(f_i)\{1 - MTF(f_i)\} \qquad (10)$$

where $\bar{l}$ and $\bar{x}$ are mean values of l and x respectively, and $MTF(f_i)$ is the value of the MTF, at the spatial frequency f_i averaged over the three or four measurements. The summation is over the n frequency components of the MTF.

Logit analysis has been most widely used for accurate modeling of bio-assay dose survival curves. Berkson assumed that when a system is exposed to a dose y the fractional response P which measures the observed por-

tion p affected out of m exposed, is a random variable that is binomially distributed.[11-13] From binomial statistical theory, the variance of the distribution p is $s_p^2 = P[1 - P]/m$. We can view the MTF as the fractional intensity response of the front-metal/film system to an input composed of sinusoidals of equal intensity for all spatial frequencies f. In our case, $P = MTF(f)$, and the regression parameters a and b can be obtained from a simple least squares calculation which minimizes the weighted-square difference between the observed $MTF(f)$ and the estimated $MTF_L(f)$. The weighting w_i, of Eq. 10, equals ms_p^2 .

The goodness-of-fit of the logit function to the $MTF(f)$ data can be specified with the regression correlation coefficient r, and the uncertainties in a and b can be specified by s_a and s_b, respectively. The best fit regression correlation coefficient is given by:

$$r = b\left(\frac{s_x}{s_l}\right) = \frac{s_{lx}}{s_x s_l} \qquad (11)$$

where s_x and s_l are the standard deviations on x and l, respectively.[14] The standard deviations of a and b are

$$s_a = \sqrt{s^2\left(\frac{1}{n} + \bar{x}^2 s_b^2\right)} \quad , \qquad (12)$$

$$s_b = \sqrt{\frac{s^2}{\sum_{i=1}^{n}(x_i - \bar{x})}} \quad , \qquad (13)$$

with

$$s^2 = \frac{\sum_{i=1}^{n}(l_i - a - bx_i)^2}{n-2} \qquad (14)$$

and the data consists of h spatial frequency observations.[15] The experimental uncertainty in the individual $MTF(f_i)$ is not taken into account in the logit model.

Results and discussion

The detectors from Falco and Fallone[9] having front-plates only, are listed in Table 1 with their best fit a and b regression parameters. Plots of the logit fits to the measured $MTF(f)$ are shown in Figures 1 and 2 for detectors irradiated by the 10 MV and Co-60 spectrum, respectively. The correlation coefficients r (Table 1) range from -0.995 to -0.999, and for a particular metal, the parameter a decreases with front plate thickness (or mass thickness). The decrease of a with front plate thickness corresponds to the decrease of the MTF with front plate thickness for a given metal.

To further demonstrate the fitting capabilities of the logit technique, the technique was also applied to the MTF's of front-metal/film detectors measured by other investigators. Table 2 shows the logit best-fit parameters for the MTF's reported by Munro *et al.*[7] for the 18 MV and Co-60 spectra. The correlation coefficients range between -0.994 and -0.999 except for one value at -0.991. Plots of the logit regression fits to these data are shown in Figure 3. To avoid clutter, some of the curves in these figures have been offset vertically. The decrease in parameter a with beam energy cannot be verified with the Munro *et al.* data because they only used one thickness for each of the front-metal plates. The data of Droege and Bjarngard[8] were not fitted because of a flaw in their technique as was discussed by Munro *et al.*[7]

In Figure 4, our measured $MTF(f)$'s are compared to the fitted $MTF_L(f)$ for the (a) typical and the (b) worst case. For the worst case, the $MTF_L(f)$ is within the uncertainty of the measured $MTF(f)$ for the whole spatial frequency range.

The regression parameters a and b for the detectors in Table 1, are plotted in Figure 5 as a function of front-plate mass thickness. The plots exhibit a linear relationship between the regression parameters and the mass thick-

Table 1. Regression coefficients *a* and *b* for the metal-plate/film detectors studied. The correlation coefficient *r*, is also shown

Front-Plate Thickness (mm)	"Intercept" *a*		"Slope" *b*		Correlation Coefficient *r*	
	Co-60	10 MV	Co-60	10 MV	Co-60	10 MV
0.95 Cu	-0.150 ± 0.010	-0.480 ± 0.014	-0.834 ± 0.009	-0.982 ± 0.012	-0.995	-0.996
1.75 Cu	-0.369 ± 0.010	-0.782 ± 0.015	-0.750 ± 0.009	-0.927 ± 0.013	-0.996	-0.995
2.40 Cu	-0.617 ± 0.008	-0.969 ± 0.007	-0.700 ± 0.009	-0.809 ± 0.007	-0.997	-0.998
0.39 Pb	0.108 ± 0.005	-0.142 ± 0.005	-1.047 ± 0.004	-0.991 ± 0.005	-0.999	-0.999
1.10 Pb	0.033 ± 0.008	-0.331 ± 0.007	-0.932 ± 0.007	-0.968 ± 0.006	-0.998	-0.999
1.31 Pb	-0.046 ± 0.007	-0.415 ± 0.010	-0.895 ± 0.006	-0.949 ± 0.008	-0.998	-0.998
2.05 Pb	-0.174 ± 0.007	-0.586 ± 0.011	-0.810 ± 0.008	-0.917 ± 0.010	-0.997	-0.997

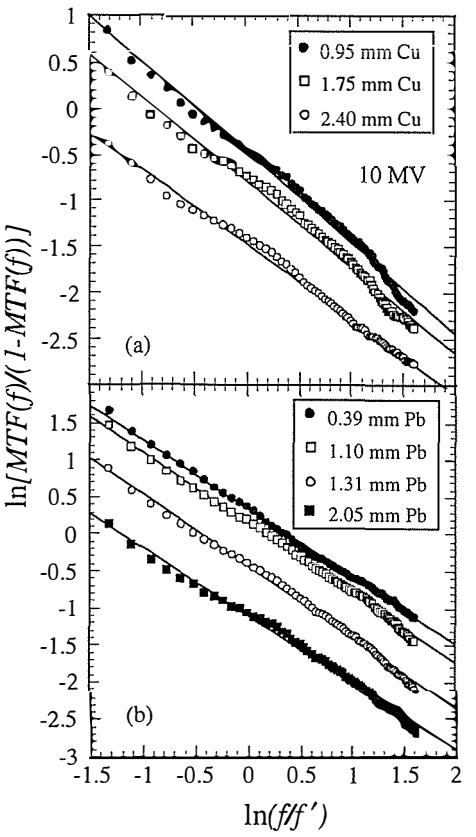

Figure 1. Logit fits to the *MTF(f)* data collected with the 10 MV spectrum for the detectors with (a) Cu, and (b) Pb front-plates. The straight lines are the logit MTF's calculated using the regression parameters in Table 1. For clarity, the curves corresponding to the 2.40 mm Cu, 0.39, and 1.10, 2.05 mm Pb front-plates were displaced vertically by -0.5, 0.5, 0.5, and -0.5, respectively.

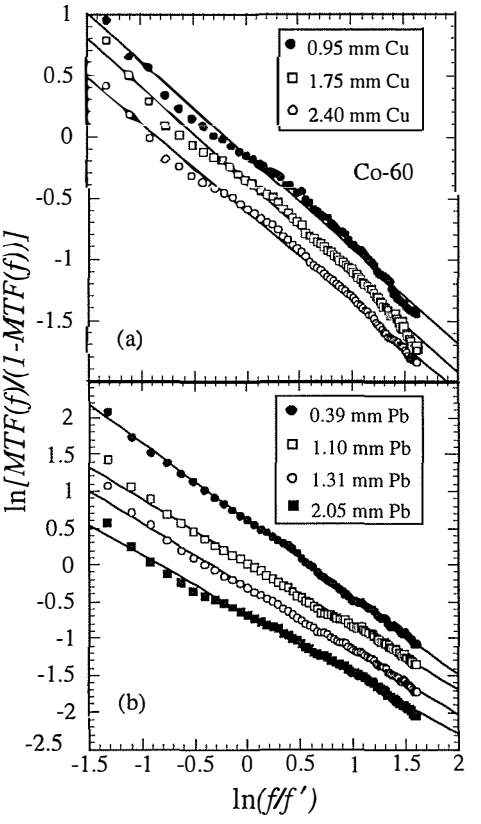

Figure 2. Logit fits to the *MTF(f)* data collected with the Co-60 spectrum for the detectors with (a) Cu, and (b) Pb front-plates. The straight lines are the logit MTF's calculated using the regression parameters in Table 1. For clarity, the curves corresponding to the 0.39, 1.10, and 2.05 mm Pb front-plates were displaced vertically by 0.5, -0.25, and -0.5, respectively.

Table 2. Regression coefficients for data from Munro et al.[7] using the 18 MV and Co-60 spectra.

Front-Plate Thickness (mm)	Energy Spectrum	"Intercept" a	"Slope" b	Correlation Coefficient r
1.0 Cu	18 MV	-0.233 ± 0.016	-0.881 ± 0.016	-0.997
1.0 Pb	18 MV	-0.160 ± 0.012	-0.902 ± 0.013	-0.998
1.5 W	18 MV	-0.001 ± 0.006	-0.880 ± 0.007	-0.999
1.5 W	Co - 60	0.281 ± 0.034	-0.689 ± 0.031	-0.991

Table 3. Slope and intercept of the lines in Figure 5.

Energy	Metal	Figure 5 (a & b)		Figure 5 (c & d)	
		slope	intercept	slope	intercept
10 MV	Cu	-0.38 ± 0.03	-0.17 ± 0.05	0.13 ± 0.02	-1.10 ± 0.03
10 MV	Pb	-0.24 ± 0.01	-0.04 ± 0.02	0.04 ± 0.01	-1.01 ± 0.01
Co - 60	Cu	-0.36 ± 0.04	0.17 ± 0.06	0.11 ± 0.01	-0.92 ± 0.01
Co - 60	Pb	-0.15 ± 0.02	0.19 ± 0.03	0.13 ± 0.01	-1.09 ± 0.02

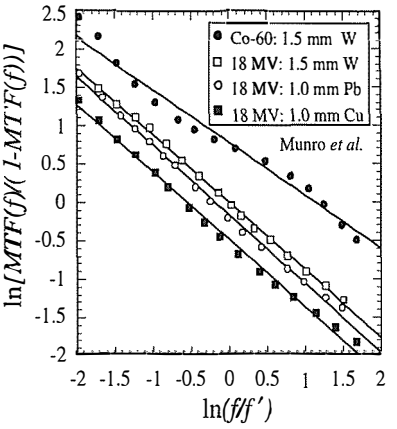

Figure 3. Logit fits to the $MTF(f)$ data from the literature [Munro et al. ref(7)]. The straight lines are the logit MTF's calculated using the regression parameters in Table 2. For clarity, the curves for 1.5 mm W at Co-60 and 1.0 mm Cu at 18 MV were displaced vertically by 0.5 and -0.25, respectively.

ness for a given metal. The slopes and intercepts describing the straight lines are shown in Table 3 for both Cu and Pb, and can be used to calculate the regression parameters (and consequently the MTF) for any other front plate thickness. The data in Table 1 were

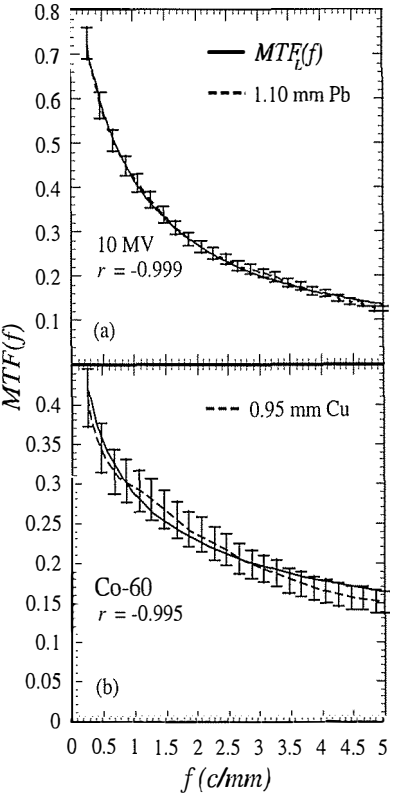

Figure 4. The $MTF(f)$ data and the calculated ($MTF_L(f)$) are shown for (a) typical case with r = -0.999 and for the (b) worst case with r = -0.995.

obtained with double-emulsion film. The Co-60 data from Munro *et al.* listed in Table 2 was not added to that of Figure 5 because they were obtained with a single-emulsion film.

Conclusion

The logit function predicts the MTF to within experimental uncertainty and the weighted linear regression analysis demonstrates that the fitting is successful with high correlation coefficient: $-0.999 \leq r \leq -0.995$. Fitting the MTF data with the logit function allowed the parameterization of the MTF with two regression parameters: *a* and *b*. We have shown that *a* and *b* exhibit a linear relationship with detector front-plate mass thickness greater than the maximum range of electrons in the plate.

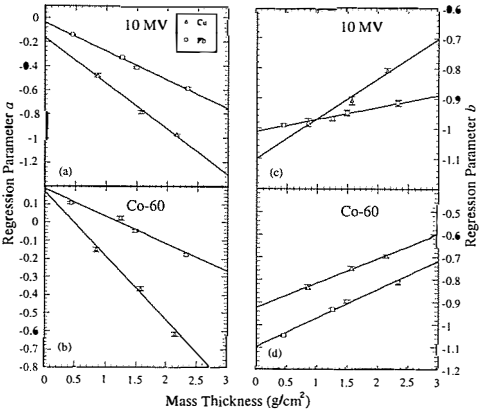

Figure 5. Plots of regression parameters *a* and b versus detector front-plate mass thickness. A linear relationship exists between the regression parameters and the mass thickness for a given metal, and parameters for the linear fits are given in Table 3.

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Current trends in diagnostic nuclear medicine instrumentation

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Introduction. *The basic principles of nuclear medicine imaging instruments are described with the emphasis on multi crystal scintillation and semiconductor gamma cameras, positron emission scanners without detector inter-ring attenuation septa, new detector materials and semiconductor CZT surgical probes for localization of metastases. For the estimation of minimal useful detector diameter the theoretical equation was derived for the 20% loss of absorbed gamma rays at the edge of the detector.*

Conclusions. *Nuclear medicine instrumentation has been passing throgh vigorous development in the last years and will be most likely also in the near future. New detection materials with much better physical characteristics than the standard NaI as regards the stopping power, energy resolution, fragility, decay time, light output, and density will most likely replace the NaI. It is expected that new imaging devices with several thousands of tiny crystals or semiconductor array of small position sensitive areas will improve the sensitivity and specificity of clinical studies. At the same time the small surgical probes made from these materials are also becoming very popular in surgery tracing the regional metastases.*

Key words: gamma cameras; tomography, emission-computed-instrumentation; multi-crystal scintillation gamma camera, semiconductor gamma camera, 2-D and 3-D PET scanner

Introduction

In nuclear medicine imaging the use of multi-detector systems for total-body, brain and heart scanning have recently gained increasing popularity. The systems with 2 or 3 Anger type gamma cameras 180°, 120° or 90° apart with small or large field of view are most popular. These systems have considerably improved the sensitivity, resolution and scanning time compared to the single camera systems. PET imaging with rings of small detectors in multi-slice configuration with lead or tungsten septa between slices (2-D) or without septa (3-D) has been successfully implemented using [F^{18}]FDG in a limited axial region and most recently also for total-body tomography. The biggest improvement in spatial resolution of PET was gained in the past mainly by the reducing the size of the crystals which currently resolve the structures to 5 mm in size. An intense development of the imaging systems is under way with a large number of tiny crystals made of the newly developed high dense and fast responding materials.

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Methods

Principles of image detection

Generally, three basic methods of nuclear medicine image formation are being used: 1. a single large scintillation crystal with a large number of photo multiplier tubes (PMT), 2. a large number of tiny scintillation crystals with position sensitive photo-multiplier tube (PSPMT) and 3. a large semiconductor crystal with an array of tiny "n-p" sensitive areas.

In the first method, the gamma ray hits a large circular or rectangle thin crystal and the induced scintillation light is distributed between the PMTs (Figure 1a) according to their viewing spatial angles. The x and y positions of PMTs are weighted by their electric signal responses from all PMTs and the X and Y coordinates of the scintillation cloud striking the array of PMT. The corresponding energy is computed (Anger type of gamma camera). The intrinsic spatial resolution of the imaging device strongly depends on the crystal thickness, slightly less on the size (number) shape of PMT and the position circuit. In contrast to the sensitivity of the system, the spatial resolution increases by the crystal thickness. The energy and time resolution depend mainly on the crystal material. Nowadays nearly all planar gamma cameras are of this kind.

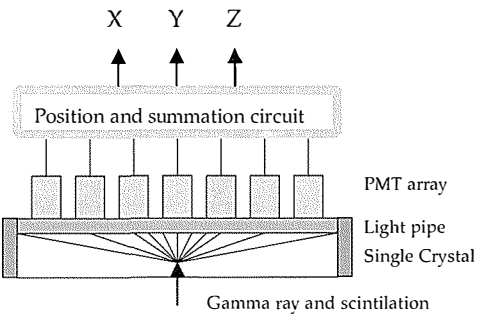

Figure 1a. Imaging detector with a single large scintillation crystal with set of PMTs.

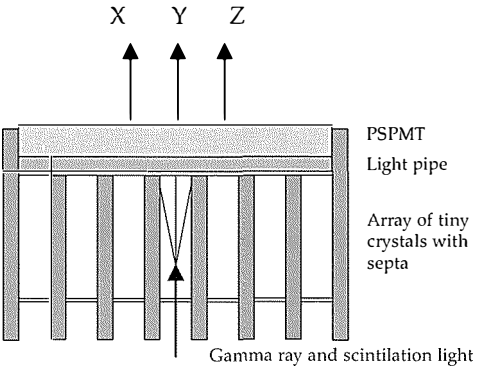

Figure 1b. Imaging detector with an array of tiny scintillation crystals with PSPMT.

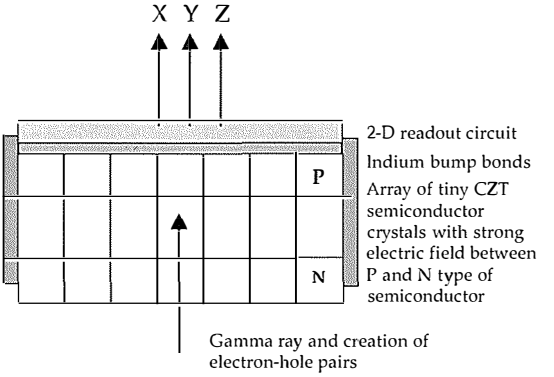

Figure 1c. Imaging semiconductor array detector.

In the second method (Figure 1b), the gamma ray is absorbed in a tiny crystal and all the induced scintillation light is collected by a small area of position sensitive photo multiplier tube which converts the incident light in a very thin layer into a charge or current which is then converted to digital E (energy) signal. Each small sensitive area of PSPMT provides also corresponding spatial coordinates X and Y for the particular exposed crystal. The spatial resolution strongly depends on the size of the crystals and on the thickness and material of the septa. Each crystal represents a pixel in the final digital image. The thinner and longer the crystal and

the thinner the septa, the better is the resolving power of the imaging system. Still, there is a limitation in the cross sectional size of the crystal (Figure 2).

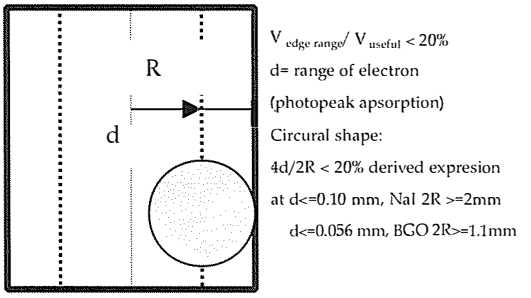

Figure 2. An estimate of the limit for the crystal cross sectional size. The shadow region represents the volume of induced ionization and the place from which the scintillation light contributes to the energy signal. The data for stopping power of electrons were taken from.[1]

If gamma ray hits the crystal too close to the reflector cover or to the optical fiber (crystal is inside optical fiber) then some of the ionization does not contribute to the scintillation light; therefore, the energy signal is weaker. Consequently, a definite volume close to the edge is not useful and is treated as scattered. An estimate is given for the circular shape of the crystal and for two popular scintillation materials (NaI and BGO). The scintillation light will be reduced in approximately 20 % of absorbed gamma rays. Some of the signals coming from these 20 % will still be included in the lower part of the photopeak but some will be lost. Therefore, there is no meaning of using thinner sized crystals than 1-2 mm depending on the material (for NaI crystal this size is limited to 2 mm and for BGO crystal 1 mm). The sensitivity increases with the crystal length, density and cross sectional size. The energy resolution is improved by more efficient PSPMT and more effective collecting of scintillation light in crystal.

In the third method (Figure 1c) the incident gamma ray is absorbed in the region of "p-n junction" region of the semiconductor crystal and a large number of electron-hole pairs is created. Their number (approximately 3 - 5 eV/electron-hole pair is spent on average) is proportional to the energy of the gamma ray and is nearly ten times greater than the quantity of the scintillation light (approximately 30 eV per ionization). For the same reason, the energy resolution is better. Because of the improved energy resolution the quantity of the Compton scattered gamma rays in the energy peak window is considerably reduced, whereas the contrast of the structures in the scan is much better (Figure 3).

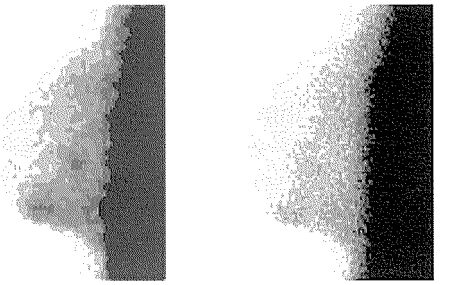

Figure 3. Comparison of breast scans from CZT and NaI Anger gamma camera.

The efficiency of the lately developed CZT crystal is even better than for NaI. The intrinsic spatial resolution of the CZT gamma camera is considerably better and is about 2 - 3 mm for 140 keV compared to 3 - 4 mm for NaI gamma camera. On the other hand, the collection time for electron-hole pairs is at least 100 times shorter than is the decay time for scintillation light in NaI crystal; therefore, the increased count rate can be achieved (250.000 counts/s). The weight of such imaging system is 100 times lower and the CZT gamma camera is easily portable to emergency departments or elsewhere. It is expected that the price for such gamma camera will also be much lower because of the less complicated production.

Table 1. Physical properties for some interesting scintillation materials. NaI-Thalium-doped sodium iodide, BGO-Bismuth germanate (Bi4Ge3O12), LSO-Lutetium oxyorthosilicate, YSO-Yttrium oxyorthosilicate

	NaI	BGO	LSO	YSO
Density (g/cm3)	3.67	7.13	7.40	4.54
Effective Z	51	74	66	34
Decay time (ns)	230	300	40	70
Relative light output	100	15	75	120
Energy resolution	7.8 %	10 %	<10 %	<7.5 %
1/μ for 140 keV	4.2 mm	0.82	1.0	7.7
1/μ for 511 keV	30 mm	11	12	26

New materials for detection crystals

Some new detector materials were developed recently which promise a considerable improvement of nuclear medicine imaging devices. These materials are presented in Table 1.[2]

The LSO is intrinsically radioactive and is not useful for SPET but can be used for PET (coincidence measurement excludes the single decay and absorption of gamma ray inside LSO crystal). The use of LSO and YSO is very promising in the so-called phoswhich detector where the YSO crystal (1 - 2 cm) is in front and the LSO crystal (1 - 2 cm) is optically coupled to the YSO. The YSO is used for attenuation of low energy (in the range of 100 keV) and LSO serves as the light pipe and for attenuation of high energy gamma rays. The induced scintillation signals from both crystals can be separated because of their different decay times.

The BGO is nearly exclusively used for PET, but will probably be replaced by this phoswhich detector.

One of the most interesting detectors is semiconductor CZT (cadmium zinc telluride) which has even better stopping power for 140 keV gamma rays than NaI (Tl) and much better energy resolution (for factor of 10). An array with a large number of very small sensitive areas can be formed so that each of these areas is a separate pixel in the digital image.

SPET

The biggest improvement in the SPET was the development of several detector heads which drastically improved the system sensitivity. In cardiac SPET, the use of two heads at 90° and the whole-body bone SPET or scanning at 180° shortens the acquisition time or doubles the acquisition counts. The improvement of the gamma camera features was mainly due to the development of the so-called digital head electronics which replaced the old analog position circuit by the digital one. The output from each PMT is digitized and the spatial coordinates are then computed. All corrections for non-linearity, spatial and energy non-uniformity can be performed on-line by the use of special fast processors.

In the future, the probable development of SPET will involve the building the tomographic system of several modular multi-crystal detectors which will introduce even greater flexibility than that with two or three big planar gamma cameras at different angular setup. Each module will probably be an array of very tiny crystals from YSO and LSO or semiconductor CZT detector.

Another possible approach in modular design of SPET will be the development of special models for each organ (*i.e.* thyroid and cardiac tomograph needs relatively small sized detector's modules) and, possibly, much lower prices for small SPET systems.

PET

The latest improvements are mainly due to the development of the so-called 3-D tomographs which do not use septa between planes with rings of crystals.[3] By omitting the septa the sensitivity is increased by ten times and the amount of scattered photons for approximately 30 %. In such configuration of several thousands tiny crystals all possible coincidence events between any two crystals are used in the reconstruction algorithm. The system works in a true 3-D mode. Another possibility of PET is the use of double-head SPET system with or without collimator (high-speed electronics is essential) in a coincidence mode. This type of PET is considerably less sensitive but is interesting to perform both PET and SPET studies.

A much better sensitivity of the system is expected in future from the new generation of the PET. It will be of extreme importance in the imaging of specific biochemical bindings, such as receptor binding. In this applications a small amount of the injected radioactivity is collected by a target organ (usually less than 1 %).

Surgical gamma probe

This application of radioactivity tracing becomes very important in surgery for identifying the regional metastases. Currently interesting clinical field where the small detector probe is of great importance is lymph node dissection of the axilla or regional nodes in the breast cancer patients and in some melanoma patients. The role of the surgical gamma probe is to localize the sentinel node transcutaneously and intra-operatively. To meet a high sensitivity, good spatial and spectral resolution and appropriate ergonomic characteristics several of different commercially available probes were evaluated.[4] It was found that CZT probe was the most appropriate for low energies (140 keV from ^{99m}Tc) and the NaI probe for high energy (364 keV ^{131}I).

Conclusions

Nuclear Medicine instrumentation has been passing through vigorous development in the last years and will be most likely also in the near future. New detection materials with much better physical characteristics than the standard NaI as regards the stopping power, energy resolution, fragility, decay time, light output, and density will most likely replace the NaI. It is expected that new imaging devices with several thousands of tiny crystals or semiconductor array of small position sensitive areas will improve the sensitivity and specificity of clinical studies. At the same time, the small surgical probes made of these materials are also becoming very popular in surgery tracing the regional metastases.

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Radiol Oncol 2000; 34(4): 319-24.

Magnetnoresonančna holangiografija (MRH) pri bolnikih z zaporo žolčnih vodov

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Izhodišča. Z raziskavo smo nameravali oceniti diagnostično vrednost holangiografije z magnetno resonanco. To je nova neinvazivna slikovna preiskava za ugotavljanje vzroka zapore žolčnih vodov.

Bolniki in metode. Pri bolnikih z zaporo žolčnih vodov smo naredili MRH z magnetnoresonančnim tomografom 1,0 T jakosti magnetnega polja. V 26 mesecih smo pregledali 44 bolnikov in sicer 23 moških in 21 žensk, povprečne starosti 51 let. Osnovo preiskave so predstavljala T2 poudarjena zaporedja za prikaz s tekočino izpolnjenih žolčnih vodov v jetrih in zaporedja hitrega spinskega odmeva. Običajna debelina rezov je znašala 4 mm. Slikali smo v dveh ravninah, koronarni in transverzalni pri zadržanem in sproščenem dihanju. Rekonstrukcije so bile narejene s tehniko "maximum intensitiy projection (MIP)". Rezultate MRH smo primerjali z rezultati ultrazvočne ali CT preiskave pred operacijo ali pred drenažo.

Rezultati. Z magnetnorezonančno holangiografijo smo pregledali 44 bolnikov z zlatenico in 100-odstotno zanesljivo ugotovili nivo zapore voda. Klinično uporabnost magnetnoresonančne holangiografije smo ovrednotili na osnovi osebnih izkušenj ter podatkov iz literature. Glavna indikacija za MRH je bila opredelitev mesta zapore žolčnih vodov, ki je na ta način mogoča brez uporabe kontrastnega sredstva ali kakršnegakoli posega v žolčnik.

Zaključki. Na osnovi izkušenj in rezultatov lahko potrdimo, da je slikanje z magnetno rezonanco zanesljivejše pri odkrivanju zapore žolčnih vodov kot sta ultrazvok ali CT preiskava.

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Ultrazvočna preiskava krvnega obtoka z dvojnim Dopplerjem v trebušni slinavki pri sladkornih bolnikih, odvisnih od inzulina

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Izhodišča. Z našo študijo smo želeleli oceniti pomen pulznega vala in ultrazvočne preiskave krvnega obtoka v trebušni slinavki z barvnim Dopplerjem ter preveriti hipotezo, da pospešeno napredovanje ateroskleroze pri sladkornih bolnikih, odvisnih od inzulina, stopnjuje vaskularno rezistenco.

Bolniki in metode. Z ultrazvokom smo pregledali gastroduodenalne arterije 40 sladkornih bolnikov, odvisnih od inzulina in 30 zdravih prostovoljcev ter pri obeh skupinah določili rezistenčni (RI) in pulzni indeks (PI). Ugotavljali smo statistično pomembne razlike Dopplerjevih indeksov med obema pregledanima skupinama ter korelacijo s starostjo in spolom bolnikov kot tudi s trajanjem sladkorne bolezni.

Rezultati. V kontrolni skupini je znašal povprešni RI 0,71, povprečni PI pa 1,46. Pri sladkornih bolnikih, odvisnih od inzulina je bil povprečni RI 0,74, povprečni PI pa 1,54. Razlike med Dopplerjevimi indeksi niso bile statistično pomembne; za RI je ta razlika bila p=0,82, za PI p=0,74. Prav tako nismo ugotovili statistično pomembne korelacije med RI in PI ter trajanjem bolezni.

Zaključki. Ultrazvočna preiskava z barvnim Dopplerjem je preprosta in neinvazijska slikovna metoda za preiskavo krvnega obtoka v gastroduodenalni arteriji. V tej študiji smo dokazali, da ta metoda nima tehtne vrednosti pri preiskavi krvnega obtoka v trebušni slinavki sladkornih bolnikov, odvisnih od inzulina.

Radiol Oncol 2000; 34(4): 331-5.

Renalna vaskularna rezistenca pri bolnikih s kronično ledvično odpovedjo

Prkačin I, Dabo N, Palčić I, Brkljačić B, Sabljar-Matovinović M, Babić Z

Izhodišča. Z ultrazvočno preiskavo z dvojnim Dopplerjem ugotavljamo fiziološko stanje ledvičnega arterijskega krvnega obtoka in njegovo rezistenco. S študijo smo nameravali oceniti vlogo in pomen ultrazvočne preiskave z dvojnim Dopplerjem za ugotavljanje renalno vaskularne rezistence pri bolnikih s kronično ledvično odpovedjo.

Bolniki in metode. Pri 30 bolnikih z ledvično odpovedjo in 20 kontrolnih osebah smo izmerili rezistenčne indekse (RI) in pulzijske indekse (PI). Vrednosti RI in PI kontrolnih oseb smo primerjali z vrednostmi RI in PI bolnikov s kronično ledvično odpovedjo ter ugotavljali korelacijo teh vrednosti z laboratorijskimi in kliničnimi rezultati.

Rezultati. Povprečna vrednost RI kontrolnih oseb je bila 0,59±0,03 (±SD), povprečna vrednost PI pa 1,00±0,11. Pri bolniki s kronično ledvično odpovedjo je bil povprečni RI 0,71±0.11, povprečni PI pa 1,69±0,21. Višje vrednosti RI in PI so bile povezane s stopnjevanjem ledvične odpovedi. Med vrednostmi RI in PI ter vrednostmi serumskega kreatinina, kreatininskega klirensa ter sistoličnega in diastoličnega krvnega tlaka je bila ugotovljena statistično pomembna korelacija ($p<0.001$).

Zaključki. Iz Dopplerjevih indeksov je pri bolnikih s kronično ledvično odpovedjo mogoče ugotoviti višjo renalno vaskularno rezistenco in njeno korelacijo z laboratorijskimi in kliničnimi parametri, medtem ko izmerjene vrednosti RI in PI kot napovedni dejavniki napredovanja bolezni niso ugodnejši od klasičnih parametrov.

Radiol Oncol 2000; 34(4): 337-47.

Zaščita kostnega mozga z amifostinom pri zdravljenju z Re-186-HEDP: prvi rezultati na živalskem modelu

Klutmann S, Bohuslavizki KH, Krüger S, Jenicke L, Buchert R, Mester J, Clausen M

Izhodišča. V zadnjih nekaj letih poročajo o radioprotektivnem delovanju amifostina (Etyhol®, USB, Philadelphia, PA). Ker se amifostin znatno kopiči v kostnem mozgu, se zdi zelo primeren za proučevanje radioprotektivnega učinka na kostni mozeg pri bolnikih, ki so zdravljeni z Re-186-HEDP. Narejene so že začetne raziskave na živalih, uporabili so novozelandske bele zajce.
Material in metode. 18 zajcem smo naredili scintigrafijo celotnega telesa s Tc-99m-HDP, ki so ob tej preiskavi prejeli 300 MBq. 9 živali smo nato zdravili z amifostinom v odmerku 200 mg/kg telesne teže, 9 zajcev pa je služilo za kontrolnio skupino in smo jim dajali le fiziološko raztopino. Vsem 18 zajcem smo nato aplicirali 400 MBq Re-186-HEDP i.v. Dva zajca pa nista prejela ne Tc-99m-HDP ne Re-186-HEDP, ker smo ju že na začetku raziskave določili - ob omenjeni kontrolni skupini - za netretirana kontrolna primera. Krvne preiskave smo naredili na začetku raziskave in jih ponavljali dva meseca v dvotedenskih intervalih pri vseh 20 živali. Določali smo levkocite, eritrocite, trombocite in hemoglobin. Dva meseca po zdravljenju smo vse živali žrtvovali in jim kirurško odstranili femurje zaradi histopatološke preiskave kostnega mozga.
Resultati. V obeh netretiranih kontrolnih živalih in v živalih, ki so prejele amifostin so bili eritrociti in hemoglobin skoraj nespremenjeni ves čas opazovanja. Pri 9 kontrolnih živalih, ki niso prejele amifostina, je bila srednja vrednost trombocitov pred apikacijo Re-186-HEDP 265.22±127.41 x 10^9/l. Dva tedna po aplikaciji omenjenega radiofarmaka je bila srednja vrednost trombocitov znižana na 211.22±52.8 x 10^9/l. Pri živalih, ki so prejele amifostin in pri tistih, ki ga niso, se pred zdravljenjem z Re-186-HEDP srednje vrednosti trombocitov niso bistveno razlikovale ($p>0.05$). Dva tedna kasneje pa se je tudi v skupini živali, ki so prejele amifostin, znižala vrednost trombocitov na 180.67±37.43 x 10^9/l in razlika vrednosti s kontrolno skupino ni bila statistično značilna ($p>0.05$). Dva tedna po aplikaciji radiofarmaka smo ugotovili le rahlo znižanje vrednosti levkocitov v kontrolni skupini živali, nasprotno pa je skupina živali zdravljenih z amifostinom imela značilno znižano vrednost levkocitov 3.39±0.91 x 10^9/l ($p<0.0002$).
Diskusija. Amifostin ne omogoča zaščite pred prehodno trombocitopenijo. Nezadostno radioprotektivno delovanje amifostina na trombocite si razlagamo z njegovo farmakokinetiko. Po aplikaciji Re-186-HEDP prihaja namreč do tvorbe prostih radikalov in njihovo nastajanje in delovanje je nekajkrat daljše kot pa radioprotektivni učinek amifostina, ki ga predhodno apliciramo v enkratnem odmerku. Znižanje vrednosti levkocitov po amifostinu pa do sedaj ni bilo poznano.
Zaključki. Če želimo uporabljati amifostin kot radioprotektivno sredstvo, je potrebno ugotoviti primernejšo aplikacijo. Predlagamo dvakratdnevno apliciranje, ki naj traja 3 do 4 dni od začetka zdravljenja z Re-186-HEDP. Prav tako je potrebno v naslednjih raziskavah na živalih proučiti zgoraj omenjeni leukopenični učinek amifostina.

Radiol Oncol 2000; 34(4): 349-55.

Algoritem zdravljenja sindroma zgornje vene cave s perkutanim stentom

Vodvářka P, Štverák P

Izhodišča. Sindrom zgornje vene cave je dolgo veljal za življenjsko nevaren bolezenski pojav. Od leta 1757, ko je W. Hunter prvič opisal ta pojav pri bolniku s sakularno anevrizmo sifilitične aorte, je bilo odkritih veliko zelo različnih vzrokov tega sindroma.
Uporaba perkutanega stenta je z razvojem radioterapije postala osnovni in glavni način zdravljenja bolnikov s sindromom zgornje vene cave. Nenaden pojav tega sindroma je zahteval takojšnje zdravljenje z radioterapijo, četudi histopatološka preiskava še ni potrdila vzroka sindroma. Z razvojem radioterapije, kemoterapije in pomožnega zdravljenja raznih vrst raka ter hkrati s spoznanjem, da sindrom zgornje vene cave ni vedno življenjsko nevaren, je zaradi različnega načina zdravljenja bolnikov s sindromom zgornje vene cave postalo nujno ločevati bolnike med seboj.
Zaključki. S perkutanim stentom že od leta 1986 učinkovito zdravimo bolnike s sindromom zgornje vene cave. Zdravljenje s perkutanim stentom uvajamo kot pomožno ali kot paliativno zdravljenje. Razvili smo tudi algoritem tega zdravljenja, ki temelji na štirih vprašanjih, osnovanih na kliničnih izkušnjah. Če hočemo, da bi bili odgovori veljavni, moramo uporabiti določene diagnostične postopke in orodja, ki ustrezajo priporočilom in zahtevam.
1. Ali se je pri bolniku zares razvil sindrom zgornje vene cave?
2. Kakšno je splošno fizično stanje bolnika?
3. Ali so bile ugotvljene kontraindikacije, ki pri zdravljenju sindroma zgornje vene cave ne dovoljujejo uporabe stenta?
4. Ali so znani rezultati histološke preiskave procesa, ki je povzročil sindrom? Kakšni so rezultati histološke preiskave procesa, ki je povzročil sindrom?

Odgovori na zgornja vprašanja odločajo o izbiri načina zdravljenja. Tako dosežemo racionalno uporabo perkutanih vstavljivih stentov pri bolnikih s sindromom zgornje vene cave z maligno etiologijo, ki potrebujejo pomožno zdravljenje in/ali paliativno zdravljenje.

Radiol Oncol 2000; 34(4): 357-61.

Elektrokemoterapija s cisplatinom pri bolniku z rakom dojke

Reberšek M, Čufer T, Rudolf Z, Serša G

Izvleček. Avtorji so zdravili kožne metastaze pri bolniku z rakom dojke z elektrokemoterapijo s cisplatinom. Elektrokemoterapija je zdravljenje s kemoterapijo, ki ji sledi lokalna aplikacija električnih pulzov na tumorske lezije; električni pulzi povečajo vnos kemoterapevtika v celice.
Prikaz primera. Avtorji so zdravili kožne metastaze raka dojke z intratumorsko aplikacijo cisplatina in 8 električnimi pulzi, ki so jih na vsako kožno metastazo aplicirali 1 minuto po vnosu cisplatina. Pri zdravljenju z elektrokemoterapijo so pri dveh kožnih metastazah dosegli popolni odgovor, pri 1 kožni metastazi pa delni odgovor. Pri kožnih metastazah, ki so jih zdravili samo z intratumorsko aplikacijo cisplatina, pa so dosegli le delni odgovor.
Zaključek. Elektrokemoterapija s cisplatinom je tako kot elektrokemoterapija z bleomicinom učinkovita pri zdravljenju kožnih metastaz raka dojk.

Radiol Oncol 2000; 34(4): 387-94.

Radiol Oncol 2000; 34(4): 363-8.

Sinhroni in metahroni bilateralni germinalni tumorji testisov

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Izhodišče. Pregledali smo 14 bolnikov z bilateralnim tumorjem testisov in proučevali, ali je potrebno med orkidektomijo opraviti tudi kontralateralno biopsijo testisov za odkrivanje karcinoma in situ.

Bolniki in metode. Z raziskovanjem teh 14 bolnikov z bilateralnim tumorjem testisov smo želeli ugotoviti incidenco, histološke podatke, napovedne dejavnike, časovno razliko med nastankom enega in drugega primarnega karcinoma, način zdravljenja in končni uspeh.

Rezultati. V letih med 1984 in 1996 smo odkrili 14 primerov bilateralnih tumorjev. Pri 5 bolnikih so se tumorji pojavili hkrati, pri ostalih pa se je kontralateralni tumor pojavil s časovnim zamikom od 6 do 107 mesecev. Najpogostejša histološka diagnoza je bila seminom, ki je bil ugotovljen v 10 primerih. Pri 4 bolnikih je bil ugotovljen retiniran testis, pri enem pa sindrom perzistentnega Müllerjevega voda. Pri vseh bolnikih je bila opravljena radikalna orkidektomija. Z ozirom na stadij bolezni so bili vsi bolniki zdravljeni z obsevanjem in/ali kemoterapijo. Štirje bolniki so umrli v času od 6 do 33 mesecev po diagnozi. Preostalih 10 bolnikov je še vedno živih in brez znakov bolezni.

Zaključki. Diagnoza sekundarnega tumorja je danes pogostejša zaradi daljšega obdobja, določenega za nadzor bolezni, rednih samopregledovanj bolnikov, ultrazvočnega pregleda testisov, uporabe tumorski markerjev AFP in HCG ter biopsije kontralateralnega testisa med orkidektomijo. Karcinom *in situ* na kontralateralnem testisu skoraj pri vseh obsevanih bolnikih z germinalnim rakom napreduje v invazivni tumor. Kljub vsemu pa ne zagovarjamo rutinskega izvajanja biopsije na kontralaateralnem testisu pri bolnikih z unilateralnim testikularnim tumorjem iz naslednjih razlogov: (1) Testikularni karcinom *in situ* je običajno prekurzor večine malignih germinalnih tumorjev, razen spermatocitnih seminomov, teratomov in tumorjev rumenjakovega mehurčka. (2) Vendar karcinom in situ ni diagnosticiran v 95% vseh testikularnih tumorjev. (3) Karcinom *in situ* je poljubno porazdeljen, zato ga je težko odkriti z enim vzorcem biopsije. (4) Testikularna biopsija povzroča manjše zaplete in obenem tudi vpliva na spermatogenezo. (5) Germinalni tumor raste od 3 do 5 let. Netipljiv testikularni tumor lahko lokaliziramo z ultrazvokom. Včasih z ultrazvočno preiskavo odkrijemo tudi karcinom *in situ*, če smo pozorni na spremembe na normalnih tubulih. (6) Ultrazvočna preiskava pa je bolj zapletena po biopsiji zaradi nastalih brazgotin. (7) Naravni potek bolezni karcinoma *in situ* ni znan, zato so tudi mnenja o natančnem postopku zdravljenja močno deljena. (8) Doslej še nimamo dokazov, da karcinom *in situ* vpliva na preživetje. (9) Izvajamo skrben zdravstveni nadzor vsem bolnikom z germinalnim tumorjem, četudi je bila biopsija negativna. Najprimernejši pristop je torej pozorno spremljanje bolnika.

Radiol Oncol 2000; 34(4): 369-74.

Odnos med stopnjo metilacije DNA in izražanjem treh različnih DNA metiltransferaz pri ovarijskem karcinomu

Cör A

Izhodišča. Metilacija DNA igra pomembno vlogo v razvoju zarodka, pri inaktivaciji kromosoma X ter pri izražanju "imprinting" genov. Raziskave so pokazale, da imajo maligne celice spremenjen vzorec metilacije DNA, spremembe DNA metilacije pa sodelujejo v procesu kancerogeneze. Namen dela je bil ugotoviti ali obstaja povezava med stopnjo metilacije DNA ter izražanjem treh DNA metil-transferaz (DNMT) in sicer DNMT1, DNMT3A in DNMT3B v vzorcih ovarijskih karcinomov.

Materiali in metode. Za določitev stopnje metilacije DNA v petih vzorcih ovarijskega karcinoma in treh vzorcih morfološko normalnih jajčnikov je bila DNA izpostavljena delovanju bodisi za metilacijo občutljive *HpaII,* ali za metilacijo neobčutljive MspI restrikcijske endonukleaze. Za določitev stopnje izražanja treh DNMT v vzorcih smo uporabili metodo kvantitativnega PCR.

Rezultati. DNA vseh petih ovarijskih karcinomov je bila globalno hipometilirana. Razlike med stopnjo metilacije DNA med ovarijskimi karcinomi in normalnim tkivom jajčnika so bile statistično značilne ($P<0.05$). Vseh pet ovarijskih karcinomov je kazalo prekomerno izražanje DNMT3A in DNMT3B, medtem ko smo našli prekomerno izražanje DNMT1 samo v dveh vzorcih. Med stopnjo globalne demetilacije in izražanjem treh različnih DNMT ni bilo statistično značilnih korelacij.

Zaključki. Hipometilacija genoma igra pomembno vlogo pri nastanku tumorjev saj vodi v strukturne in numerične kromosomske nepravilnosti v tumorskih celicah, vendar pa ostaja paradoks med stopnjo globalne hipometilacije na eni strani in povečanim izražanjem DNMT na drugi še vedno nerazjasnjen

Radiol Oncol 2000; 34(4): 375-80.

Analiza modulacijske prenosne funkcije za kovinske filmske slikovne detektorje s pomočjo logit modeliranja

Falco T in Fallone BG

Izhodišča. Logit analizo uporabljamo za prilagajanje izmerjenih podatkov modulacijske prenosne funkcije (MTF) za kovinske filmske detektorje v območju megavoltnih energij. Detektorji so sestavljeni iz rtg filma z dvojno emulzijo in frontalnih bakrenih ali svinčenih kovinskih plošč z debelinami od 0,39 mm do 2,40 mm. Analizirani so bili tudi MTF podatki drugih raziskovalcev. Logit funkcija napoveduje MTF znotraj eksperimentalne nenatančnosti, utežena linearna regresija pa pokaže, da je prilagajanje uspešno z visokim korelacijskim koeficientom: $-0.999 \leq r \leq -0.995$. Logit funkcija parametrizira MTF z dvema regresijskima faktorjema, a in b. Parametra kažeta linearno odvisnost, če je masna debelina frontalne kovinske plošče večja od maksimalnega dosega elektronov.
Zaključki. Analiza logit prilagajanja nam dovoljuje izračun MTF za kovinske plošče, kar lahko uporabimo pri izdelavi prednjega dela elektronskih slikovnih naprav.

Radiol Oncol 2000; 34(4): 381-5.

Razvojni trendi v nuklearnomedicinski instrumentaciji

Fidler V

Izhodišča. Prikazane so fizikalne osnove nuklearnomedicinskih slikovnih tehnik s poudarkom na razvoju novih tankih mnogokristalnih scintilacijskih in polprevodniških gama kamer, PET skenerjev brez vmesnih sten med obroči detektorskih kristalov, novih detektorskih materialov ter nove polprevodniške CZT kirurške detektorske sonde za ugotavljanje lokalnih metastaz. Za oceno minimalnega premera scintilacijskih kristalov je narejen izračun, ki upošteva 20% izgubo absorbiranih gama žarkov ob robu kristala.
Zaključki. V zadnjih letih se instrumentacija v nuklearni medicini hitro razvija predvsem, po zaslugi novih detekcijskih snovi, ki imajo v primerjavi z NaI kristalom boljšo atenuacijo, energijsko ločljivost, manjšo krhljivost, krajši razpadni čas za scintilacijsko svetlobo, večji svetlobni izkoristek in gostoto. Zelo verjetno bodo gama kamere z mnogokristalnimi detektorji ter pozicijsko občutljivimi polprevodniškimi detektorji znatno izboljšale občutljivost detekcije kot tudi energijsko in prostorsko ločljivost, s čimer se bo povečala tudi specifičnost pri kliničnih scintigrafskih preiskavah. Pomemben je tudi razvoj kirurških detekcijskih sond, ki so izboljšale zaznavnost majhnih lokaliziranih metastaz.

Radiol Oncol 2000; 34(4): 387-94.

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.*

Radiation therapy

January 30 - February 2, 2001

The International Meeting ICRO 2001 will take place in Melbourne, Australia.

Contact Frederique Arts, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium, or call +32 2 775 9342; or fax +32 2 779 5494; or e-mail info@isro.be

Radiation therapy

January 31 - February 2, 2001

The International Meeting ICRO 2001 will take place in Melbourne, Australia.

Contact Frederique Arts, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium, or call +32 2 775 9342; or fax +32 2 779 5494; or e-mail info@isro.be

Cardiovascular radiation therapy

February 5-7, 2001

The conference on cardiovascular radiation therapy will take place in Washington DC, USA.

Contact Cardiovascular Research Institute, 110 Irving st. NW, STE 6D, Washington DC 20010-2976; or call +1 202 877 7942; or fax +1 202 877 8141; or see Internet http://www.radiationonline.com

Brachyradiotherapy

February 25-27, 2001

The ESTRO teaching course "Endovascular Brachytherapy" will take place in Wien, Austria.

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 Internet http://www.estro.be

Colorectal cancer

Spring, 2001

The ESO conference will take place in Milan, Italy.

Contact ESO Office, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 0258317850; or fax +39 0258321266: or e-mail esomi@tin.it

Radiotherapy

March 11-14, 2001

The "European Conference on Cancer Strategy and Outcomes" will take place in Edinburg, U.K.

Contact ECSO 2001, ICM Conference Associates, 4 Cavendish Square, London WiM OBX, U.K.; or call +44 207 499 0900; or fax +44 207 629 3233; or e-mail boa@icmgb.com

Radiotherapy

March 25-29, 2001

The ESTRO teaching course "Radiotherapy Treatment Planning: Principles & Practice" will take place in Dublin, Ireland.

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 Internet http://www.estro.be

Brachyradiotherapy

March 25-29, 2001

The ESTRO teaching course "Modern Brachytherapy Techniques" will take place in Paris, France.

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 Internet http://www.estro.be

Oncology

April 1-5, 2001

The ESTRO teaching course "Molecular Oncology for Radiotherapy" will take place in Venezia, Italy.

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 Internet http://www.estro.be

Rectal Cancer

April 6-7, 2001

The "2nd International Symposium on Sphincter Saving Treatment in Rectal Cancer" will take place in Lyon, France.

Contact FCSANTE@rockefeller.univ-lyon1.fr

Clinical research

April 22-26, 2001

The ESTRO teaching course "Clinical Research in Radiation Oncology" will take place in Izmir, Turkey.

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 Internet http://www.estro.be

Lung Cancer

April 26-30, 2001

The "4th International Congress on Lung Cancer" will take place in Halkidiki, Greece.

Contact FORUM International Congress Organisers, 18 Mitropoleos str., GR-54624 Thessaloniki, Greece; or call +30 31 257 128; or fax +30 31 231 849; or e-mail forup@otenet.gr; or see Internet http://www.forumcongress.gr

Prostate cancer

May 13-14, 2001

The ESTRO teaching course "Brachytherapy for Prostate Cancer" will take place in Leeds, United Kingdom.

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 Internet http://www.estro.be

Radiophysics

May 20-24, 2001

The ESTRO teaching course "Dose and Monitor Unit Calculations for High Energy Photon Beams: Basic Principles & Application to Modern Techniques" will take place in Coimbra, Portugal.

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 Internet http://www.estro.be

Hyperthermic Oncology

May 31 - June 2, 2001

The "19th Annual Meeting of the European Society of Hyperthermic Oncology" (Joint with the "12th European BSD Users Conference") will take place in Verona, Italy.

Contact elmaluta@tin.it; or see Internet http://www.esho2001.com

Lung Cancer

June 3-6, 2001

The "7th Central European Lung Cancer Conference" will take place in Prague, Czech Republic.

Contact 7th CELCC, Conference Partners, Sokolska 10, 120 00 Prague 2, Czech Republic; or call/fax +420 2 2426 1371; or e-mail info@conference.cz

Radiosurgery

June 4-7, 2001.

The "5th International Stereotactic Radiosurgery Society Congress" will be offered in Jerusalem, Israel Republic.

Contact 7ISRS Secretariat, c/o International Travel & Congresses Ltd., 20 Rothschild Boulevard, POB 29313, Tel Aviv 61292, Israel; or phone +972 3 795 1444; or fax +972 3 510 7716; or email congs@internationaltc.co.il; or see http://www.isrs-jerusalem.com.

Radiotherapy

June 7-9, 2001

The Annual Brachytherapy Meeting GEC/ESTRO will take place in Stresa, Italy.

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 Internet http://www.estro.be

Radiobiology

June 10-12, 2001

The "1st ESTRO Workshop on Biology in Radiation Oncology" will take place in Fuglso (Aarhus), Denmark.

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 Internet http://www.estro.be

Radiotherapy

June 24-28, 2001

The ESTRO teaching course "IMRT and Other Conformal Techniques in Practice" will take place 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 Internet http://www.estro.be

Radiotherapy

June 24-28, 2001

The ESTRO teaching course "Imaging for Target Volume Determination in Radiotherapy" will take place in Krakow, Poland.

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 Internet http://www.estro.be

Obstetrics and gynaecology

July 10-13, 2001

The "29th British Congress of Obstetrics and Gynaecology (BCOG)" will take place in Birmingham, U.K.

Contact info@conforg.com

Radiophysics

August 26-30, 2001

The ESTRO teaching course "Physics for Clinical Radiotherapy" will take place in Leuven, Belgium.

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 Internet http://www.estro.be

Brachytherapy

August 29 - September 2, 2001

The ESTRO teaching course "Modern Brachytherapy" will take place in Bratislava, Slovakia.

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 Internet http://www.estro.be

Radiophysics

September 17-22, 2001

The "6th Biennial ESTRO Meeting on Physics for Clinical Radiotherapy" and the "6th ESTRO Meeting on Radiation Technology for Clinical Radiotherapy" will be held in Sevila, Spain.

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 Internet http://www.estro.be

Radiotherapy

October 7-11, 2001

The ESTRO teaching course "Evidence-Based Radiation Oncology: Principles & Methods" will take place in Cairo, Egypt.

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 Internet http://www.estro.be

Radiotherapy

October 7-11, 2001

The ESTRO teaching course "Basic Clinical Radiobiology" will take place in Tenerife, Spain.

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 Internet http://www.estro.be

Radiation therapy

October 21-25, 2001

The "20th Annual ESTRO Meeting / ECCO 11 Meeting" will take place in Lisbon, Portugal.

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; web: http://www.estro.be

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Editors greatly appreciate the work of the reviewers who significantly contributed to the improved quality of our journal.

Radiol Oncol 2000; 34(4): 398-402.

Author Index 2000

Subject Index 2000

ZVEZA SLOVENSKIH DRUŠTEV
ZA BOJ PROTI RAKU
LJUBLJANA

BASIC ACTIVITY OF ASSOCIATIONS FIGHTING AGAINST CANCER

Due to considerably high incidence and longer survival, there is more and more cancer patients all over the world as well as in Slovenia. In 1997, the cancer incidence in Slovenia was as high as 8,178; of these 4,142 were males and 4,036 women. According to the information by Cancer Registry of Slovenia (1997), it is possible to predict that, until the age of 75, one of three males and one of four females will fall ill. Cancer is the direct or indirect cause of death in 60% of cancer patients, meaning that only 40% patients recover. Today, it is well known that about 70% of cancer-related deaths have their root cause in personal lifestyle and environmental conditions. Consequently, a significant reduction in cancer and cancer-related mortality can be achieved only if the population could be persuaded to change certain habits and attitudes.

A Eurobarometer survey recently conducted in the European Union show that one European in three did not believe that cancer could be prevented and that it is possible to avoid cancer by giving up noxious habits and also by healthier way of living. That is why the primary task of the associations fighting against cancer within the ten year program "Slovenia 2000 and Cancer" shall be to inform the Slovenian population that cancer can be avoided and successfully treated provided that the recommendations of Slovenian and European codex against cancer are taken into consideration. In order to get the population better informed, the recommendations in the form of folders, leaflets, posters and brochures were issued containing also the description of the most frequent cancers and of their early symptoms. Special conferences how to prevent or avoid and treat different cancers are being organized on local and national radio and TV stations.

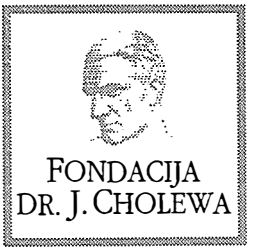
Special attention should be paid to young people warning them to give up smoking. Our latest campaign called "Don't light the first cigarette and the solemn promise" among 90.000 school children was favorably accepted and had a resounding success. We are convinced that a lot of school children will avoid smoking after having heard about the activity of our association. It is generally known that a balanced diet, including a sufficient amount of fruit and vegetables, offers significant protection against some of the most common cancers. Specific mention of the projects on proper nutrition should be made to target groups, such as young people, teachers and children. To obtain better alimentary habits of school children we started with campaigns, such as: "A new day should begin with an apple and carrot!"

In addition to the campaigns for general population, information campaigns are also organized for health professionals in order to be able to relay the cancer prevention messages to their patients. Family doctors and other health service staff should educate the population. We are organizing yearly meetings of specialists led by experts from several spheres of activities. We would like to convey the necessary knowledge which could be helpful to health service staff in such education, specially on prophylaxis or early detection of cancer.

When planning our work we can count on the assistance and knowledge of foreign and domestic specialists and on cooperation with several organizations. We have now been for a long time one of the members of International Union against Cancer - UICC. We are very proud to become a fully authorized member of European Cancer League - ECL this year. Having joined the European program in fighting against cancer we shall extend our program to include, in the future, also the areas, such as rehabilitation and screening. Several associations, together with health service staff, are taking care of rehabilitation of patients with cancer. We should stimulate the cooperation between them and also between regional associations.

Last year, we observed that, despite the rapid increase of cancer, the mortality was increasing slower owing to early detection and successful treatment of cancer. Early detection of cancer, specially in risk groups of population, is possible only with screening programs. The Association of Slovenian Cancer Societies is very active at the early detection of uterocervical cancer (ZORA program) and, together with regional associations, in the education of breast examinations. We would really wish to organize and to cooperate in early detection of breast and intestine cancers according to the recommendations valid in European Union.

Assist. Prof. Borut Štabuc, M.D., Ph.D.
PRESIDENT OF SLOVENIAN ASSOCIATIONS
FOR FIGHTING AGAINST CANCER



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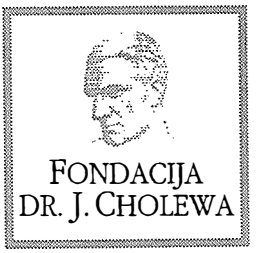

Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education - A Report for the Third Quarter of 2000

As through the whole year 1999, it has been generally agreed that it has become increasingly difficult to entice individuals and business subjects to contribute to the special type of charities, as is the activity of the "Dr. J. Cholewa" Foundation. Fortunately, there are some of the donors from Slovenia and abroad who tirelessly continue to try to support it, and the members of the Foundation and its Executive and Supervisory Committees feel obliged to express their gratitude to all who understand the importance of its goals and activities to reach them.

The Foundation helped to finance the Annual Conference of the International Breast Cancer Study Group in Bled, Slovenia; the International Conference on Cancer in Opatija, Croatia; and the Plečnik Memorial Meeting in Ljubljana, Slovenia, in the course of 1999. A "14th Oncological Weekend" meeting with the themes concerning lung and thyroid cancers was also organised later with the help of the Foundation, and the Proceedings of this meeting were published in a special publication. Several grants for participation on various international congresses and symposia were provided for the applicants from different regions of Slovenia.

The Foundation continued to support the regular publication of "Radiology and Oncology" international scientific journal, and the regular publication of the "Challenge ESO Newsletter" in 1999. Both medical journals are edited, published and printed in Ljubljana, Slovenia. In the past year the Foundation also contributed support for the publication of the Slovenian Dictionary of Medical Terminology, while it will continue to further facilitate the access to oncology research and education to as many interested individuals and institutions in Slovenia as possible. In addition, special attention will be given to the requests for grants coming from the regions of Slovenia outside Ljubljana, it's capital city.

The Foundation continued with its activity at an increasing pace throughout the autumn of 2000. To improve and upgrade its activity still further, the meetings of its Executive Board and Advisory Board are to take place in the near future in order to take some necessary decisions, including those concerning some of the personnel changes to be undertaken in the near future.

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

The Croatian Radiation Protection Association (CRPA) has the honour to organise the next

IRPA REGIONAL CONGRESS ON RADIATION PROTECTION IN CENTRAL EUROPE

Dubrovnik, Croatia, May 20-25, 2001

in co-operation with

The Austrian Association for Radiation Protection
The Czech Society for Radiation Protection
The German-Swiss Radiation Protection Association
The Health Physics Section of the Roland EŲtvŲs Physical Society, Hungary
The Italian Radiation Protection Association
The Polish Radiation Protection Association
The Romanian Society for Radiological Protection
The Slovak Society for Nuclear Medicine and Radiation Hygiene
The Radiation Protection Association of Slovenia

The topic of the Congress is

Radiation Protection and Health

This topic enables an increased participation of health physicists and encourages the submission of papers on medical aspects of radiation protection in addition to all other subjects.

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Congress Secretariat
c/o Croatian Radiation Protection Institute
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E-mail: crpa.dubrovnik@hzzz.hr

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- *v svetu največ predpisovani sistemski antimikotik*
- *edini peroralni sistemski antimikotik za zdravljenje vaginalne kandidoze, ki ga je odobril FDA*

Skrajšano navodilo
Flukonazol je sistemski antimikotik iz skupine triazolov.

Odmerjanje pri različnih indikacijah:

vaginalna kandidoza	*150 mg v enkratnem odmerku*
mukozna kandidoza	*50 do 100 mg na dan*
dermatomikoze	*50 mg na dan ali 150 mg na teden*
sistemska kandidoza	*prvi dan 400 mg, nato od 200 do 400 mg na dan Največji dnevni odmerek je 800 mg.*
preprečevanje kandidoze	*50 do 400 mg na dan*
kriptokokni meningitis	*prvi dan 400 mg, nato od 200 do 400 mg na dan*
vzdrževalno zdravljenje	*200 mg na dan*

Kontraindikacije: Preobčutljivost za zdravilo ali sestavine zdravila. **Interakcije:** Pri enkratnem odmerku flukonazola za zdravljenje vaginalne kandidoze klinično pomembnih interakcij ni. Pri večkratnih in večjih odmerkih so možne interakcije s terfenadinom, cisapridom, astemizolom, varfarinom, derivati sulfonilureje, hidroklorotiazidom, fenitoinom, rifampicinom, ciklosporinom, teofilinom, indinavirom in midazolamom. **Nosečnost in dojenje:** Nosečnica lahko jemlje zdravilo le, če je korist zdravljenja za mater večja od tveganja za plod. Doječe matere naj med zdravljenjem s flukonazolom ne dojijo. **Stranski učinki:** Povezani so predvsem s prebavnim traktom: slabost, napenjanje, bolečine v trebuhu, driska, zelo redko se pojavijo preobčutljivostne kožne reakcije, anafilaksija in angioedem – v tem primeru takoj prenehamo jemati zdravilo. Pri bolnikih s hudimi glivičnimi obolenji lahko pride do levkopenije in trombocitopenije in do povečane aktivnosti jetrnih encimov. **Oprema in način izdajanja:** 7 kapsul po 50 mg, 28 kapsul po 100 mg, 1 kapsula po 150 mg. Na zdravniški recept. 1/99.
Podrobnejše informacije so na voljo pri proizvajalcu.

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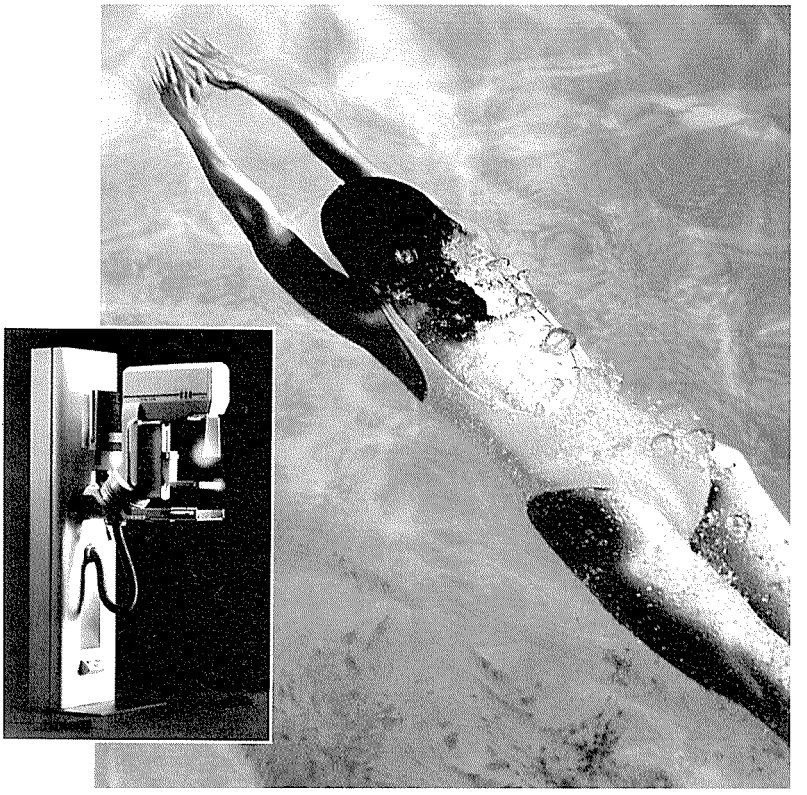

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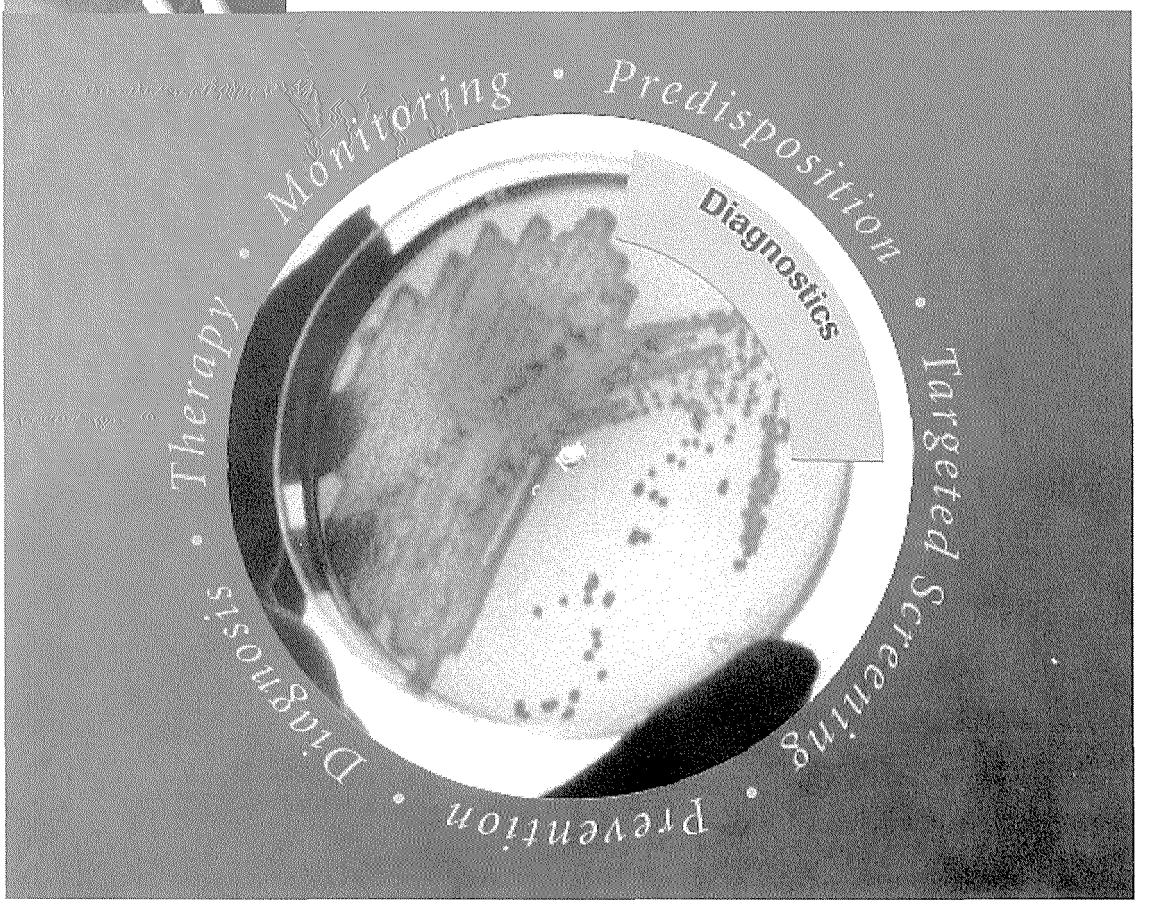

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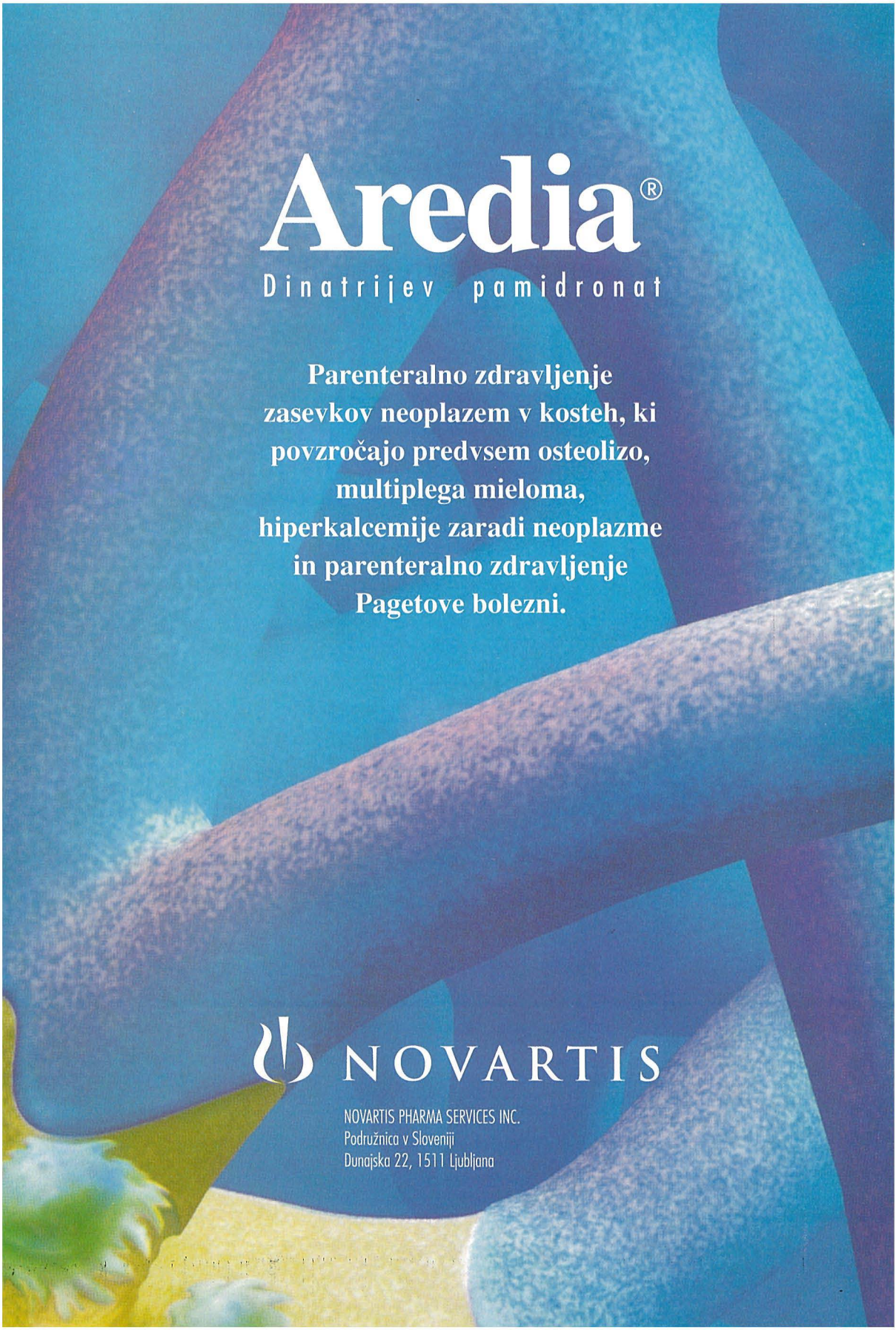
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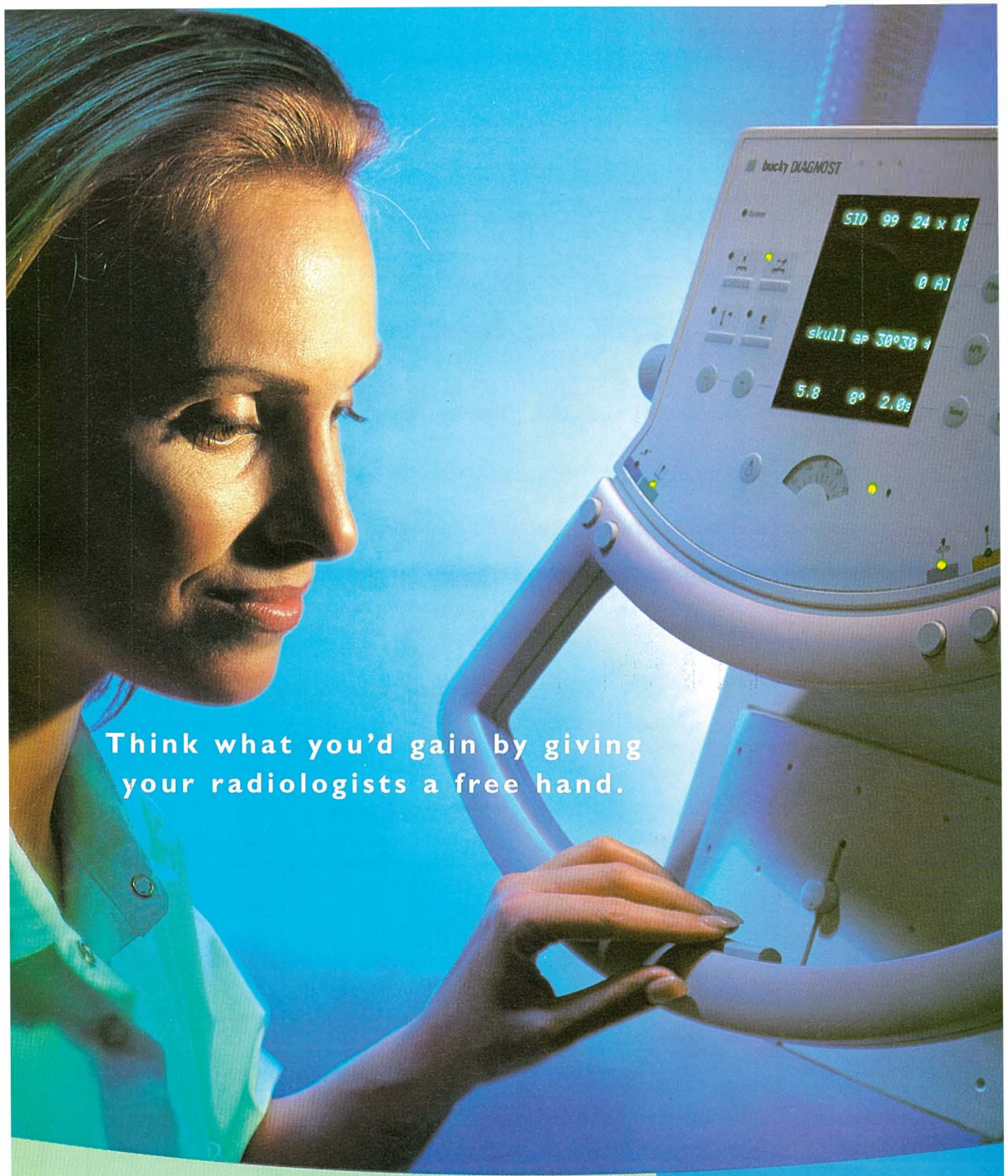

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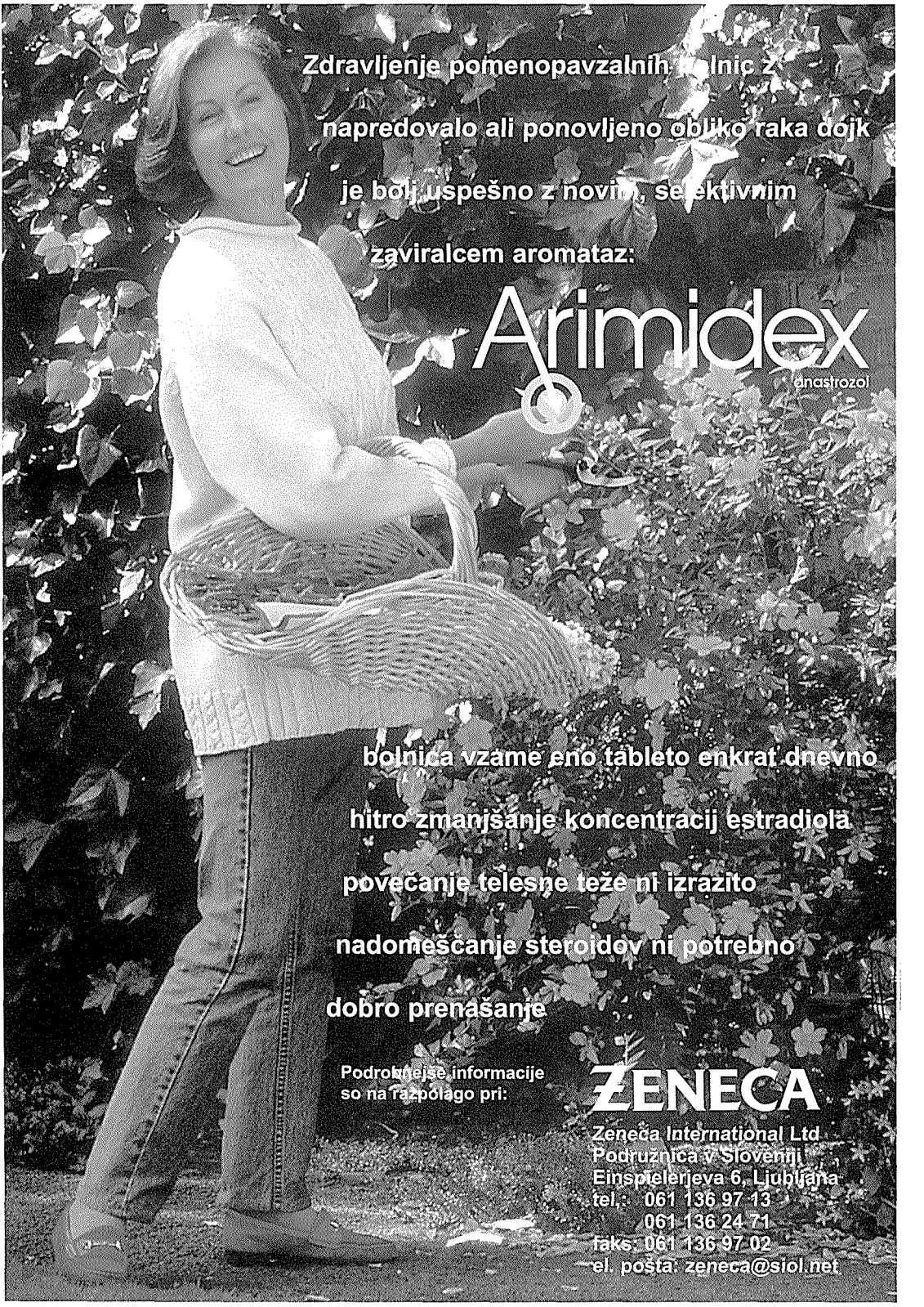
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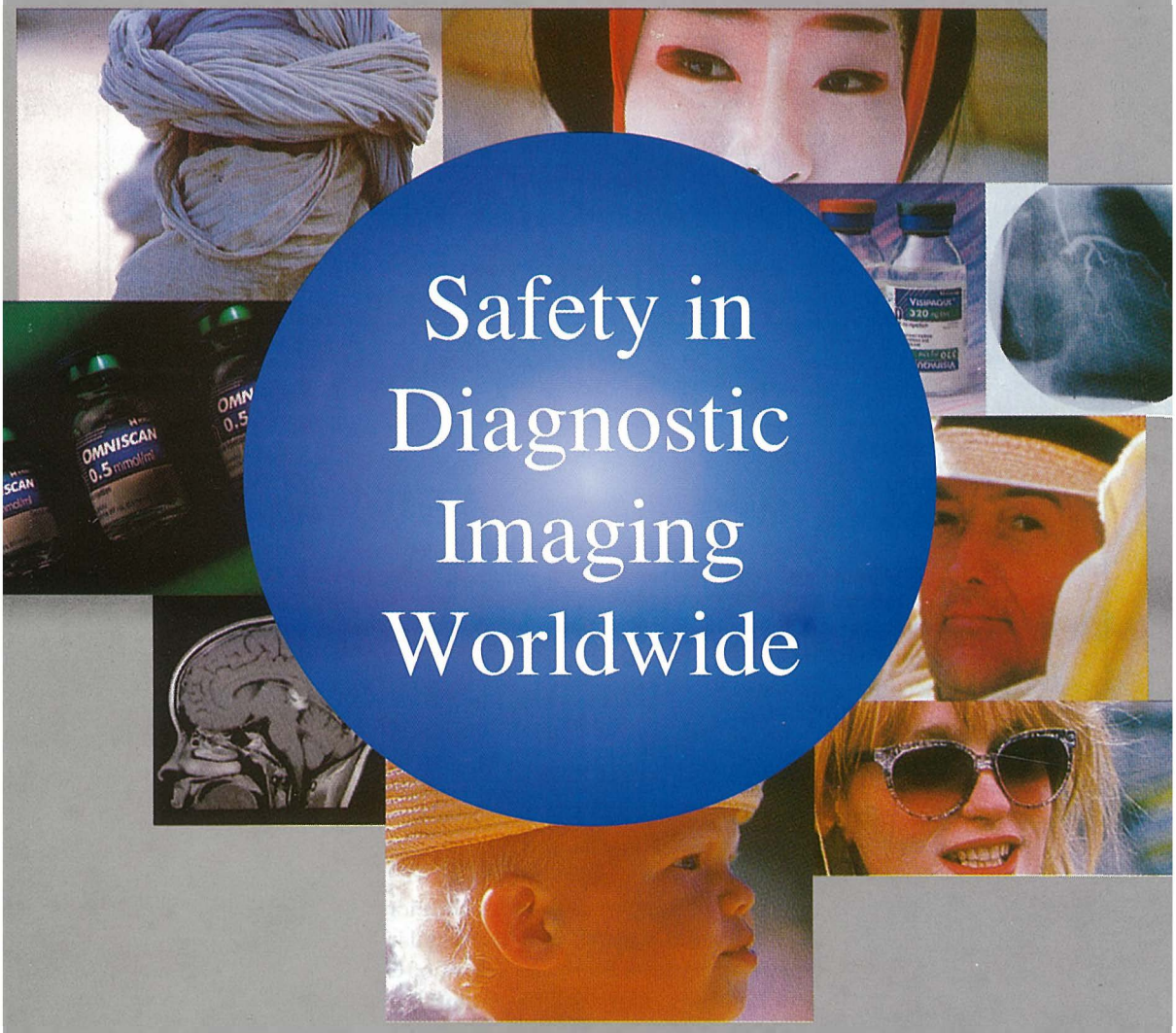

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