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CONTENTS

DIAGNOSTIC RADIOLOGY

Congenital depression of the skull. A case report
Giannakopoulou CC, Hassan EA, Hatzidaki EG, Koumantakis EE **345**

NUCLEAR MEDICINE

T1-201 SPECT for the detection of viable hybernating myocardium in chronic coronary occlusion
Gŭrcheva M, Piperkova E, Djorgova J, Petrov I **348**

Long term follow-up after radiosynovectomy with yttrium-90 in patients with different rheumatic diseases
Kos-Golja M, Budihna N V, Batagelj I **353**

Influence of the radiation source on the quality of transmission bone phantom images
Séra T, Mester J, Skretting A, Csernay L **358**

EXPERIMENTAL ONCOLOGY

Vinblastine increases antitumor effectiveness of bleomycin
Čemažar M, Auersperg M, Serša G **364**

Requirements for a clinical electrochemotherapy device – electroporator
Puc M, Reberšek S, Miklavčič D **368**

A role of a gender on the dimethylhydrazine induced colorectal tumors in Wistal rats
Breskvar L, Cerar A **374**

CLINICAL ONCOLOGY

Cytology of mediastinal tumors
Mermolja M, Kern I, Terčelj M, Jereb M **380**

Early pyriform sinus cancer – results of treatment with partial vertical pharyngectomy
Élö J, Balatoni Z, Tar T **384**

REPORT

2nd international meeting on interventional cardiology
Hadjiev J **388**

SLOVENIAN ABSTRACTS 390

NOTICES 394

REVIEWERS IN 1997 399

AUTHOR INDEX 1997 400

SUBJECT INDEX 1997 403

Radiol Oncol 1997; 31: 345-7.

Congential depression of the skull. A case report

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Congenital depressions of the calvaria are rare. They are usually due to exaggerated or prolonged mechanical pressure applied to the head before or during birth. A female newborn, 3200 grams, was delivered after 38 weeks of gestation by cesarean section due to fetal distress. At birth, physical examination revealed a depression of 5 cm in diameter and 2 cm in depth on the upper and back part of the right parietal bone. The neurological examination was normal and the CT scan showed no associated fractures. Due to the absence of abnormal neurological symptoms conservative management was followed. By the age of 6 month, the neonate follow up revealed normal development and tendency to spontaneous resolution.

Key words: skull-abnormalities; craniofacial abnormalities; cephalometry; parietal bone-abnormalities

Introduction

Congenital depressions of the skull are due to mechanical factors that operate either before or during birth. Exaggerated or prolonged pressure applied to the head of the embryo in utero or during delivery may result in depression of a localized area of the skull. Theoretically, depressions of more than 5 cm may impinge on the cerebral cortex resulting in localized compression of the brain with resultant cerebral edema and decreased blood flow. Due to depression, simultaneous fracture of the skull may occur. Thus, a distinction must be made between congenital depressions with or without fractured skull.[1] Treatment depends on intracranial complications. Traditionally, depressed skull fractures have been considered as an indication for neurosurgical elevation.[2,3] A case of congenital depression of the skull with fully spontaneous resolution at the age of six months is reported.

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Case report

A female newborn, 3200 grams, was delivered after 38 weeks of gestation by cesarean section due to fetal distress. The mother, aged 24 years, gravida 1 para 1, was healthy and no pregnancy complications were noticed. Immediately after birth the neonate needed resuscitation Tracheal intubation and mechanical support ventilation took place and the newborn was transferred to the intensive care unit. Physical examination revealed a depression 5 cm in diameter and 2 cm in depth on the upper and back of the right parietal bone. The overlying skin was normal without edema or hematoma. No other abnormalities were noted and neurological examination was normal. Skull X ray showed a deformed skull depression without fracture. Laboratory examinations and chest x ray were within normal limits. The respiratory system was mechanically supported for 48 hours. Ultrasound examination showed no intracranial abnormality. Computerized tomography showed no obvious pathological findings in brain parenchyma (Figure 1).

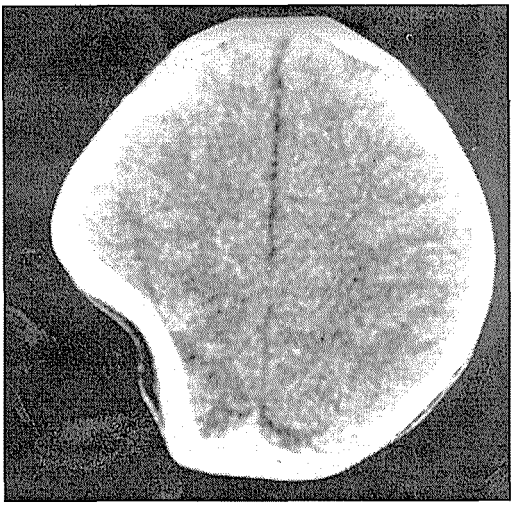

Figure 1. CT scan showing a congenital parietal depression.

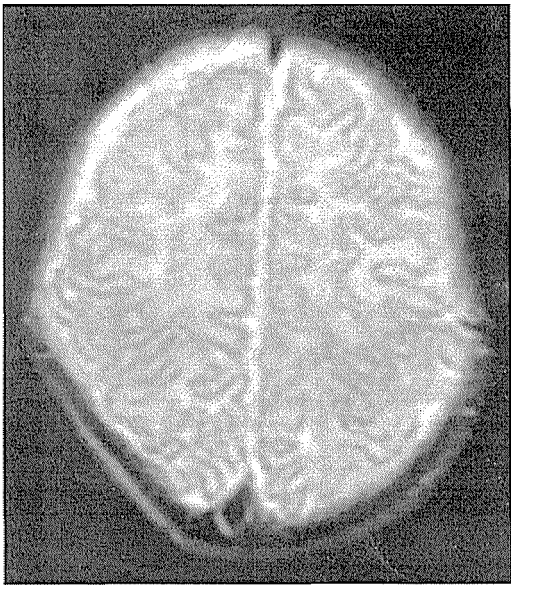

Figure 2. 3-month follow-up magnetic tomography showing tendency to spontaneous resolution of the depression.

The combination of all findings is conclusive for a chronic pressure on the skull during intrauterine life. Due to newborn's good health and absence of abnormal neurological symptoms, a conservative non-surgical management was followed. During hospitalization, the neonate's reflexions were normal with a good muscle tone, and no evidence of, neurological abnormality. At discharge, ten days after birth, the newborn was in good health.

Follow up at 2 weeks, 2 and 3 months revealed normal development. The 3-month follow-up magnetic tomography showed tendency to spontaneous resolution of the depression (Figure 2). Furthermore, no picture of underlying brain damage is observed.

Discussion

Congenital depressions of the neonatal skull are rare and their incidence was found to be about 0,01 %.[1] Usually, two types pathogenesis are distinguished: deformation with or without skull fracture. The demorphity is usually due to mechanical factors that operate either before or during birth. Depressions present at birth and not associated with edema or hematoma of the underlying soft tissues are usually due to long-standing faulty fetal position rahter than to recent birth injury. Application of forceps to the fetal head and traction with excessive force is another although less common cause of congenital depressions that occur in labor. Severe cranial deformities may also develop earlier during fetal life, long before labor sets in, owing to sustained abnormal fetal positions. Other rare causes are maternal pelvis and fibromas of the uterus. Diagnosis is simple as the depressions are visualized by direct inspections, but roentgenograms are often made in the search for associated fractures or bone fragments that might have injured the brain.

Depressed skull fractures have been considered as an indication for neurosurgical elevation. Some authors have proposed non-surgical treatment by either digital or negative pressure after the exclusion of intracranial complications.[1, 4, 5] Spontaneous elevation of the depression during the first year without adverse residual effects was reported.[6] CT scan should be performed before the initiation of nonsurgical treatment in order to exclude intracranial complications. Spontaneous elevation as an approach to congenital skull depression is less traumatic to the infant. We believe that this treatment should be tried for selected cases where no neurological intervention is needed.

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Tl-201 SPECT for the detection of viable hybernating myocardium in chronic coronary occlusion

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Twelve patients with 17 chronic occlusions over the last 1- 14 months were examined with the SPECT Tl-201 myocardial perfusion scintigraphy and angiography before and 2 months after the PTCA (CABG), for the assessment of the improvement of the perfusion and kinetics. This improvement served as a reference method for the positive and negative predictive value of the SPECT study for the detection of viable hybernating myocardium. There were 52 segments (67%) with severe reduced uptake of Thallium from the infarcted area and 44 (56%) were viable. On the basis of angiography the kinetics of 55 segments was assessed. Of the segments with mild wall motion abnormalities (WMA) (19/55), 95% (18/19) were viable. Of the segments with severe WMA (36/55), 14/36 (39%) were viable. A good correlation between the severity of perfusion defects and WMA was demonstrated. The positive and negative predictive values of the SPECT-study were 87% and 84%. No influence of the duration of occlusion was proved. The presence of angiographycally detected collateral circulation was related to the higher percentage of viable segments. The kinetic improvement after PTCA was detected in 34 segments (16 of those with mild WMA - 84%, and 16 of those with severe WMA - 45%). Functional improvement was detected in 8 patients. The left ventricular ejection fraction increase was 5.6% + 4.6%. It was greater in the group with left ventricular dysfunction (7.6%4.8% versus 1.75%1.08%, p<0.01).

Key words*: coronary disease; tomography, emission-computed, single-photon; thallium radioisotopes; myocardial stunning*

Introduction

The detection of viable hybernating myocardium is important for the prediction of the functional improvement after revascularization.[1-4]

The comparison of different radio- and non-radionuclide methods for the evaluation of myocardial viability demonstrates a good position of Tl-201 rest-redistribution technique.[5-8] In this method the accepted criteria of viability are: a significant increase of delayed (redistribution) uptake with >10% in the infarct area, and final (post- procedure) Tl-201 content ≥ 50%.[9,10]

The aim of the study was to evaluate the viable hybernating myocardium in chronic occlusions with previous myocardial infarction according to the SPECT criteria of Tl-201 myocardial perfusion scintigraphy. The influence of both: the duration of occlusion and of the presence of collateral circulation were also under estimation. The post-procedural changes in the function and perfusion served as a reference method.

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Material and methods

Twelve patients intended for PTCA with chronic occlusions and documented myocardial infarction during the last 1 to 14 months were included in the study. The left ventricular function was altered to a different degree (Table1). In 10 patients the revascularization (PTCA,CABG) was carried out and the changes in the function and the perfusion were evaluated 2 months later. They were the base for the evaluation of the accuracy of previous viability determination.

SPECT studies

The myocardial perfusion abnormalities were assessed before and reassessed 2 months after revascularization. SPECT was performed using a rotating large-field-of-view camera equiped with a low-energy all-purpose parallel hole collimator. Thirthy-two projections (40 sec/ projection) were being: 0-normokinetic, 1-hypokinetic, 2-akinetic and 3-dyskinetic.

Table 1. Pre- and post-procedural characteristics of patients.

			Before PTCA (CABG)							Ater PTCA (CABG)		
No	Sex	Age	MI-WMA	Occlu -sion	Dura -tion (mon)	Coll. circul	IA sgts	Viable sgts	LVEF %	Procedure	Res stenosis	ΔLVEF
1	M	48	Ant A/D	LAD	6	0	7	0	31			
2	M	65	Inf,PB H	RCA	3	0	7	7	50	PTCA	0%, 0%	+ 10%
				Rcx		1						
3	M	38	Apic H	LAD	6	1	1	1	69	PTCA	0%	0%
4	M	60	AL,Apic H	LAD	14	2	9	3	62	CABG	CABG	+3%
5	M	50	AL H	LAD	11	1	10	9	35	PTCA	50%	+10%
			Apic D			1						
			Inf, PB A	RCA								
6	M	50	AB H	RCA	2	0	7	4	31	PTCA	40%,	+14%
			AL A			0					100%	
			Apic D	LAD								
			PB A									
7	F	47	Inf H	RCA	12	2	5	5	62	PTCA	100%	+2%
			PB H	Rcx		2					0%	
8	M	58	AB,AL H	LAD	6	0	6	5	50	PTCA+	dis+	0%
			Apic, Inf H							CABG	CABG	
9	M	64	Apic H	LAD	12	1	7	4	37	CABG	CABG	+8%
			Inf A	Rcx		0						
10	M	56	Al,	LAD	8	1	4	3	65	PTCA+	15%	+2%
			Apic H							CABG	CABG	
11	M	17	AL A	LAD	2	0	9	1	34	PTCA	20%	+1%
			Apic D									
12	M	63	Apic D	LAD	7	br.	7	2	45			
			Ant A									
Total							79	44	47.6%± 14.4%			+5.6%± 4.6%

MI - myocardial infarction, WMA- wall motion abnormalities
IA - infarction area, Ant - anterior, AL - anterolateral
AB - anterobasal, Inf - inferior, PB - posterobasal
Apic - apical, A - akinesis, H - hypokinesis, D - dyskinesis
sgts - segments, LVEF - left ventricular ejection fraction
br. - bridging, Res - residual, dis - dissection
Δ LVEF - left ventricular ejection fraction improvement

Angiographic examinations

The coronary anatomy was evaluated before and 2 months after the revascularization. Seventeen occlusions (10 of LAD, 4 of RCA and 3 of Rcx) were detected. Collateral circulation was detected in 10 vascular territories and graded from 0 to 3. The wall motion abnormalities (WMA) were estimated from the contrast ventriculography at 30 degrees of the right anterior oblique projection (RAO) with the Stanford method and semiquantitatively, the score obtained over a semicurcular 180 arch, which extended from 30 of the right anterior oblique to the left posterior oblique position. A 20% symmetric energy window centered on the 68 kev peak was used. All projection images were stored on a magnetic disk in 64x64 word matrix. After the filtered backprojection of the raw images the data were proceeded with Butterworth filter with a cutoff frequency of 0.5 cycles/pixel, order 5.0 to reconstruct transverse axial tomograms of 6.2 mm thickness per slice.

Sagittal and oblique tomograms parallel to the long-axis and the short axis of the left ventricle were extracted from the filtered transaxial tomograms. No attenuation, or scatter corrections were applied. Two sets of images were obtained on the 30-th minute and on the 4-th hour after application of 92 MBq Tl-201.

Analysis of SPECT images of myocardial perfusion

Six tomograms (2 apical, 2 mid-ventricular and 2 basal) were divided into 4 myocardial segments for each study (anterior, inferior, lateral and septal). For the quantitative assessment of regional tracer activities, a circumferential profile analysis was performed on an operator-defined region of interest (ROI), around the left ventricular activity. The maximum pixel activity within each of 60 sectors for the early and delayed images was standartized to the peak activity, which was assigned a value of 100%, without correction or normalization relative to a normal data base. Resting Tl-201 defects were defined as relative regional activities < 80% of peak. The sectors were then grouped into four segments and the segmental activity was obtained as the average of the individual segmental activities within each segment. The extent of the defect was determined by the number of segments with the rest perfusion defect within the vascular territory or in adjacent territories of the occluded artery.

Comparison of perfusion and WM abnormalities

The left ventricle from the RAO 30 degrees projection of angiography was divided into 5 segments: antero-basal, antero-lateral, apical, posterior, postero-basal. They corresponded to the segmentation from the vertical long axis of SPECT perfusion scintigraphy. The projection of WMA on the short axis slices is shown in Figure 1. The segments in septal and lateral regions remained without wall motion determination.

Statistic

The variation analysis was used. All data were presented as the mean value ± SD. The significance of the differences was evaluated by Students t-test.

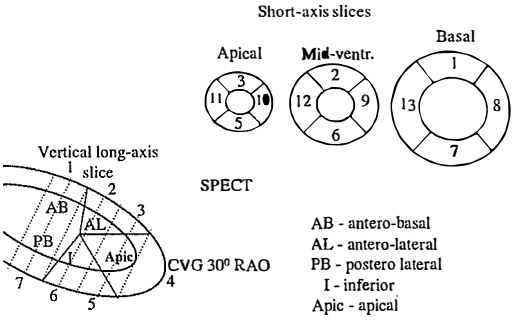

Figure 1. SPECT and CVG segments

Results

PTCA was done in 11 vascular territories. The primary success (residual stenosis <50%) was achieved in 7 of them. From those 2 months later 1 reocclusion occured. In 4 occlusions the procedure was unsuccessful (including 1 dissection and 3 residual stenoses >50%). In 2 of the patients a CABG was performed in the second stage because of the dissection in one case and because of the developpement of the LCA-stem stenosis in the other one. Functional improvement was detected in 8 patients. The mean left ventricular ejection fraction (LVEF) increase was 5.6%±4.6%. One patient demonstrated deterioration of left ventricular function (dissection) and one remained without changes. The group with the left ventricular dysfunction (initial LVEF 39.5%±2.63%, n=6) had an increase of 7.6%±4.8%. The group without dysfunction (initial LVEF 64.5%±2.87%, n=4) had an increase of 1.75%±1.08%.

Detection of viable hybernating myocardium. The quantitative analysis of the percentage of Tl-201 uptake in the segments with perfusion abnormalities before and after revascularization. Of 79 segments included in the infarct area, 52 were with severe uptake reduction of Tl-201 uptake(<50%) and 27-with moderate or mild reduction (≥50%). Forty-four segments (56%) were evaluated to be viable.

Fifty-seven segments were reassessed after revascularization: 38 viable and 19 without viability according to the SPECT study. An improvement in Tl-201 uptake after PTCA was determined in 33 segments. Five segments remained without improvement and showed Tl-uptake after procedure <50%. They were accepted to be false positive. Of the nonviable segments 16 showed no improvement

after revascularization and 3 increased their Tl-uptake to more than 50%. They were accepted to be false negative.

The positive predictive value of the study was 87% (PPV= TP/TP+FP=33/38). The negative predictive value of the study was 84% (NPV= TN/TN+FN=16/19).

Perfusion, wall motion abnormalities and viability. Determination of WMA was done for 55 segments. 36 segments (66%) showed severe WMA (akinetic, dyskinetic) and 19 segments (34%) mild WMA (hypokinetic). According to this analysis, 31/36 (86%) of segments with severe WMA showed severe uptake reduction and 14 of them (39%) were viable. Sixteen out of 19 with mild WMA (84%) showed moderate uptake reduction (>50%) and 18 (95%) of them were viable (Figure 2).

Relation between the viability and the duration of occlusion, as well as the collateral circulation. The patients with duration ≤3 months (n=3) had 52% viable segments (12 from 23 segments) . The patients with duration >3 months (n=9) were with 57% viable segments (32 from 56). For the vascular territories with angiographically detected collateral circulation (n=10) the percentage of viable segments was higher 69% (34/49) than for the territories without collateral circulation (n=7) 33% (10/30 segments). The extent of perfusion defects and the viability score (the number of viable segments) are shown in Table 1.

Changes in the wall motion and perfusion after revascularization. WM improvement appeared in 45% (16/36) from akinetic (dyskinetic) segments and 84% (16/19) of hypokinetic segments. There was a good coincidence of the percentage of the segments with improved WM and the percentage of the previously detected viable segments for both: the severe and the mild WMA (Figure 2).

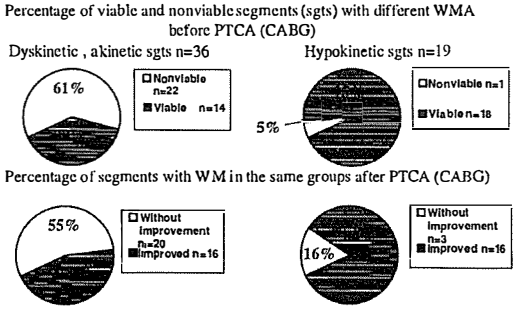

Figure 2. Kinetic changes after PTCA (CABG)

Changes in Tl-201 uptake after revascularization (Figure 3). Of all segments included in the infarcted area (n=79), 27 (x=58.9%±7.3%) were with mild altered uptake and 52 segments showed severe altered uptake (x=33.1%±8.4%). Four hours later, there was an increase in the delayed uptake in both groups as a sign of viability. After revascularization, 37% (21/57) of of reassessed segments remained with severe reduced uptake, while 63% (36/57) of segments showed an uptake ≥50%. It seemed very important that while 66% of the segments (52/79) were with severe uptake abnormality, 58% (32/55) of the segments reassessed after procedure demonstrated functional improvement.

Discussion

There was a substantial number of viable segments in the vascular territory of the coronary arteries with chronic occlusions and previous myocardial infarction. The patients were with different alterations of left ventricular function: n=4 were with saved left ventricular ejection fraction and n=8 were with severe or moderate alterations. Segments with viable hybernating myocardium existed in both groups. The initial Thallium uptake was not predictive for the viability of myocardium. According to our findings, the group of segments with severe reduced early Thallium-uptake (<50%) contained segments with uptake improvement on the delayed images and with uptake improvement after procedure to > 50% (Figure 3). The WMA were not

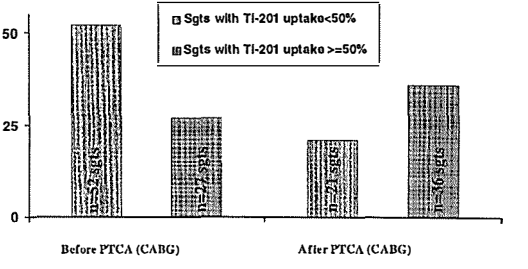

Figure 3. Changes in T1-201 segmental uptake after procedure

predictive and improvement in the kinetic after revascularization occured in both hypokinetic and akinetic (dyskinetic) segments (Figure 2). The myocardial perfusion criteria for viability seemed most important for the determination of hybernating myocardium in the segments with severe WMA-aki-

netic segments. The percentage of viable segments in this group was high enough according to our data (39%). The demonstration of viability in the hypokinetic segments was not so important because almost all of them (95%) were viable. The positive and negative predictive value of the study were similar to those in the literature.[10,11]

The influence of the duration of the occlusion was not proved in this study. The presence of collateral circulation was a predictor of high percentage of viable segments, its absence-predicted 2-fold lower percentage of viable segments.

A substantional functional improvement was detected in 8/10 patients post revascularization. The improvement was more pronounced in the patients with left ventricular dysfunction.

Conclusions

Tl-201 perfusion scintigraphy has high positive predictive value for the detection of hybernating myocardium in patients with chronic occlusions and previous infarction, and can predict the benefitial effect of revascularization.

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Long term follow-up after radiosynovectomy with yttrium 90 in patients with different rheumatic diseases

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The aim of the retrospective study was to evaluate the efficacy of radiosynovectomy (with yttrium 90) mainly in patients with rheumatoid arthritis, less with some other rheumatic diseases. The evaluation period varied from half to nine years. The procedure was performed in 273 patients (225 females, 48 males) or in 463 joints (402 knees, 61 shoulders and ankles). The effect was evaluated by change in degree of morning stiffness, pain and swelling (score from 0 to 9). Very good results were obtained in 69 (15 %), good in 142 (30.5 %), moderate in 197 (42.5 %) and no effect in 55 (12 %) joints. Six months after the procedure 38 joints (8 %), half to two years after 221 joints (48 %) were in good remission, after 3 to 4 years 95 joints (20 %), after 5 to 6 years 57 joints (12%) were well, 7 to 9 years later 52 joints (11 %) showed no signs of arthritis. Joint pain and swelling were the most frequent procedure complications (5.6 %). In two patients with additional immunomodulating therapy chronic myeloid and lymphocytic leukaemia were diagnosed. Radiosynovectomy is considered to be an effective and safe treatment for synovitis in different rheumatic diseases.

Key words: arthritis rheumatoid, synovial membrane-surgery; ytthrium radoisotopes

Introduction

Synovitis is a frequent cause of pain, swelling and functional joint impairment in different rheumatic diseases. For more than 100 years the removal of an inflamed synovial membrane (surgical synovectomy) has been a cornerstone in management of joint inflammation refractory to standard medical treatment. However, the difficulty of removing all the diseased synovium often leads to regrowth, surgical reintervention is often contraindicated because of fibrosis and scar tissue from the previous surgery. The interest for the non-invasive methods of synovectomy was raised and stimulated by easier procedure, lack of complications and lower costs. Many isotopes have been therefore suggested and tested as the potential synovial ablative agents.[1] The development of open arthroscopic, chemical and radiosynovectomy was the consequence of better knowledge of the pathophysiology of synovitis. Radiosynovectomy became an alternative to a surgical method. The interest in this procedure markedly increased in 1950, especially as a prevention method against recurrent and progressive damage in rheumatoid arthritis (RA).[2] It can in principle also be applied to joints in the variety of other inflammatory joint diseases, most frequently in haemophilic synovitis, osteoarthritis and pigmented villonodular synovitis. The first reported use of radiosynovectomy was in 1952 with gold-198.[3] Most often yttrium-90 with tissue penetration 3.6 mm is applied in large joints, rhenium-186 with 1.2 mm tissue penetration in medium sized joints, erbium-169 with tissue penetration of 0.3 mm in small joints. Phosphorus-32,

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radium-224 and dysprosium-165 are also used. All are high-energy ß-emitting radio-pharmaceuticals.[4,5] The average absorbed radiation dose for 180 MBq of administered yttrium-90 is about 100 Gy to 100 g of synovium. Radiosynovectomy is suitable local treatment of synovitis in the case of unresponsiveness to conventional at least half a year long antirheumatic therapy and when surgical synovectomy is contraindicated. It is well known that at early stage the response is better than at late or end-stage of the disease.[6-8] The advantage of radiosynovectomy compared to surgical synovectomy is the relative simplicity of the procedure, lower cost, shorter hospitalisation, quicker rehabilitation, less surgical complications and complications due to anaesthesia especially in elderly patients. Its drawbacks are radiation dose delivered to non-target organs due to leakage of radioactive material from joint cavity to liver, spleen and regional lymph nodes and occasional side effects.

Patients and methods

Indication for ^{90}Y-citrate synovectomy

^{90}Y-citrate was applied to patients over 45 years old with synovitis caused by RA and in some cases of synovitis in the course of other rheumatic diseases such as ankylosing spondylitis, osteoarthritis and haemophilic haemarthropathy. In rheumatic diseases ^{90}Y-citrate was used when the response to previous conventional at least half a year long antirheumatic therapy was insufficient. The procedure was also performed when surgical synovectomy was contraindicated

Inclusion criteria

The patients in whom radiosynovectomy was performed between 1985 and 1994 and were followed for at least 6 months after the application of ^{90}Y-citrate were included and evaluated in the retrospective study. Conventional radiographs of the treated joints were performed before procedure for exclusion of the patients with very severe secondary osteoarthritic changes.

Two hundred and seventy three patients (225 females and 48 males) have been selected for the evaluation. The mean age of the patients was 57±10 years. Mean time of the disease duration was 8.5±6.5 years. In 261 patients (448 joints) RA was present, 3 patients had osteoarthritis, 8 ankylosing spondylitis and one haemophilic haemarthrosis (12 patients, 15 joints). Four hundred and two knees and 61 ankles or shoulders were treated and evaluated. The mean number of treated joints per patient was 1.7±0.9. In knees and shoulders 185 MBq (5 mCi) and in ankles 111 MBq (3 mCi) of ^{90}Y-citrate was applied.

Method of application

The procedure was performed under strict aseptic conditions. The joint was punctured without prior application of local anaesthetic. Synovial fluid if present in excessive amount was removed from the joint and discarded. Subsequently ^{90}Y-citrate was injected intraarticularly. No corticosteroids were given and no additives were admixed to the radiopharmaceutical. After withdrawing the needle the joint was passively flexed and extended several times. Afterwards it was immobilised with semicompressive bandage. Patients were hospitalised for three days and were advised to stay in bed for 48 hours. They had access to bathroom facilities but they were not allowed to bear any weight on the joints.

The evaluation of therapeutic effect

The evaluation of therapeutic effect was retrospective. The data about pain, swelling and morning stiffness in the joint before and after therapy were collected from in- and out-patients files. The period between the procedure and the last visit was considered as the follow-up period. The average frequency of patients' visits was 2 - 4 times yearly, the evaluation of the treatment effect was made by physician in charge.

Each of the three parameters were graded according to the severity of signs and symptoms as normal (0), mild (1), moderate (2) or severe (3). The three scores were summarized to get the overall improvement which was graded with regard to achieved score (from 0 to 9).

No improvement after treatment was considered if the change of score has been less than 1, moderate if the change was between 1.1 and 3, good between 3.1 and 6, and excellent between 6.1 and 9.

The duration of the improvement was measured as well. The treatment was considered unsuccessful if improvement lasted less than 6 months. The side effects of radiotherapy were concurrently recorded.

Results

The mean follow-up period was 4±2.6 years, with the range of 0.5 to 9 years. Mean morning stiffness score before therapy was 1.85±0.93 and after therapy it was 1.10±0.75 (p>0.001).

Mean pain score was 2.84±0.39 before and 1.47±0.7 after therapy (p>0.001). Mean joint swelling score was 2.59±0.56 and 1.43±0.7 before and after therapy respectively (p>0.001).

The improvement was achieved in 88 % of treated joints. No significant improvement was noticed in 12 % of joints. Excellent effect of the treatment was achieved in 15 % of joints (Table 1).

The patients were followed-up in average for 4.03±2.6 years. The mean duration of observed therapeutic effect was 2.79±2.3 years. In 8 % of treated joints the effect lasted about 6 months and in 11 % the improvement lasted for 7 to 9 years. In majority of patients the effect was observed from six months to 7 years (Table 2).

The complications of therapy were noted in 23 patients. Joint pain and swelling were the most frequent side effects (17 patients or 5.6 %). In one transient fever and in two cases radiation necrosis at the injection site developed. In two patients chronic myelogenous and lymphatic leukaemia, respectively, was diagnosed, in one four years and in the other six months after radiosynovectomy. In a single patient hypernephroma and liposarcoma less than one year after radiotherapy were incidentally found.

Discussion

Since the introduction radioisotope synovectomy remained one of the few possible radical treatments of severe joint pain due to chronic synovial inflammation in RA and some other chronic rheumatic diseases. According to the joint size yttrium-90 colloid for large joints, rhenium-186 sulphide for me-

Table 1. Patients according to degree of improvement.

Follow-up (years)	Number of joints	Without effect*	Moderate effect	Significant effect	Excellent effect
1	122	16	48	36	22
2	43	7	15	15	6
3	55	7	19	23	6
4	46	9	21	8	8
5	33	0	19	10	4
6	53	7	27	15	4
7	58	5	29	15	9
8	25	2	9	9	5
9	28	2	10	11	5
sum (%)	463 (100%)	55 (12 %)	197 (42,5 %)	142 (30,5 %)	69 (15 %)

Legend: *This group is considered as "no effect" according to score of improvement of less than 1.1.

Table 2. Duration of improvement according to the years of follow-up.

Follow-up (years)	Number of joints year*	Effect <0.5 years	Effect 0.5 - 2 years	Effect 3 - 4 years	Effect 5 - 6 years	Effect 7 - 9
1	122	21	101	0	0	0
2	43	0	43	0	0	0
3	55	5	15	35	0	0
4	46	5	12	29	0	0
5	33	0	10	7	16	0
6	53	1	12	11	29	0
7	58	3	19	8	4	24
8	25	2	4	3	6	10
9	28	1	5	2	3	17
sum (%)	463 (100%)	38 (8%)	221 (48%)	95 (20%)	58 (13%)	51 (11%)

Legend: *This group is considered as "no effect" according to too short duration of improvement.

dium sized joints, erbium-169 citrate for small joints are usually applied.[5] Allergic reactions, fever and radiation necrosis at the injection canal are considered the early complications.[5] Radiation necrosis was reported after synovectomy with yttrium-90 in an ankle. The authors warn against injecting this radioisotope in small and medium sized joints.[9] Yttrium-90 was used in our patients without serious side effects in spite of few medium sized joints included. In only two cases self-limited radiation necrosis was noticed in needle canal after yttrium injection in the ankle. Side effects were rare in our group as well as in the reports of others where flare up of synovitis is most often reported.[10, 11, 5] Myelogenous and lymphatic leukaemia after 4 years and after six months of radiotherapy occuring in our patients, could be considered as the late complications, although according to the literature they have not been reported anywhere else with the exception of chromosomal aberrations in lymphocytes.[5] On the other hand it is known that lymphatic leukaemia occurs with higher frequency in patients with RA.[12] Besides, the immunomodulatory treatment given to those patients in course of their disease could possibly play a role in development of leukemia. Hypernephroma and liposarcoma occurring in one of our patients less than one year after radiotherapy, cannot be considered as a consequence of radiation exposure after synovectomy.

As already mentioned most of the radiation dose emanates from leaking of the radioactivity from the joint cavity. Leakage of radioactivity to the regional lymph nodes is considered to cause chromosomal aberrations.[13] It is not possible to measure the leakage when yttrium-90, pure ß emitter, is used. Therefore the dose to lymph nodes was calculated for dysprosium-165. Doses of 13 Gy in the immobilised and over 80 Gy in mobilised patient were measured. The leakage is higher if the particles are very small.[1] To reduce the leakage our patients were immobilised for 2 to 3 days.

Although 40 years of use of radiosynovectomy have already passed the reports on long term effects of this therapy are not numerous.[10, 14] Although our study was large and long term it has a drawback of being retrospective. The natural course of inflammatory rheumatic disease is quite variable and especially in retrospective studies it is sometimes not possible to tell the influence of different factors on rheumatic disease progress.[15] In spite of this the evaluation of therapeutic effects in patients with RA could be satisfactorily performed because they keep visiting rheumatologist regularly on long term basis when the mentioned criteria of efficacy of radiosynovectomy are evaluated, thus enabling conscientious follow-up.

Most of the authors report favourable results of the radiosynovectomy in 60 to 80%.[1, 16, 17] We were able to see the favourable effects of the radiosynovectomy in significant number of our patients. The results of our study are satisfactory compared with the results of others.[14, 18, 19] Our experience is mostly limited to the patients with RA, since the number of patients with ankylosing spondylitis, osteoarthritis and haemophilic arthropathies was quite small. The effect of treatment in a single patient, a young boy, with haemophilic arthropathy of the ankle was excellent and in accordance with the report of Van Kasteren et al.[10] In our patients the recommended age limit of 45 years[20] was respected with the exception of the patient with haemophilic arthropathy. Hemophiliacs who need treatment are of younger age since chronic arthropathy is the major complication of haemophilia.[21] Fortunately the radiation dose for gonads is 1.05 µG/MBq which is not high.[22]

In conclusion we can tell that the results of our study are in agreement with the reports in the literature. We consider radiosynovectomy effective, safe and suitable non-invasive therapy for inflammed joints in rheumatoid arthritis and in some other rheumatic diseases that are not responding to conventional antirheumatic therapy. The long-term effects are satisfactory, the side effects after synovectomy are not numerous and not severe. The method seems promising in haemophilic arthropathy as well. Less favourable results were achieved in osteoarthritis.

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Influence of the radiation source on the quality of transmission bone phantom images

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Different types of flood sources were applied to produce bone phantom images, and the quality of the resulting phantom images was studied. The measurements were made with 37-PMT circular detector gamma cameras and with rectangular detectors SPECT devices, with the Scanflex Transbone transmission bone phantom. Phantom images were produced with a 99m-Tc fillable flood source, a 57-Co flood source and a dynamic line phantom (Veenstra Instrumenten B.V.). Images were acquired with the number of counts collected under routine clinical conditions (600 000-800 000 counts) and also with a high number of counts (2 million counts) and were documented on X-ray films. The images were interpreted by three independent experienced observers. From the scores, ROC (receiver operating characteristic) curves were generated. The quality of the images was characterized by the area under the ROC curves. There were no significant differences between the ROC curve areas of the images produced with the same parameters. The differences between the routine and the high-count images were significant. It is concluded that all of the investigated flood sources are suitable for the production of bone phantom images for the quality control of nuclear medicine imaging procedures.

Key words: phantoms; imaging; quality control; bone and bones-radionuclide imaging

Introduction

For more than ten years the World Health Organization (WHO) and the International Atomic Energy Agency (IAEA) have organized interlaboratory comparison studies to analyse the quality of medical investigations using nuclear medicine imaging devices. To reproduce the clinical conditions, organ phantoms have been applied. Measurements with these phantoms allow the determination of parameters which simultaneously characterize the imaging device, the clinical investigation method, and the physician performance.[1,2] The reports returned to the laboratories permit the participants to re-examine their own performance and to correct any errors. The quality control measurements series organized by the WHO to date have involved liver,[2,3] thyroid[4] and heart[5] phantoms. Bone scintigraphy is one of the most widely used nuclear medicine investigation procedures, and the production of a bone phantom is therefore also necessary. The prototype of the "black box" transmission bone phantom was developed by Skretting and co-workers. With this phantom, the first interlaboratory study was carried out in Norway[6,7] as part of an ongoing WHO/IAEA coordinated study. Interlaboratory measurements with a version of this phantom were also performed in Hungary at the beginning of 1994, in 22 nuclear

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medicine laboratories on 28 gamma cameras and SPECT devices; the results were reported earlier. The aim of the present study was to investigate whether the type of flood phantom utilized for imaging the transmission bone phantom influences the quality of the phantom images.

Materials and methods

Our investigations were performed on three 4C/15 type 37-PMT gamma cameras Hungarian made under Picker licence, equipped with a circular detector, and on two modern 59-PMT SPECT devices with a rectangular-shaped detector (Siemens Diacam, Elscint Helix). For the measurements, we utilized the Scanflex Transbone transmission bone phantom, which was applied in the international interlaboratory quality control study organized by the WHO and IAEA.

The schematic diagram of the phantom is presented in Figure 1. The "black box" phantom represents the thoraco-lumbar region from the posterior view. It is rectangular in shape, with constant thickness, and contains absorbing material with a relatively high absorption coefficient, and filling material mostly with a water-equivalent absorption coefficient.

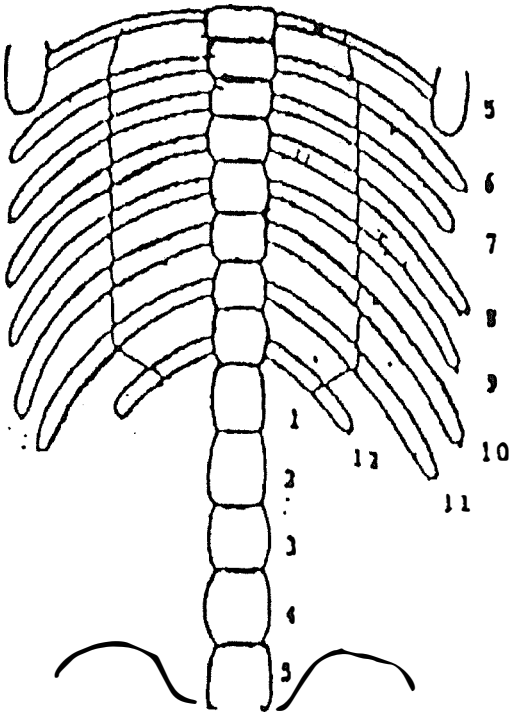


Figure 1. Design of the bone phantom.

The variation in the intensity of the gamma rays is caused by the variation in thickness of the absorbing material.

The phantom is divided into 45 regions; 23 of them contain built-in lesions (22 are hot lesions with relative intensities varying between 1.10 and 2.30, and one is a cold lesion with a relative intensity of 0.58).

Seven lesions are located on the vertebrae, 3 in the medial and 3 in the distal regions of the left ribs, and 5 in the medial and 5 in the distal parts of the right ribs (Figure 2).

	LEFT RIBS		COLUMN VERTEBRA	RIGHT RIBS	
	Distal	Medial		Medial	Distal
5			1.8		1.93
6		1.65		2.04	1.48
7	1.41		(disc)	1.32	
8				1.52	
9		1.18		1.25	1.76
10	2.18		1.32		2.30
11	1.60	1.86		1.72	
12			1.7		1.10

	LUMBAR VERTEBRA
1	0.58
2	
3	1.9
4	
5	

Figure 2. Localization of lesions built into the bone phantom.

In our investigations, the phantom was imaged by three different types of flood source: a 99m-Tc flood source, a 57-Co flood source and a dynamic line phantom.

The 99m-Tc flood source was obtained by filling a plastic disc with bubble-free 99m-Tc solution; a commercially available 57-Co flood source with 120 MBq activity (Amersham) was purchased; and the dynamic line phantom was the one produced by Veenstra Instrumenten B.V. The first of these is a movable capillary tube, controlled by a microprocessor, filled with 350 MBq 99m-Tc solution. The diameters of the 99m-Tc and 57-Co circular flood sources corresponded to the diameter of the 4C/15 type 37-PMT detector. With the dynamic line phantom, a 500x500 mm surface uniform flood source was produced.

Static images

To obtain static images, the phantom was placed on the collimator of the upward-facing detector, and the 99m-Tc or the 57-Co flood source was then positioned on the phantom. When the dynamic line phantom was used, the bone phantom was placed on the special holder above the capillary tube and the images were made with the downward-facing detector.

The parts of the detector which were not covered by the phantom were shielded with lead foil. Images were produced with routine clinical parameters, and were printed on X-ray film, using the exposure parameters elaborated for the clinical routine for each device and a standardized method for film development.

In order to maximize the available information, high-count images, not applicable in clinical practice, were also produced.

Whole body images

With the SPECT devices, images were also produced in whole body scanning mode, utilizing 99m-Tc or 57-Co flood sources: the flood source was placed on the patient investigation bed, and the bone phantom was placed on top of it. The whole body clinical program was activated. To produce the whole body images with the Siemens SPECT, the phantom placed on the patient bed was moved under the surface of the detector at constant speed; with the Elscin SPECT, the images were obtained in a step mode, and the software then generated the whole body image of the phantom. Images were produced with clinical parameters, and high-count images were also obtained. The images were printed on X-ray film.

All the X-ray films were exposed and developed within a few days.

Interpretation of the images

Images were interpreted independently by three experienced observers, using a score method.

The WHO study protocol was applied, and the image of the phantom was divided into 45 regions (Figure 2).

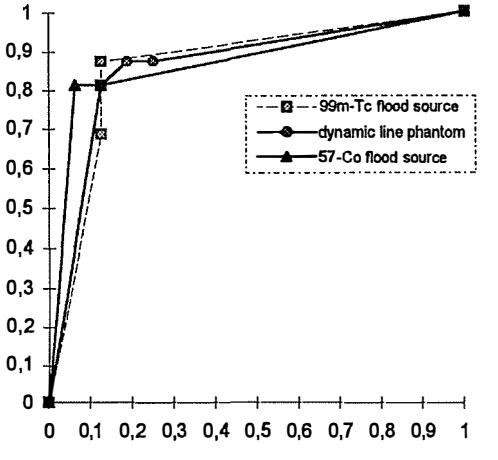
The observers were asked to decide whether they could observe lesions, and with what certainty of detection, within each of the defined regions of the images. The certainty of the detection was characterized by score values on the scale 1-4, 1 indicating a definitely negative region, and 4 a definitely positive region.

Before the interpretation, the images were mixed and given to the observers in a random sequence at long intervals, so that they did not remember the position of the lesions in the already interpreted images. Images were interpreted by ROC (receiver operating characteristic) analyses [8, 9, 10]. The results of the images produced on the same gamma cameras with identical parameters, using the three flood sources, were analysed in pairs.

Results

With the 99m-Tc flood source, the 57-Co flood source and the dynamic line phantom, totals of 19, 14 and 17 images, respectively, were produced. From the results of the three observers, a total of 50 ROC curves were generated. Figure 3 relates to these ROC curves. The observers' performances are characterized by the area under the ROC curve.

Source	ROC area
99m-Tc flood source	0.863
dynamic line phantom	0.861
57-Co flood source	0.869



No. of collected counts = 600 000.

Figure 3. ROC curves and areas of phantom images produced with routine clinical parameters. on a 59-PMT gamma camera with three different flood sources.

The ROC areas vary between 0.73 and 0.96. The best value for the ROC curve area was obtained from the data pertaining to the image produced with the 59-PMT SPECT device with the 57-Co flood source and a high number of counts. The lower value for the ROC area derived from image data obtained with the 59-PMT SPECT device, using the 99m-Tc flood source in the whole body acquisition mode.

The differences in the ROC areas obtained from the interpretations by the individual observers varied between 0.03 and 0.08. The highest differences were obtained with the 59-PMT SPECT device with the 57-Co flood source in the whole body acquisition mode, for a high number of counts, and with the image produced with the 59-PMT SPECT device with the 99m-Tc flood source, for static images with clinical parameters.

In the evaluation of the high-count images, the important differences between the observers were caused by the three false-positive findings of one observer, while in the case of the low-count images, the differences stemmed from the relatively high number of false-negative findings of another observer. However, significant differences were not found between the results of the different observers (Table 1).

Table 1. Comparison of ROC curve areas of images produced with the same gamma cameras but with different radiation sources.

	99m-Tc flood source	line phantom	
ROC area (mean ± SD)			
Observer 1	0.87±0.04	0.87±0.03	n.s.
Observer 2	0.86±0.03	0.86±0.03	n.s.
Observer 3	0.86±0.04	0.87±0.03	n.s.
All	0.86±0.04	0.86±0.03	n.s.
	99m-Tc flood source	57-Co flood source	
ROC area (mean ± SD)			
Observer 1	0.87±0.04	0.85±0.03	n.s.
Observer 2	0.87±0.04	0.89±0.04	n.s.
Observer 3	0.86±0.04	0.89±0.04	n.s.
All	0.87±0.04	0.88±0.04	n.s.
	line phantom	57-Co flood source	
ROC area (mean ± SD)			
Observer 1	0.87±0.03	0.85±0.04	n.s.
Observer 2	0.87±0.03	0.88±0.04	n.s.
Observer 3	0.89±0.02	0.89±0.03	n.s.
All	0.88±0.03	0.87±0.04	n.s.

The results obtained from the images produced with the same cameras, with the same acquisition parameters, but with different flood sources, are presented in Table 1. From the images obtained using the 99m-Tc flood source, 15 were matched with the dynamic line phantom images, 12 with 57-Co images, and 8 of the images obtained with the 57-Co source were compared with their counterparts by using the dynamic line phantom. The quantitative interpretation of the ROC curves does not reveal significant differences in quality of the phantom images produced with the different flood sources.

From the analysis of the influence of the different numbers of counts acquired for the phantom images on the ROC curve area, significant differences in quality were observed between the routine and high-count images (Table 2). The highest difference (0.2) was obtained with the 37-PMT gamma camera, with the dynamic line phantom.

The results obtained with the SPECT devices were usually better than those obtained with the planar cameras, but the low number of SPECT devices involved in the study does not permit a statistical interpretation of the differences.

Table 2. Comparison of ROC curve areas of images produced with the same gamma cameras but with the standard clinical number or a high number of counts.

	99m-Tc flood source		
Acquisition	routine	optimal	
ROC area (mean ±SD)			
Observer 1	0.85±0.04	0.88±0.04	n.s.
Observer 2	0.83±0.04	0.89±0.03	p<0.05
Observer 3	0.82±0.04	0.88±0.03	p<0.05
All	0.83±0.04	0.88±0.03	p<0.05
	dynamic line phantom		
Acquisition	routine	optimal	
ROC area (mean ±SD)			
Observer 1	0.83±0.04	0.90±0.03	p<0.05
Observer 2	0.83±0.03	0.90±0.02	p<0.05
Observer 3	0.85±0.03	0.89±0.02	p<0.05
All	0.84±0.03	0.90±0.02	p<0.05
	57-Co flood source		
Acquisition	routine	optimal	
ROC area (mean ±SD)			
Observer 1	0.83±0.01	0.87±0.03	p<0.05
Observer 2	0.87±0.01	0.92±0.03	p<0.05
Observer 3	0.86±0.02	0.92±0.02	p<0.05
All	0.85±0.01	0.90±0.03	p<0.05

Discussion

Regular quality assurance is one of the important conditions of correct diagnostic investigations.[11]

Routine quality control investigations in nuclear medicine laboratories provide mostly data on the technical parameters of the imaging devices,[12] but

the information relating to the clinical performance in patient investigation results is not reliable.

The detectability of different lesions can be evaluated by using organ phantoms. "Black box" phantom measurements provide valuable data which simultaneously reflect the performances of the imaging instrument and the decision-making physician. It is important, of course, that the basis of the study is the evaluation of the phantom images produced in the same mode as the clinical reports on the patients.

Various national and international organizations and working groups have so far reported results of intercomparison studies with thyroid, liver, heart and brain phantoms.[2,4,13,14]

Their conclusions indicate that the differences in the performances of the imaging instruments, in the acquisition and processing parameters of the images, and in the performances of the observers lead to significant differences in the clinical evaluation.

The procedures applicable for intercomparison measurements of the information lines between the imaging device and the patient report are becoming more effective. The images were initially evaluated by detecting the numbers of true-positive and false-negative findings. Later, different semiquantitative score methods were introduced which take into account the accuracy of lesion detection.[8] So, due to the evaluation of the images, ROC curves can be generated.[8,9,10] The area under such a curve is an objective parameter for the characterization of the performance of an imaging and evaluating system.

The list of available organ phantoms was supplemented by the bone phantom developed by Skretting and co-workers.[6,7,14] to meet the increasing clinical importance of bone scintigraphic investigations. We consider transmission phantoms to be a useful compromise between practicability and reality, but a bone phantom based on the emission would have been closer to the clinical conditions. To establish the fine limitations of the devices, phantoms with lesions on the border of detectability are needed.

Since examinations of the skeleton comprise a considerable proportion of nuclear medicine investigations, we considered it important to investigate how certain technical measurement conditions influence the quality of bone phantom images.

We have studied how the type of the isotope source applied to generate the uniform radiation flood influences the medical performance measurable by the ROC curves while other technical parameters remaining constant. Having emphasized the clinical use, tests were performed on different types of cameras routinely used for bone scintigraphy. In order to achieve realistic results, acquisition parameters corresponding to the clinical routine on each particular device were chosen for the phantom investigation. This was extended with a second, high-count data set in order to maximize the available information.

The results of our measurements with three different radiation flood sources (a 99m-Tc flood source, a 57-Co flood source and the dynamic line phantom) demonstrate that all of these sources are suitable for imaging the transmission bone phantom.

We concluded by saying that a higher number of counts than that applied in routine clinical investigations greatly improves the area under the ROC curves. This is especially important in whole body acquisitions, where an apparently good image quality is needed in a relatively short time. The radionuclide imaging equipment has nowadays nearly reached the limits of resolution achievable. The time during which a patient can remain motionless is limited. The theoretical alternative is to increase the activity injected.[15] This proposal has limitations. The approved levels of injected activity vary from country to country. It would seem that the activities used rely on the tradition and/or the expense, and there is no a generally accepted scientific basis for determining the activity employed.[15]

In accordance with the results of Skretting and co-workers,[6] our investigations based on the images produced with routine clinical parameters demonstrated that whole body images usually produced lower ROC curve areas than in the case of static image evaluations.

Our results reveal that the quality control of bone scintigraphy performed in a whole body or static mode with the transmission bone phantom is a procedure which can be included and applied in the quality assurance system of nuclear medicine laboratories.

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Vinblastine increases antitumor effectiveness of bleomycin

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In our previous study, vinblastine (VELBE) was shown to increase the plasma membrane fluidity. This effect of VELBE might be exploited for better transport of drugs through the plasma membrane. Bleomycin (BLM) is a highly cytotoxic drug when present inside the cells but has a hampered transport through the plasma membrane. The aim of the present study was to determine whether pretreatment with VELBE can increase the effect of BLM on intraperitoneal SA-1 tumors in mice. BLM and VELBE were used as single agents or in various combinations, i.e. VELBE and BLM injected simultaneously, BLM injected 24 h before VELBE or VELBE injected 24 h before BLM. Mice survival was the end-point used for determining the effect of this combined treatments. VELBE and BLM as a single treatment significantly prolonged median survival time of study animals compared to controls. Furthermore, when VELBE and BLM were combined, all three tested combinations were more effective than VELBE or BLM as single treatments. The effect on animal survival was equal when VELBE was given 24 h after or simultaneously with BLM. The longest survival, however, was obtained when VELBE was injected 24 h before BLM. From these results we can conclude that the underlying mechanisms for more than additive effect of VELBE and BLM when VELBE was given 24 h before BLM could be attributed to an increased membrane fluidity, possibly in combination with a cell kinetic effect.

Key words: sarcoma experimental-drug therapy; vinblastine; bleomycin; antineoplastic aagents, combined

Introduction

Vinblastine (VELBE) is an antimitotic alkaloid isolated from periwinkle plant Catharanthus roseus G. Don (Vinca rosea L.). It exerts cytotoxic activity against various tumors and is presently used mainly in combined chemotherapeutic schedules for treatment of testis tumors, Hodgkin's and non-Hodgkin's lymphomas, breast carcinoma, gastric carcinomas, squamous cell carcinoma, thyroid carcinomas, sarcomas and many others.[1-5]

Most presently used combined chemotherapeutic schedules are designed empirically. However, the increasing knowledge of mechanisms of action of cytotoxic drugs forms the basis for rational planning of clinical chemotherapy. In our previous study we have demonstrated that VELBE increases the plasma membrane fluidity and consequently its permeability.[6] Therefore, the rationale of the use of VELBE in combined chemotherapeutic schedules would be that VELBE is administered before an agent which has a hampered transport though the plasma membrane. One of such agents is bleomycin (BLM), a highly cytotoxic drug when present inside the cells.[7] It was shown that as little as several thousand molecules of BLM present inside the cell induce cell death.[8] Based on these properties of VELBE and BLM we conducted a study with the aim to determine the effect of BLM on i.p. SA-1 tumors pretreated with VELBE. Animal survival was the end-point used for determining the effect of this combined treatment.

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Materials and methods

Drug formulation

VELBE (Vinblastine sulphate, Lilly France S.A.) was dissolved in 0.9% NaCl solution at a concentration 2.5 μg/ml. BLM (Mack, Germany) was dissolved in 0.9 % NaCl solution at a concentration 500 μg/ml. The drugs were injected intraperitoneally in 0.5 ml. According to Freireich *et al.,* the corresponding doses for VELBE in humans would be 0.2 mg/m^2 (0.005 mg/kg) and for BLM 37 mg/m^2 (1.0 mg/kg).[9]

Animals

Inbred A/J mice were purchased from the Rudjer Boskovic Institute (Croatia). Mice were maintained at a stable room temperature (24°C) and natural day/night light cycle in a conventional animal colony. Before experiments, mice were subjected to an adaptation period of at least 10 days. Mice of both sexes in good condition, weighing 20-22 g, without signs of infection, 10-12 weeks old, were included in the experiment.

Tumor model

Intraperitoneal (i.p.) SA-1 fibrosarcoma syngeneic to A/J mice was used in the study. The tumor was maintained i.p. as ascites by serial transplantation once a week. For induction of i.p. tumors, tumor cells from the donor mouse were harvested by peritoneal lavage with 4 ml of 0.9 % NaCl solution, washed and resuspended at a concentration of 6 x 10^5 cells/ml. Tumors were induced by i.p. injection of 3 x 10^5 viable SA-1 cells in 0.5 ml 0.9 % NaCl solution. Cell viability, determined by dye exclusion test, was over 95 %.

Study design

To determine the effect of BLM on i.p. SA-1 tumor pretreated with VELBE, mice were treated with VELBE (2.5 μg/mouse) and 24 hours later with BLM (250 μg/mouse). The control groups were as follows: a group without treatment (same procedure; injected with 0.9 % NaCl solution instead of VELBE or BLM), groups treated with VELBE or BLM as single treatment, a group treated with VELBE and immediately afterward with BLM (simultaneously), and a group treated with BLM 24 h before VELBE. Each experimental group consisted of 10 mice.

Statistical analysis

Survival curves were plotted by the Kaplan-Meier method and the differences between the survival curves were determined using the log-rank test.

Results

The effect of BLM and VELBE injected in different combinations on SA-1 tumors was evaluated by animal survival. VELBE and BLM as single treatment significantly prolonged median survival time of animals compared to controls (Table 1. 2., Figure 1.). Furthermore, when VELBE and BLM were combined, all three tested combinations were more effective than VELBE or BLM as single treatments. The effect on animal survival was equal when

Table 1. Antitumor effect of VELBE and BLM treatment on SA-1 i.p. tumors.

Group	n	median survival time (days)
control	10	8.0
VELBE	10	9.5
BLM	10	13.5
BLM-24h-VELBE[1]	10	15.0
BLM-0h-VELBE[2]	10	14.5
VELBE-24h-BLM[3]	10	17.0

[1] BLM injected 24 h before VELBE
[2] BLM and VELBE injected simultaneously
[3] VELBE injected 24 h before BLM

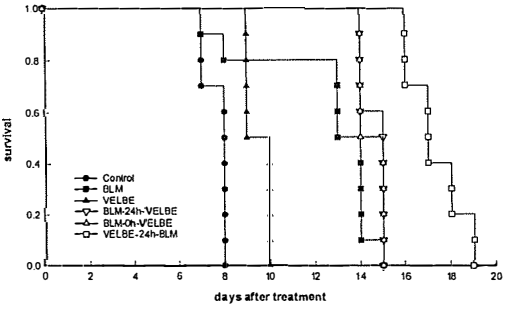

Figure 1. Effect of BLM and VELBE injected in different combinations on survival of mice with i.p. SA-1 tumors. Each experimental group consisted of 10 mice. The survival curves were plotted by the Kaplan-Meier method.

Table 2. Comparison of survival of mice with i.p. SA-1 tumors treated with VELBE and BLM injected in different combinations.

		p compared to			
Group	control	BLM	VELBE	BLM-24h-VELBE	BLM-0h-VELBE
BLM	0.0011				
VELBE	0.0092	0.0042			
BLM-24h-VELBE[1]	<0.0001	<0.0001	<0.0001		
BLM-0h-VELBE[2]	<0.0001	<0.0001	<0.0001	0.6613	
VELBE-24h-BLM[3]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[1] BLM injected 24 h before VELBE
[2] BLM and VELBE injected simultaneously
[3] VELBE injected 24 h before BLM

VELBE was given 24 h after or simultaneously with BLM. However, the longest survival was obtained when VELBE was injected 24 h before BLM.

Discussion

Our study showed that VELBE administered 24 h before BLM increased BLM antitumor effectiveness on i.p. SA-1 tumors in mice.

This study was based on the results of our previous study showing that VELBE increases the plasma membrane fluidity of SA-1 tumor cells at low doses which do not affect cell viability.[6] Membrane fluidity was increased already 0.5 h after VELBE treatment with the maximum values at 24 and 48h. Therefore, in the present study aiming to determine the influence of pretreatment with VELBE on BLM effectiveness we have used a schedule with a 24 h time interval between the two drugs. The antitumor effectiveness was evaluated on the same tumor model, i.e. SA-1 fibrosarcoma, as in our previous study.[6]

VELBE and BLM have different mechanisms of action. VELBE interferes with polymerization of tubulin, a protein which is involved in formation of mitotic spindle microtubules and is also an important component of cytoskeleton. In accordance with its effect on mitotic spindle microtubules, VELBE blocks the cells in the metaphase of mitosis and thus acts as a cell synchronizing agent.[10] The effect on cytoskeleton, however, might influence the plasma membrane fluidity. On the other hand, BLM acts directly on DNA inducing single and double strand DNA cleavage produced by a C-4' deoxyribose hydroperoxide, which is the result of radical abstraction.[7] An additive effect was obtained when VELBE and BLM were given simultaneously or when BLM was injected 24 h before VELBE. In contrast, more than additive effect was obtained when VELBE was given 24 h before BLM. This increased effect of chemotherapy could be the result of either an increased plasma membrane fluidity or a cell kinetic effect caused by VELBE or a combination of both effects. In our previous study we found that VELBE increases membrane fluidity of SA-1 tumor cells and thus we assumed that this could be exploited to facilitate BLM uptake into the cells.[6] To prove that increased plasma membrane fluidity facilitates better accumulation of BLM in the cells, a measurement of BLM concentration in the cells after VELBE treatment would be necessary. In order to facilitate the transport across the plasma membrane other methods were used in addition, such as electroporation.[8,11] In the study of Poddevin *et al.*, an increased accumulation of Co labeled BLM was determined after electroporation of plasma membrane.[11] In our previous clinical studies using ^{99m}Tc labeled BLM (Tc-BLM) we showed that an increased accumulation of Tc-BLM was found in the tumors from approximately 24-48 h after infusion of VELBE.[5,12] In addition, a cell kinetic effect of VELBE was proven by DNA single cell measurement.[12] During the period of increased Tc-BLM an accumulation of cells in S and G2/M compartments of the cell cycle was demonstrated. Cell kinetic effect of VELBE seems to be dose dependent. Higher doses prolong the transition of cells through S phase, whereas lower doses stopped the cells in the G2/M compartment.[13] BLM is reported to be the most effective in G2/M and G1 and less in S phase of the cell cycle.[14] Based on these properties of VELBE and BLM, we assumed that in the present study, a combination of increased membrane fluidity and accumulation of cells in BLM-specific phase of cell cycle could be responsible for the best effect of VELBE and BLM combination in which VELBE preceded BLM by 24 h.

In conclusion, understanding of interactions of agents in combined chemotherapeutic schedules could lead to better planning and timing of drugs in clinical chemotherapy.

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Requirements for a clinical electrochemotherapy device - electroporator

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In the paper we discuss requirements for a clinical electrochemotherapy (ECT) device. These requirements are discussed in the light of the hardware that is needed for ECT. The hardware needed for ECT consists of an electroporator and a set of electrodes. The electroporator is a device that has to fulfill both electrical and safety requirements. Under electrical requirements we understand output characteristics of the electroporator that make the treatment efficient. This is why they have to be consistently fulfilled. On the other hand, the electroporator has to be built and operate in a way that the safety requirements defined by IEC standards are met. Safety requirements are intended to protect both the patient and the personnel from an accidental electric shock. In addition, these safety requirements have to define who can use the electroporator, a device which is similar to a defibrillator with respect to its high voltage output. The second hardware component that is needed for ECT are the electrodes. We classified them as internal and external, based on whether they are used for treatment beyond the skin or superficially. Both types have been studied since the start of ECT application. We also describe the electroporators that are currently being used in clinical situation today. Notwithstanding the availability of some electroporators, we have to conclude that a true clinical electroporator is still needed, since the currently used electroporators do not fulfill all requirements.

Key words: electroporation-instrumentation; neoplasms-drug therapy

Introduction

The combined treatment in which delivery of chemotherapeutic agent is followed by pulsed high electric fields has been termed electrochemotherapy (ECT). This treatment relies on the physical effect of locally applied electric fields that cause permeabilization of cell plasma membrane. This permeabilization of plasmalema allows increased entry of the drug molecules into the cell. The comparison of ECT and conventional chemotherapy shows that much lower amounts of drugs are needed in ECT to achieve equal antitumor effect. Thus the effectiveness of chemotherapeutic drugs with intra-cellular target which do not readilly cross the plasma membrane can be greatly potentiated.

Since the first report of this type of treatment, many studies have been conducted with encouraging results. Studies focused on the optimization of ECT by testing various chemotherapeutic agents, electrodes and electric pulse parameters. In most *in vivo* studies, however, the same electrical parameters were used, i.e. 4 or 8 square-wave electric pulses of 100μs duration, delivered at 1Hz repetition frequency and 1000-1500Vcm^{-1} voltage to electrode distance ratio.[1] The ECT parameters from *in vivo* studies were then transferred to experimental clinical trials and, in all cases, the same pulse generators were used. For experimental clinical trials, laboratory equipment can be used, but it needs to be

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emphasized that safety requirements for clinical devices are much more severe than for laboratory devices. If we want the ECT to become a cancer treatment of choice, appropriate clinical electroporation devices have to be developed.

In this paper, we explore all the important parameters for a clinical electroporator and electrodes that are currently available. Every clinical electric device has to fulfill safety requirements, and in the same time has to be efficient. We can meet these requirements with appropriate electronic design, assuring the output parameters that are based on preclinical studies.

Currently there are many electroporators available, but only few of them could be used in clinical situation. One of the electroporators that could be used in clinical situation is BTX's T820. It generates square wave pulses and can work in high voltage or low voltage mode. In the high voltage mode T820 can generate pulses of 5μs to 99μs and 100V to 3000V. In the low voltage mode it can generate pulses of 0.3 ms to 99 ms and 50V to 500V. The BTX T820 can generate up to 99 consecutive pulses with repetition frequency of 1Hz. This instrument is designed in a way that electrodes are floating all the time.[2]

A new clinical electroporator is also being developed by Genetronix, USA.

Parameter description

The hardware that is used in ECT consists of an electroporator and a set of electrodes. Our classification of parameters is based on such a division of hardware equipment. The parameter values refer to preclinical and clinical ECT studies as well as to the theoretical analysis.

The electroporator

The electroporator is an electronic device that has to meet several requirements. Appropriate choice of electrical parameters makes ECT efficient by facilitating the uptake of chemotherapeutic drugs by cell. Therefore, it is of extreme importance to be able to deliver pulses of specific width, amplitude, and to meet the power requirements. Table 1 shows the parameters, used in representative ECT studies.

Table 1. Parameters of representative electrochemotherapy.

First author; year of publication	Shape of the pulses	Duration	Number of pulses	Electrode to distance ratio	Electrodes
Okino; 1987, 1990 [8,11]	exponential	2 ms	1	5 $kVcm^{-1}$	external
Kanesada; 1990 [12]	exponential	4 ms	1	3 $kVcm^{-1}$	external
Mir; 1991, [9] Belehradek; 1991 [13]	rectangular	100 μs	8	1.5 $kVcm^{-1}$	external
Salford; 1993 [14]	exponential	325 μs #	8 to 12	400V or 600V *	needle
Belehradek; 1994 [15]	rectangular	100 μs	8	>1050Vcm^{-1}	external
Serša; 1995 [10]	rectangular	100 μs	8	1.3 $kVcm^{-1}$	external
Heller; 1995 [16]	rectangular	99 μs	8	1.5 $kVcm^{-1}$	external
Heller; 1997 [17]	rectangular	99 μs	8	1.3 $kVcm^{-1}$	external
Jaroszeski; 1997 [18]	rectangular	99 μs	6	1 $kVcm^{-1}$	needle array
Mir; 1997 [4]	rectangular	100 μs	4+4 ℘	800 Vcm^{-1}	needle array

* Pulse amplitude
\# Time constant
℘ Four pulses of each polarity

The second one is Jouan's Cellular Electropulsator PS 10 (or newer model PS 15) that generates square wave pulses of 5μs to 24 ms and 0V to 1500V. The design of the older model is a bit awkward, but it could be improved so that it would become safer.[3,4]

The third one, Antony's CELTEM MKO, is still a prototype and is able to deliver electric pulses to needle arrays. So far it has only been used in France.[4]

From Table 1 it is evident that the electrical parameters of ECT have been optimized since the first trials. According to the *in vivo* and clinical studies performed so far, a clinical electroporator should generate pulses with amplitude up to 3000V, but probably not much higher, since excessive strength of electric field strength diminishes the viability of cells,[5] thus killing the cells around electrodes, causing necrosis. On the other hand, the electric field has to be strong enough to induce

sufficient transmembrane voltage change $\Delta\Phi_m$ to cause permeabilization of the cell membrane. The equation which defines induced transmembrane voltage reads:[6]

$$\Delta\Phi_m = f_S ER\cos\theta \cdot \left[1-\exp\left(-\frac{t}{\tau}\right)\right] \quad (1)$$

where E is the magnitude of electric field, t is the time, R is the cell radius, θ is the polar angle measured with respect to the direction of the field, f_S is a function reflecting the electric and dimensional properties of the cell and the surroundings, and τ is the time constant of the membrane (for detailed description, refer to reference 6).

The rate of transmembrane voltage change depends on the ratio in the exponential term in the equation (1). Under physiological conditions, τ is in the microseconds range. In case where the electric pulse duration (T) is much longer than τ (i.e. $T \geq 3\tau$), $\Delta\Phi_m$ reaches its peak value during of the duration of the pulse and at that point the membrane permeabilization occurs.[6] Therefore, an electroporator should generate electric pulses that have duration of 10μs or more.

In addition, the electroporator needs sufficient energy for its operation. Estimated energy W is calculated according to the equation (2), where U is the voltage amplitude of the pulse, I is the electric current, Z is the impedance of the tissue between the electrodes (including the tumor), and T is the pulse width:

$$W = U \cdot I \cdot T = \frac{U^2}{Z} \cdot T \quad (2)$$

Since the electroporator provides constant voltage, the energy load increases with decrease of impedance Z, which is evident from equation (2). Impedance Z is given by the equation (3), where ρ is specific resistivity of the tumor, l is the distance between the electrodes, and S is the effective surface of the electrodes.

$$Z = \frac{\rho \cdot l}{S} \quad (3)$$

The easiest way to calculate energy is to measure the electric current, the voltage amplitude of the pulse, and the pulse width during the treatment. According to the study of Rudolf et al.[19] the electric current was estimated to be 4A, at the voltage amplitude of 910V, and the pulse width of 100μs. These values give, according to the first part of equation (2), energy of 0.37J. If we consider that maximum of 8 pulses are currently delivered in one session and that during this treatment the electroporator does not obtain any energy, then it has to store at least 2.96J of energy at the beginning of the treatment.

If these power requirements are not met, the amplitude of pulses will decrease and with it the electric field magnitude. Therefore, we have to assure that the electroporator stores enough energy.

The purpose of safety precautions when using electrical devices in medicine is to protect the patient, the person who is operating the device – a medical doctor, and any other medical worker who can come in touch with the device. In general, we have to assure that electric devices are used by qualified, responsible, and authorized personnel only.

Electric current used for electrochemotherapy helps the patient, but if not properly controlled and handled, it can become dangerous. The treatment of internal tumors is especially critical. In such cases, the natural barrier, i.e. skin, is by-passed and with it the body's natural protection.

Reaction to electric current varies from person to person. Sensitivity depends on many parameters, such as the state and the level of contact with electric wire, moistness and thickness of skin, etc. Regarding those parameters, the designer of the clinical electric device has to consider levels of protection and provide written rules.

If a malfunction of clinical electric device occurs, it must occur in a controlled maneuver. This means that in case of a single malfunction, which can be caused by a defect of one component in the protection chain, the device must not cause any danger either to the patient or to the person who is operating it. We can achieve this with double protection construction, redundant checks, and special protection components. The state of the single malfunction has to be time limited, because otherwise the electric device could become dangerous to the patient and the operator in case of a second malfunction. It is therefore important that the personnel is notified in case of the single malfunction. In

most cases, this is not achievable immediately and the malfunction is discovered indirectly by means of periodical test measurements. Such control of medical equipment is performed by a clinical engineer.

If the clinical electric device has a single malfunction, and then the second malfunction occurs, the clinical electric device must stop operating automatically, and must stay in that state until it is repaired.

The detailed classification of clinical electric devices is defined by IEC standards. This classification refers to: the level of electric shock protection, the level of protection in presence of flammable and explosive gases and fluids, the level of electric connection between the patient and the electric device, and the operation of the device according to the time.

The electroporator is a device that can produce electric pulses with amplitude up to 3000V, although the pulses usually are as short as 100μs, they can be delivered rapidly. It is important to stress that the electroporator is similar to a defibrillator, with the respect to the high voltage output, so the safety requirements for the electroporator have to be as severe as they are for the defibrillator. The electroporator must be galvanically separated from the main supply voltage, the electrodes must float, the output should be monitored during the treatment in case of any malfunction, etc. Finally, we have to stress that the electroporator should only be used by authorized and qualified personnel as it is in the case of defibrillator.

Electrodes

Electrodes represent the second part of the hardware that is needed for ECT. Basically, there are two types of electrodes, external and internal. Both types of electrodes have been tested first in preclinical studies, where they showed their advantages and disadvantages. For all types of electrodes it is important that they deliver electric field and to cover effectively as large volume of a tumor as possible.

At the beginning of electrochemotherapy studies, external parallel plate electrodes were used. These electrodes represent the only external type of electrodes currently used, there are different designs of them, but basic principle is the same. One of possible designs is presented in Figure 1A. The parallel plate electrode is mounted on a plastic vernier caliper. The faces of the electrodes measure 1 cm by 1 cm. The movement of the caliper allows adjustment of the distance between the electrodes to accommodate tumors of different sizes. The usual voltage to electrode distance ratio for this type of electrodes is 1500 Vcm^{-1}.[7] The main disadvantage of surface electrodes is small electric field penetration. Consequently only superficial tumors can be effectively treated.

The advantage of internal electrodes is that they allow treatment of the deepest parts of the tumors even in the thickest skin nodules, as well as internal tumors. With the implanted needles, the electric field will be delivered approximately to the same depth as the electrodes. The first treatment with internal needle electrodes was reported in 1993, by Salford et al.[14] Part B of Figure 1 shows the needle electrodes that were used. Electrodes were 1.5 cm long and 0.070 cm in diameter. Both needles were inserted on either side of the tumor.[7]

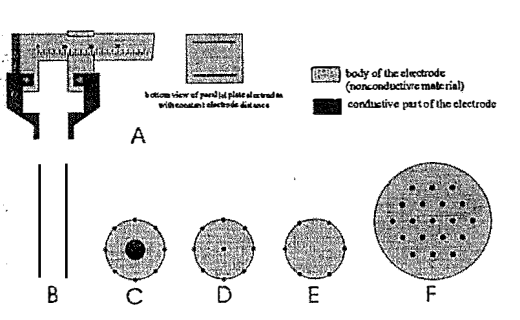

Figure 1. Different electrodes used for electrochemotherapy: (A) Parallel plate electrodes, (B) needle pair electrode, (C) 8+1 solid electrode, (D) 8+1 needle electrode, (E) 3 × 3 and 2 × 2 arrays, (F) 'honeycomb' array. Electrodes are not drawn to a scale.

Figure 1 also shows four different geometries for needle array electrodes that have been designed in last few years. Parts C and D of figure show 8+1 solid and 8+1 needle electrodes. The two designs are similar in their construction - they are both composed of eight electrically connected 30 gauge stainless steel needles equispaced around 1 cm annulus. They differ with respect to the type and location of the center electrode. The 1 mm diameter solid electrode is located 0.465 cm from the circumferential needles in the 8+1 solid design. The central needle (30 gauge) of 8+1 needle electrode is positioned 0.50 cm from the circumferential electrodes. All needles in these two designs extend 0.5 cm from their electrode bodies. The circumferentially arranged needles are inserted into the perime-

ter of the tumor. The central electrode of the 8+1 solid configuration extends 0.15 cm from the electrode body and is in contact with the tumor during the treatment. The central needle in the 8+1 needle configuration is inserted into the tumor. The central electrode is usually anodic during pulsation for both designs, and the voltage to electrode distance ratio is 1500 Vcm^{-1}.[7]

Figure 1E illustrates the electrode geometry for the 3 × 3 and 2 × 2 needle arrays. This design comprises six 28 gauge stainless steel acupuncture needles. The needles are spaced at 60° intervals around a 1cm diameter circle and extend 1 cm from the electrode body. Both arrays were constructed so that each needle has an independent electric connection. Although both arrays utilize the same fundamental geometry, their operation differs with respect to the sequence in which voltages are applied to the needles. The usual voltage to electrode distance ratio is 1500Vcm^{-1}. To determine the voltage amplitude that has to be applied to the needles, minimal distance between the oppositely polarized needles is used.[7]

Figure 1F illustrates internal electrodes consisting of seven parallel equidistant needles, 1.5 cm long , 6 mm apart, arranged as a centered 'honeycomb'. Electric pulses are delivered to each pair of closest electrodes. The usual voltage to electrode distance ratio is 800Vcm^{-1}.[4]

All types of electrodes have proved to be effective to a certain extent in preclinical studies, but it is difficult to state which type of electrodes are better. Namely, the electric field distribution in the tissue is not known so it is difficult to compare them, especially with respect to efficient coverage of the tumor with sufficiently high electric field magnitude, which is their prime objective.

ECT studies of electrode design have shown that internal or needle electrodes are much more effective than the external ones. With the insertion of needle electrodes into a large tumor, the electrodes split the tumor in smaller volumes, and electric pulses are delivered to each of this volumes. Smaller volume requires lower voltage and thus a safer treatment in comparison to the one in which electric pulses are delivered to the whole tumor using only two external electrodes. Two external electrodes placed at each edge of the tumor nodules have large interelectrode distance that requires higher voltage. Therefore, needle electrodes seem to be more appropriate for the treatment of large tumors. In addition, needle electrodes allow penetration into the body so that in principle any location can be reached.

General considerations

ECT has shown promise in treating a variety of tumors in humans. The basic principles for its effectiveness are reasonably well understood. At present, there is enough hardware to evaluate ECT in clinical trails. There are at least six different designs of electrodes, and there are at least three different electroporators which can be used in clinical treatment.

Nevertheless, there is a demand for a clinical electroporator with the following expectations to meet: safety requirements, pulse amplitude up to 3000V, pulse width from few microseconds up to few hundreds of microseconds, variable repetition frequency of pulse delivery, enough power to allow very small impedance between electrodes, connections for any kind of electrodes, onboard computer which would suggest parameters of treatment for different electrodes and could control the process during treatment. In addition, electroporator needs to be easy and practical to use. Based on the above specifications, we have to conclude that currently no known electroporator meets this requirements.

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A role of gender in the occurrence of dimethylhydrazine induced colorectal tumors in Wistar rats

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Human colorectal carcinoma appears more frequently in males. The aim of our study was to evaluate the influence of gender on the induction of colorectal carcinoma by 1,2-dimethylhydrazine (DMH) in Wistar rats. Sixty Wistar rats (30 males, 30 females) were subjected to weekly subcutaneous injections of DMH (20 mg/kg) for 15 weeks. After 25 weeks from the beginning of the experiment the animals were sacrificed and autopsied. All macroscopical lesions were evaluated histologically. Induction of colorectal tumors succeeded in 37% of males and 17% of females. There were 21 tumors of the large bowel found, of these 15 in males and 6 in females. Histologically, males had 11 adenomas, 2 signet-cell carcinomas and 2 adenocarcinomas, while females had 4 signet-cell carcinomas and 2 adenomas. We also found extracolonic tumors, mainly those of the small intestine and of the Zymbal glands. Wistar rats showed lower incidence of DMH-induced colorectal tumors in comparison with other strains of rats. The gender-dependent difference in the incidence of colorectal tumors was found to be statistically marginally significant ($p<0.08$), whereas the difference in the incidence of all induced tumors between genders was significant ($p<0.02$). Males showed a greater incidence of colorectal tumors and also a greater histological resemblance to human colorectal tumors than females. That is why we recommend Wistar males rather than females for research on colorectal tumors.

Key words: Colorectal neoplasms-chemically induced; dimethylhydralazines; rats

Introduction

Nowadays, colorectal cancer (CRC) represents one of the most frequent malignant neoplasms of man in the developed world. With respect to its incidence as well as mortality rates, in the United States of America it takes the third place[1] while in Slovenia it is on the second place.[2] It is a well known fact that in humans, males will contract CRC more frequently than females.[1] A few studies that have been carried out on animal models yielded similar results.[3,4,5] The models in those studies differed from each other considerably, so with respect to the type and strain of animals used as well as with respect to tumor induction methods. Nowadays, Wistar rats are the strain most commonly used for research purposes. As most authors give preference to male specimens while the published information on sex-related differences in the induction of CRC with DMH is very scarce, we have decided that this issue is worth of further studies.

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Materials and methods

Animals

Sixty Wistar rats (provider: Medical Experimental Center, Ljubljana) 9 weeks of age were used. At the onset of the experiment the weight of males ranged between 220-280 g, and that of females between 140-180 g. The experiment was carried out at a

room temperature of 20-23°C, humidity 40-70%, and at a natural day/night cycle. The animals were fed on M-K-02 briquettes (supplier: Biotechnical Faculty, Ljubljana) and tap water.

Carcinogenic agent

CRC was induced by means of DMH (producer: Fluka Chemie, Switzerland) prepared according to the standard method [6,7]: DMH-HCl was dissolved in 0.001 M EDTA and pH value adjusted to 6.5 using 0.1 M NaOH solution. Fresh solutions were prepared once weekly.

Study design

The animals were distributed into groups of 10 per cage. Males and females were kept separately. Every three weeks the animals were weighted and the dose of DMH adjusted accordingly, so that it always amounted to 20 mg/kg of body weight. The solution was injected subcutaneously (s.c.) into the skin fold on the hip once weekly throughout a period of 15 weeks. The animals were left to live 10 weeks after completed DMH injection, and thereupon sacrificed by CO_2 inhalation.

Morphological investigation

On autopsy, all internal organs except the central nervous system were examined. Particular attention was paid to possible presence of tumors in the outer auditory canal. The stomach was opened via the major curve while the intestine was approached longitudinally on the antemesenterial side; after opening, the organs were rinsed with water. The end part of the ileum, large intestine, anus and neoplasms in the small intestine were spread over a polystyrene board, with intestinal mucosa facing upwards. The tissue was fixed in 10% buffered formaldehyde.

Three tissue samples of the large intestine were taken for histological examination from the following sites: the rectum, transversal colon and ascending colon. All the macroscopically visible lesions were sampled as well. The tissue samples were paraffin embedded and cut into 4mm thick histological sections. The sections were afterwards stained by thrichrome method according to Kreyberg. In the cases when histological picture or tumor stage could not be determined from a single section, a stepwise series of sections was made. All intestinal lesions were assessed by histological criteria used in human pathology.[8]

Carcinomas were distributed into three stages according to their phase of development:[9]

– Stage A: tumor tissue is limited to the intestinal wall;

– Stage B: tumor tissue grows through the lamina muscularis propria;

– Stage C: tumor tissue grows through the lamina muscularis propria and disseminates into the lymph nodes and distant organs.

Histological criteria for diagnosis of adenoma were 1) cytological (multiplied mitoses, polymorphism, and hyperchromatism of the nuclei, basophilia of the cytoplasm, decreased mucine excretion), and 2) histological (stratification of the nuclei, irregular proliferation of the glandular formations). The criteria for diagnosis of carcinoma was the evidence of tumor growth through the muscularis mucosae.

Statistical methods

The significance of sex-related difference in the numeric results was tested by Pearson's Chi-square test.

Results

Ninety-five percent of animals survived throughout the duration of the experiment. One male was sacrificed 7 weeks before the end of experiment because of a large tumor of the Zymbal gland while another two males died spontaneously due to intestinal tumors (1 in the large and 1 in the small intestine) 10 and 1 days respectively before the end of experiment.

During the experiment the animals were fed normally, their body weight was increasing by advancing age. In the last two weeks, the body weight of five males was found to have decreased, and the presence of carcinomas of the Zymbal gland or intestine was confirmed in all of them.

Tumors of the large intestine and rectum

Twenty-one tumors were found in the large intestine, 15 of these in males and 6 in females (Table 1). Tumors developed in 37% of males and 17% of females, i.e. in 27% of all animals. Three males (10%) and one female (3%) had multiple primary tumors.

Sex-related difference in the occurrence of all colonic tumors was borderline significant ($p<0.08$).

Table 1. The number of tumors induced in the large intestine

Sex	Histological type of tumor			
	Adenoca.	Signet-cell ca.	Adenoma	Total
Males	11	2	2	15
Females	0	4	2	6
Total	11	6	4	21

An analysis of sex-related differences in the number of colorectal carcinomas also showed a borderline significance ($p<0.08$).

A majority of the induced tumors were found in the transverse colon (30%), followed by the ascending colon (17%), rectosigmoid (10%) and descending colon (7%) (Figure 1).

Most tumors in males were polypoid (Figure 2); a majority of them were situated in the transverse colon (73%), and none in the rectosigmoid. Intussusception in the transverse and descending colon respectively was observed in two males.

In females, the tumors induced in the large intestine were rare and relatively evenly distributed (Figure 1). Three females presented with tumors in the rectum. There were neither tumors in the descending colon nor intussusception observed. Macroscopically, most tumors in females were flat. On a subsequent histological examination they were recognized as signet-cell carcinomas.

In the review of histological samples 21 tumors were analysed (Table 1) as follows: there were 11 adenocarcinomas (Figure 3), 6 signet-cell carcinomas and 4 adenomas.

All the neoplasms were macroscopically visible. Further microscopic examination also revealed the presence of adenomas consisting of a single or a few glandular formations.

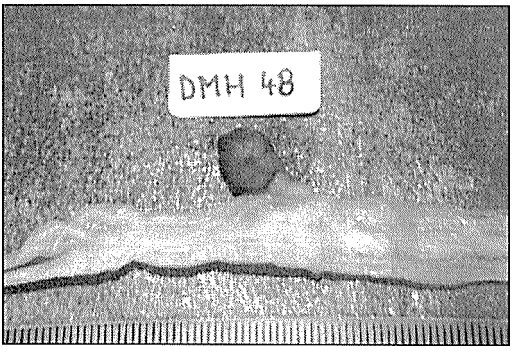

Figure 2. Polypoid tumor of the large intestine. The tumor is attached with a short stem. A prestenotic dilatation of the intestinal wall is visible on the right.

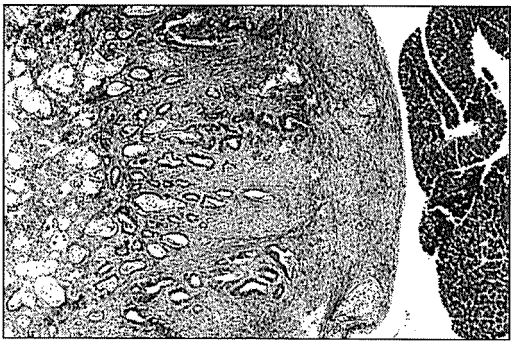

Figure 3. A well-differentiated adenocarcinoma which infiltrates to the serosis

The majority of polypoid tumors were found to be well or moderately differentiated adenocarcino-

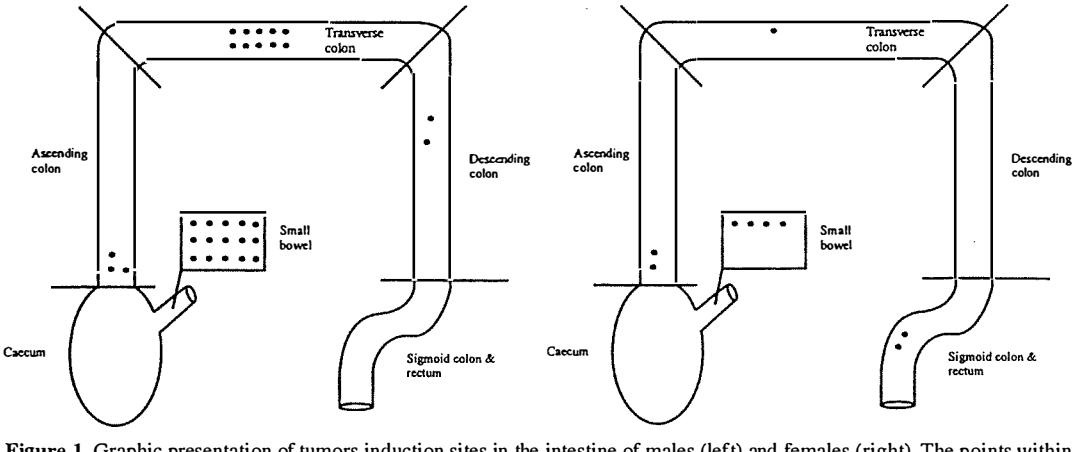

Figure 1. Graphic presentation of tumors induction sites in the intestine of males (left) and females (right). The points within the intestine represent individual tumors.

mas. Poorly differentiated adenocarcinomas were rare. In contrast to that, signet-cell carcinomas were mostly flat lesions which infiltrated the wall.

The sex-related differences in the number of tumors induced in the large intestine were not statistically significant. In males 15 tumors were found in the colon and rectum as follows: there were 11 adenocarcinomas, 2 signet-cell carcinomas and 2 adenomas. In females 6 tumors were induced: 4 signet-cell carcinomas and 2 adenomas.

When determining the stage of colorectal carcinomas, the majority of tumors (71%) were found to be stage A (Figure 4). Many smaller, well-differentiated stage A tumors could be interpreted as adenomas, and therefore step-wise sections had to be made in a few cases in order to ascertain the invasion through the *muscularis mucosae.*

The comparison of stage distribution by sex did not show statistically significant differences ($p<0.14$). In males the majority of carcinomas (77%) were stage A while the rest were stage B, the latter being invariably situated in the transverse colon. None of the males presented with a stage C tumor. Most tumors in females were stage A, all of them were signet-cell carcinomas. One female had a stage C tumor. Histologically, this was a signet-cell carcinoma with evidence of lymph node involvement and carcinosis of the liver and peritoneum.

Other tumors

Apart from tumors of the large intestine, there were also 19 tumors of the small intestine and 5 tumors of the Zymbal gland found along with 1 hemangioma of the liver and one hepatocellular carcinoma.

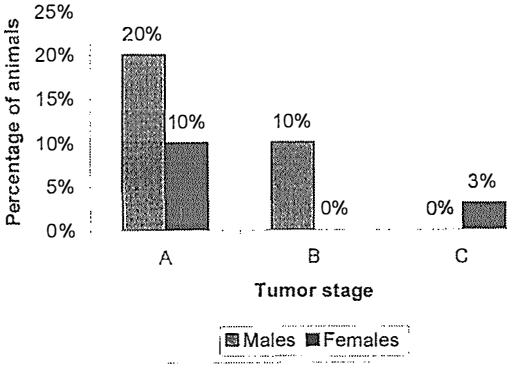

Figure 4. Comparison of grades of large intestine carcinomas.

The tumors of the small intestine were mostly large, polypoid and macroscopically similar to those found in the large intestine, although they were histologically different: a half of these tumors were signet-cell carcinomas, the majority (80%) of them being stage B. The rest were adenocarcinomas exhibiting focally increased mucine production. Tumors of the small intestine occurred in one third of males (33%); 80% of these presented with signet-cell carcinomas while the rest had moderately differentiated adenocarcinomas. Three males had multiple primary tumors, and two showed evidence of intussusception. In females, tumors of the small intestine were found in 13%. A half of these were adenocarcinomas, while the other half were signet-cell carcinomas; 75% of all tumors were in an advanced stage B.

The sex-related differences in the incidence of small-intestinal tumors were found borderline significant ($p<0.07$). The sex-related difference in the number of all tumors induced was statistically significant ($p<0.02$).

Discussion

While CRC is a relatively frequent tumor in humans, its spontaneous occurrence in rats is rare.[10] DMH is one of the most effective CRC inducers in small rodents.[11] This substance has been studied in large-scale experiments,[12] and the tumors induced have been compared with those occurring naturally in humans[10,13,14], although any sex-related differences were not clearly defined.

Some authors claim to have established a lower incidence of DMH induced tumors in Wistar rats as compared to other strains of rats.[15] These findings have also been confirmed by our results showing that tumor induction was successful in 27% of the experimental animals only. The occurrence was considerably lower in females than in males, although the difference was only borderline significant.

Histological examination revealed a few adenomas in the large intestine, which consisted of one or more glands. These lesions were not macroscopically evident. Nevertheless, this finding is interesting as it confirms probable development of carcinoma from adenoma [16,17], and points out the similarity with colorectal carcinogenesis in humans. Such adenomas were also reported by other authors[18] although they were not evaluated quantitatively. Un-

doubtedly, there would have been even more adenomas found in our study, had we decided to examine the entire intestine by systematic microscopy. This will be the subject of our further research.

Our data on the sites of primary tumor induction in males are consistent with those of other authors, who report the greatest number of tumors in the transversal colon.[19] Comparable with our results, other authors also found rare tumors in the ascending and descending colon but not in the caecum.[19] It is of interest to note that not a single tumor of the rectum could be found in males. Consistent with this observation, other authors also report rare tumor occurrence in this site (5%).[7,20] In females as well tumors of the wide intestine were induced in the same sites as reported by other authors,[12] the only exception being the ascending colon where the numbers of induced tumors reported by other authors are somewhat higher.

Likewise other authors, macroscopically we also found prevailingly polypoid tumors.[10,12] There was however, sex-related difference found with respect to the site of their occurrence. Thus males had a prevailing majority of polypoid tumors in the central part of the colon. Sessile tumors exhibiting endophytic growth were extremely rare. The latter were found prevailingly in the proximal part of the ascending colon. Intussusception, which was observed in a few animals, has also been reported by other authors.[6,10] The site of origin is just as usual in the transverse colon, which is consistent with the sites of origin of polypoid tumors.[6] It is well known that large polypoid tumors are associated with more aggressive invasion of the intestinal wall.[19] This is responsible for hardening of the wall and consequential invagination into the distal part of the intestine.

In females, most tumors were situated in the rectum and proximal part of the ascending colon. Macroscopic differences were evident as well: a majority (70%) of tumors were sessile and wall-invading. Intussusception was not noted. This could partly be attributable to the fact that those tumors were relatively small.

Histologically, our number of adenocarcinomas was smaller than those reported by other authors who used other strains of rats and the same dose of DMH.[6,7] The descriptions of histological pictures of tumors in males were consistent with our results, although the rate of signet-cell carcinomas in our series was greater (13% of all tumors). According to some authors, the occurrence of the latter tumors is attributable to a higher dose of DMH.[21] It has been found that all those tumors were flat and that they occurred in the proximal part of the ascending colon. This finding is consistent with the reports of other authors.[13,22] The majority of polypoid tumors that were found in the transverse colon were adenocarcinomas. Their histological picture depended on the tumor size. Thus, smaller tumors mostly showed a well differentiated adenocarcinomatous component with a minimal or no mucinous component, whereas larger polypoid tumors showed a greater rate of mucinous component, which has also been described by some other authors.[19]

Our results of tumor stage analysis were comparable with those obtained by other authors, according to which a majority of tumors (71%) were in stage A.[9] Our comparison of carcinoma stage by sex has not shown statistically significant differences, however it seems noteworthy that none of the females presented with a stage B tumor. The fact that most of those tumors were signet-cell carcinomas renders this information all the more interesting. A majority of authors[10,16] believe that this very type of tumors is the most aggressive. Stage was also associated with the degree of differentiation of colorectal tumors: the majority of stage B tumors were moderately or poorly differentiated carcinomas. Stages were rarely described in experimental studies with DMH, the only exception being individual cases of stage C with carcinosis and distant metastases.[6,16,23].

Few authors studied the origin of sex-related differences in the occurrence of DMH induced tumors. The majority of investigations were centred on the study of the influence of sex hormones.[24] A stimulating effect of male sex hormones on tumor induction with DMH was established.[5]

Our results have shown that males developed significantly more colorectal tumors than females. Furthermore, the tumors in males were histologically more similar to colorectal tumors in humans. Therefore, we recommend male rather than female Wistar rats to be used for experimental work with the mentioned tumor model.

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Cytology of mediastinal tumors

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Our experience with cytological examinations of tumorous mediastinal lesions is evaluated. A group of 117 patients with mediastinal tumor have been included into the study. Among them carcinomas prevailed (60.7%), followed by lymphomas (18.8%), other tumors (15.4%) and thymic neoplasms (5.1%). Malignant or suspicious cells were found in 77.4% of patients with carcinoma. The cells indicating a possibility of non-Hodgkin's lymphoma were found in 9 out of 14 patients. In 5 out of 6 thymic neoplasms the cytological pattern was consistent with the diagnosis of thymic neoplasm. One case of thymoma was cytologically falsely diagnosed as malignant lymphoma. One case of neurofibroma was falsely diagnosed as adenocarcinoma. The sensitivity of cytological examinations was 67.5%. If 18 patients with diagnostically unsatisfactory material were excluded from the analysis, the sensitivity would increase to 80.8%. Owing to the wide variety of primary and metastatic tumors that can occur in the mediastinum, apart from the routine cytological techniques, additional staining methods should be used. For final cytological diagnosis the integration of cytological findings with clinical and radiological data is often required. Owing to the characteristics of the obtained material and biological behaviour of some mediastinal tumors, some tumors cannot be definitively diagnosed by cytological examinations alone.

Key words: mediastinal neoplasms-pathology; biopsy, needle

Introduction

The mediastinal space is the site of many benign and primary or metastatic malignant tumors. The introduction of transthoracic fine needle aspiration biopsy (TFNAB) has facilitated the determination of the cytopathologic nature of the mediastinal lesions.[1,2] It may provide information otherwise obtainable only by more invasive diagnostic techniques, such as mediastinoscopy, thoracoscopy or thoracotomy. It can also be performed at a relatively small discomfort to the patient; in experienced hands it provides a rapid and reliable guidance to further treatment.[3,4]

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This article reports our experience with cytological examinations of tumorous mediastinal lesions. The results and reliability of cytological examinations are evaluated. A special attention is paid to the possibility of cytological determination of mediastinal tumors and diagnostic problems. Other factors that may influence the cytological examination are also taken into account.

Materials and methods

In ten years' period (1986-1995), 204 TFNAB of the mediastinum from 182 patients were cytologically examined. In this study 117 patients with mediastinal tumors were included. Final diagnoses were established by means of histopathological examination, clinical documentation and follow-up. All TFNAB of the mediastinum were performed under radiologic guid-

ance. In some cases a cytopathologist was present to evaluate the quality of the specimen. The smears were air dried, stained by May-Grünwald-Giemsa method and fixed in Delaunay solution followed by Papanicolau staining method. If material was suitable, immunocytochemistry was performed as well. Mediastinal tumors were classified into carcinomas, lymphomas, thymic neoplasms and other tumors. The carcinoma group includes squamous cell, small cell carcinoma, adenocarcinoma, large cell carcinoma and nonspecified carcinoma. Lymphomas were divided into Hodgkin's and nonHodgkin's. Thymic neoplasms included thymomas and thymic carcinoids. Other tumors included germ-cell tumors, neurogenic tumors, benign soft tissue tumors and miscellaneous tumors. Cytological diagnoses were categorized as positive, suspicious and negative. By these terms, the presence or absence of tumorous cells was indicated regardless of their biological potential. In statistical analysis the samples with nondiagnostic material were included among negative ones.

Results

In 117 patients with proved mediastinal tumor, there were 76.5% males and 32.5% females (Table 1). Among tumors of the mediastinum, carcinomas prevailed (60.7%), followed by lymphomas (18.8%), other tumors (15.4%) and thymic neoplasms (5.1%). Among carcinomas (Table 2) the adenocarcinomas prevailed (22.5%), followed by large cell carcinomas (21.1%), small cell carcinomas (16.9%), squamous cell carcinomas (11.3%) and nonspecified carcinomas (9.9%). In 18.3% of patients carcinoma was microscopically verified by examination of the extramediastinal lesions. Among lymphomas, 63.6% were nonHodgkin's and 36.4% Hodgkin's lymphomas. Among thymic neoplasms there were 5 cases of thymoma and one case of thymic carcinoid. Among other tumors there were 6 germ-cell tumors, 4 neurogenic tumors, 5 benign soft tissue tumors and 3 miscellaneous tumors (angiosarcoma, plasmocytoma, unclassified epithelial tumor).

Table 1. TFN AB of mediastinal tumors

Tumors	Men	Women	N	Total %
Carcinomas	56	15	71	60,7
Lymphomas	11	11	22	18,8
Thymic neoplasms	3	3	6	5,1
Other tumors	9	9	18	15,4
Total	79	38	117	100

Table 2. Frequency distribution of mediastinal tumors

Carcinomas	N	%
Squamous cell carcinoma	8	11,3
Small cell carcinoma	12	16,9
Adenocarcinoma	16	22,5
Large cell carcinoma	15	21,1
Nonspecified carcinoma	7	9,9
Nonverified	13	18,3
Total	71	100
Thymic neoplasms	N	%
Thymomas	5	83,3
Thymic carcinoid	1	16,7
Total	6	100
Lymphomas	N	%
Hodgkin's	8	36,4
nonHodgkin's	14	63,6
Total	22	100
Other tumors	N	%
Germ cell tumors	6	33,3
Neurogenic tumors	4	22,2
Benign soft tissue tumors	5	27,8
Miscellaneous tumors	3	16,7
Total	18	100

The results of cytological examination were most satisfactory in carcinomas, as malignant or suspicious cells were found in 77.4% of cases. Cells indicating the possibility of nonHodgkin's lymphoma were found in 9 out of 14 patients with nonHodgkin's lymphoma. In 8 cases with Hodgkin's lymphoma suspicious cells were found in two patients. In thymic neoplams one case was cytologically falsely diagnosed as malignant lymphoma. In four patients cytological pattern was consistent with the diagnosis of thymic neoplasm (three thymomas and one thymic carcinoid). In one patient with thymic neoplasm the obtained material was not diagnostically relevant. In the group of other tumors, in nearly half of the patients the tumorous cells were correctly identified so that cytological findings were consistent with final diagnoses. An exception was the case of neurofibroma which was cytologically diagnosed as adenocarcinoma.

These data indicate that in patients with mediastinal tumors the sensitivity of cytological exami-

Table 3. Cytological examination of TFN AB of mediastinal tumors

	Positive		Suspicious		Negative	
Tumors	N	%	N	%	N	%
Carcinomas	50	70,4	5	7,0	16	22,5
Lymphomas	7	31,8	4	18,2	11	50,0
Thymic neoplasms	4	66,7	1	16,7	1	16,7
Other tumors	7	38,9	2	11,1	9	50,0
Total	68	58,1	12	10,3	37	31,6

nation was 67.5%. If 18 patients, with unsatisfactory material (Table 3), were excluded from the analysis, the sensitivity of cytological examination would rise up to 80.8%.

Discussion

TFNAB has proved to be a useful diagnostic procedure in the evaluation of patients with mediastinal lesions.2,5 By cytological examination of this type of material more than 80% of tumorous mediastinal lesions may be diagnosed.

Owing to the wide variety of primary and metastatic mediastinal tumors, interpretation of cytologic pattern requires large experience and precautions. Most metastatic carcinomas (Figure 1) and some non-malignant mediastinal tumors can be accurately diagnosed by cytological examination of only routinely stained smears. However, reliable determination of lymphomas, thymic neoplasms, neurogenic tumors and some other tumors often requires additional cytological techniques. Immunocytochemistry has mostly been used in the last years. In some cases even the electron microscopy is recommended.[6] According to our experience, some mediastinal tumors cannot be definitively diagnosed by cytology. The reasons are different.

In our patients with lymphomas, the lymphatic cells were present in only about half of the samples.

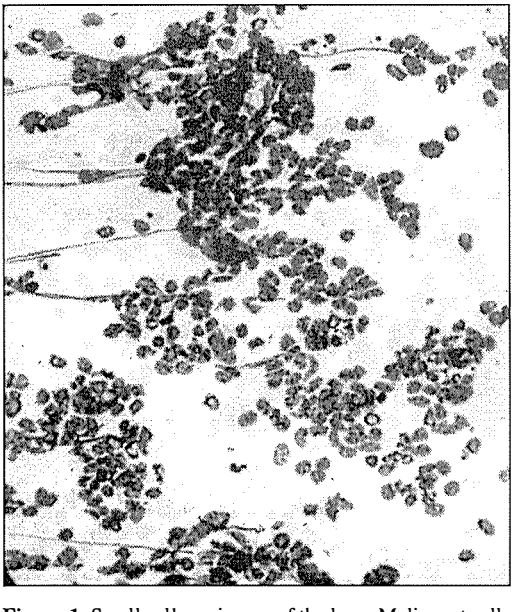

Figure 1. Small cell carcinoma of the lung. Malignant cells are in loose groupings. Mostly only stripped nuclei are visible.

Apart from that, even if lymphatic cells were present, there were frequently only few of them, or they were destroyed (Figure 2), so that the obtained material was often not suitable for performing the necessary immunocytochemistry, without which lymphoma can not be diagnosed and classified reliably.[7,8]

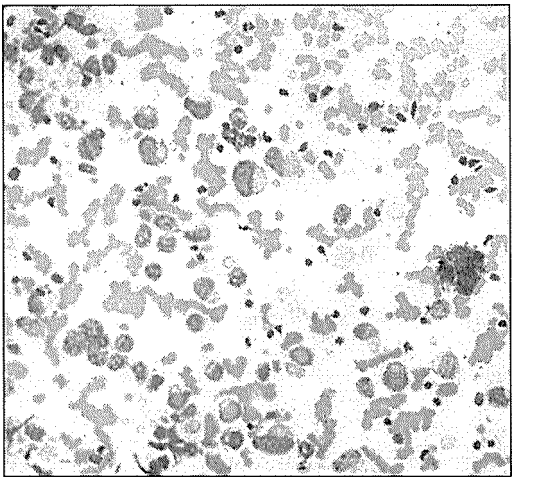

Figure 2. Malignant lymphoma of the mediastinum. Poorly preserved abnormal lymphoid cells with enlarged nuclei and small amount of cytoplasm.

In the thymic neoplasms one case of thymoma was cytologically falsely interpreted for malignant lymphoma. So, our experience is in accordance with the opinion that although thymomas have characteristic biphasic pattern,[9,10] a few other differential diagnostic possibilities should be considered as well.[11]

In the group of other tumors all three neurogenic tumors were diagnosed correctly. Namely, the cytological features of benign schwannoma (Figure 3)

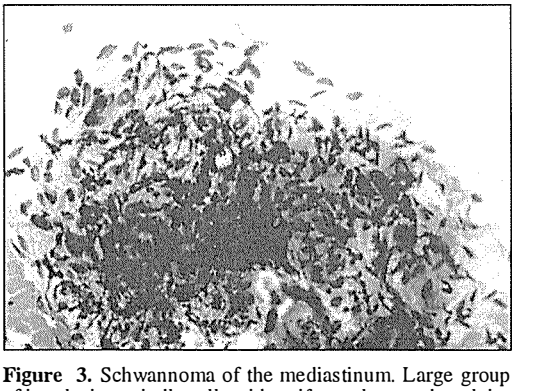

Figure 3. Schwannoma of the mediastinum. Large group of interlacing spindle cells with uniform elongated nuclei.

reproduce characteristic and distinctive pattern of interlacing spindle cells[12] thus allowing a reliable cytologic diagnosis. In one female patient the neurofibroma was cytologically falsely diagnosed as adenocarcinoma. By re-examination of the smears it was proved that several groups of interlacing spindle cells have been overlooked, while numerous atypical epithelial cells, being also in groups, were falsely identified as malignant.

It could be concluded that our results of the cytological examination of mediastinal tumors are comparable with the results of other authors.[13,14] However, it should be considered that the mediastinum is a host of numerous relatively unusual primary neoplasms as well as a frequent site of metastatic tumors. Therefore, the performance of TF-NAB of mediastinal tumors is an exciting field of diagnostic cytology. For carcinomas, where the concordance between cytopathological and histopathological examination is high,[15] cytopathological diagnoses do not need to be additionally verified prior to therapy procedure. In most other tumors, apart from the routine cytological techniques, immunocytochemistry should be used frequently. In addition to cytological examination, a cytopathologist always needs to integrate both clinical and radiological data to formulate the final diagnosis. For different reasons, some mediastinal tumors cannot be definitively diagnosed by cytological examination alone.

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Early piriform sinus cancer - results of treatment with partial vertical pharyngectomy

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Between 1986-1995, 179 patients with hypopharyngeal carcinoma were surgically treated at our department. Among them, 35 had functional partial resection. Out of these, 13 patients had vertical partial pharyngolaryngectomy carried out after ipsilateral neck dissection. The access to the primary tumors was made via lateral pharyngectomy.
Eight out of thirteen patients are disease free two years after the treatment, with well functioning larynx. Some complications occurred, but there were no cases of surgery related death.
The hypopharyngeal cancers are considered as supermalignant tumors. The achieved good functional results and survival rate prove that conservation surgery -partial laryngopharyngectomy - in selected cases of early hypopharynx carcinoma is a good altrnative to radical surgery.

Key words: hypopharyngeal neoplasms-surgery; pharyngectomy; partial pharyngolaryngectomy

Introduction

Regardless the modern therapeutic approach used, the pyriform sinus cancer remains one of the most aggressive lethal human diseases.[1] Most of these tumors have high grade of malignancy and cause few symptoms at an early stage.

In a great number of cases, clinically positive neck nodes call attention to hypopharyngeal tumors.

This region is characterized by special anatomical and functional conditions contributing to the rapid progression of cancer. The submucosal space is built up of loose connective tissue, rich in lymphatics and blood vessels. Neither caudal nor cranial direction have anatomical barrier against tumor dissemination. That is why the hypopharyngeal cancers can be regarded as a three-dimensional disease.[2] The irritation and permanently changing pressure caused by swallowing of foods and drinks are important factors in spreading of cancer cells.[3]

The decision about indication for conservation surgery for hypopharyngeal cancers should be made with responsibility; it requires great experience, good surgical technique, as well as careful examination and selection of patients, because an adequate resection of cancer is imperative.[4,5] Despite these facts, in 15-20 per cent of patients the hypopharyngeal cancer can be removed with total or partial preservation of the larynx. A one-stage reconstruction of pharyngeal defects is a very important part of surgery. In the presented paper, authors report on their surgical method for the treatment of early hypopharyngeal carcinoma, with which they preserve the larynx and swallowing function.

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Material and methods

In the last ten years, 179 patients with hypopharyngeal tumors were treated surgically in our depart-

ment under the same conditions. After careful selection of patients with respect to their age, cardiorespiratiory status, prognostic nutrition index (PNI),[6] and after examination comprising directoscopy, histology, US,CT,MRI, among the evaluated 148 pyriform sinus cancer cases 35 were considered suitable for organ preserving surgery. Table 1 shows the types of conservation surgery used.

Table 1. Distribution of 35 conservation procedures.

No	Procedure	Access to the primary tumor
16	Horizontal PLP*	Extended supraglottic resection of the larynx
6	Partial resection of posterior wall	Lateral pharyngotomy
13	Vertical PLP*	Lateral pharyngotomy

* PLP: partial pharyngolaryngectomy

In 13 patients vertical partial pharyngectomy was performed. These are subject of the present report. All of them had planocellular carcinoma: 4 patients had grade I, 6 grade II and 3 grade III of the disease.

Table 2 summarizes the distribution of these 13 patients according to the UICC TNM classification.[7] In 8 of them Tl primary tumors were localized on the upper part of the lateral wall of pyriform fossa.

Table 2. TN distribution - UICC classification.

TN	No	N1	N2b	N2c	All
T1	4	3	1	0	8
T2	1	1	2	1	5
All	5	4	3	1	13
St.I.: 4,	St.II.: 1,		St.III.: 4,	St.IV.: 4	

In five cases T2 tumors also involved a part of the oropharynx. In four cases ipsilateral radical neck dissection (RND), in 6 modified radical neck dissection (MRND) and in one patient ipsilateral radical and contralateral MRND were performed.

The indication and type of functional conservation surgery was tailored to the extent of the primary disease. The access to the tumor was made via lateral pharyngotomy. The upper cornu and a part of thyroid cartilage were removed in T2 tumors together with the hyoid bone process. (Figure 1).

The hypoglossal nerve was mobilized and elevated. Before entering the pharynx, a *videolaryngoscope* was introduced into the cancer infiltrated region, so as to enable the surgeon to judge on a TV screen the right place and distance from the tumor for appropriate access during pharyngotomy.

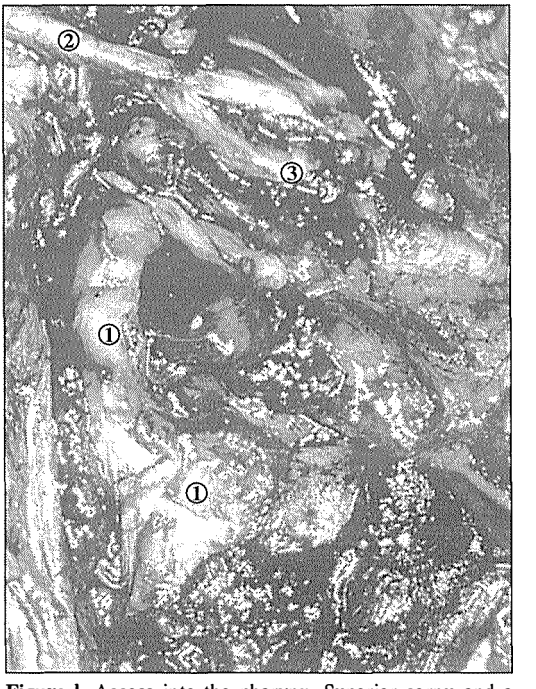

Figure 1. Access into the pharynx. Superior cornu and a piece of thyroid cartilage (1), hypoglossal nerve (2), lingual artery (3).

If the disease was not too extended - most of the early T1 cancers - the mobilized surrounding soft tissue was suitable for covering the defect. (Figures 2-3).

In cases of T2 cancers, a pectoralis maior (PM) myocutaneous flap was used for reconstruction. (Figures 4-5).

Seven patients with pathologically positive neck received postoperative radiotherapy.

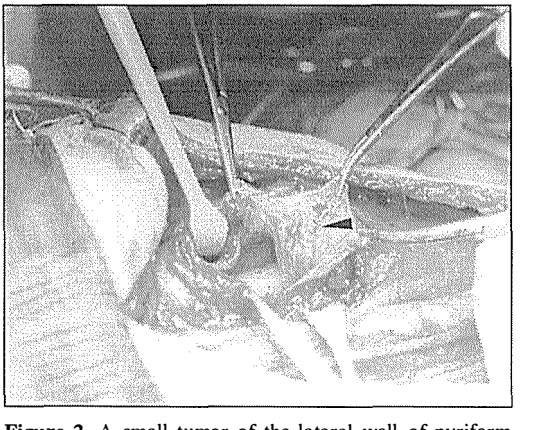

Figure 2. A small tumor of the lateral wall of pyriform sinus.

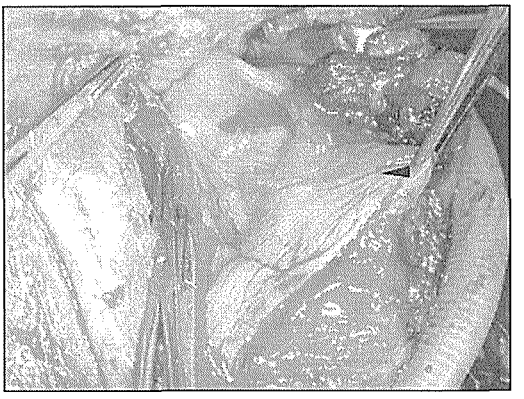

Figure 3. The mobilized pharyngeal mucosa.

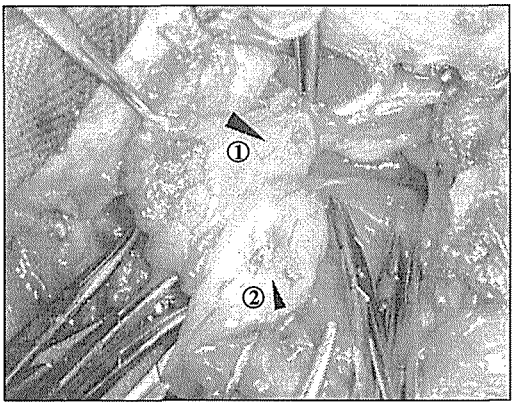

Figure 4. Double tumor: 1. on the pharyngeal wall, 2. on the lateral wall of pyriform fossa.

Results

All thirteen patients have been followed-up until death or for at least 2 years. Within the first two years, 4 patients died, 3 of them from recurrence above the clavicles, and one from an intercurrent disease. Nine patient (69.2%) were alive, 7 of them (53.8%) free of tumor. In one patient, radical surgery was carried out for local recurrence. In one case with no evidence of a primary tumor, occult neck metastases appeared, and RND was performed successfully. Eight of thirteen patients (61.5 %) survived the first two years tumor-free, with well functioning larynx, and one with total laryngectomy. There were no surgery-related deaths among operated patients, however *some complications* occurred in the postoperative period. In 3 cases, partial skin and soft tissue necrosis with pharyngocutaneous fistula developed. Fibrosis with pharyngeal stenosis caused delay in *per os* feeding in 2 cases.

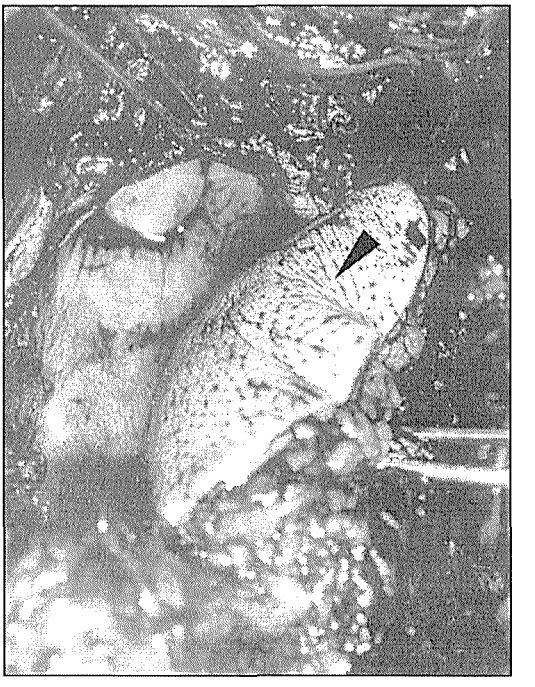

Figure 5. Reconstruction of a pharyngeal defect with a myocutaneous flap.

Bronchopneumonia in 1 patient caused postoperative difficulties. Two of our patients received preoperative radiotherapy (60 Gy) in some other institute. The surgical salvage was done after radiotherapy failure. Both of them had postoperative complications but have recovered within 4-5 weeks.

Discussion and conclusions

The hypopharyngeal tumors represent a specific entity of head and neck cancers. In this region there are no morphological barriers against the spread of disease. Because of the lack of symptoms at early stages of the disease, most cases are recognized as an advanced disease. In view of these facts, the indications for conservation surgery in cases of pyriform sinus tumors should be a very responsible decision, requiring careful examination and selection of patients, great experience and good surgical technique.

During a ten-year period, 179 patients with hypopharyngeal carcinoma were surgically treated at our department, but only 35 of them met the criteria for conservation surgery. Among them, in 13 cases vertical PLP was carried out. Eight patients sur-

vived the first two years free of disease. In one patient successful salvage surgery - total pharyngolaryngectomy - was carried out for local recurrence. 3 patients died from locoregional recurrences within the first two years.

In reviewing reliable reports - Fletcher, Jesse,[8] Harrison,[2] Kirchner,[9] Ogura et al.[4] - two year cut-off period was chosen for analyzing the results, since in hypopharyngeal cancers a two-year interval seems to be sufficient for the evaluation of treatment effect.

The prerequisites for improving the survival rates and quality of life are as follows: early diagnosis, careful examination, - TNM stating, tailored and proper surgical procedures, reliable one-stage reconstruction, planned combined treatment with postoperative irradiation. We prefer surgery as primary treatment, because it reduces the rate of complications. Patients treated for hypopharyngeal cancer need a careful and long-term follow-up. In the first and second postoperative years, frequent endoscopic examinations are necessary for recognizing any residual or recurrent tumors. Preoperative radiotherapy does not represent a contraindication to later functional surgery.

According to the results presented by Leroux-Roberts,[10] Marks et al.,[11] Ogura et al.,[4] and according to our own experience, the conservation surgery for selected hypopharyngeal tumor patients is an effective procedure which ensures voice preservation and a better quality of life.

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Radiol Oncol 1997; 31: 388-9.

Meeting Report

2nd international meeting on interventional cardiology

Jerusalem, Israel, June 30-July 3, 1997

The 2nd International Meeting on Interventional Cardiology offered several plenary papers by acknowledged international specialists. The organizing committee chaired under Rafael Beyar, Gad Keren (Israel), Martin Leon (USA), and Patrick Serruys (The Netherlands) did a tremendous work to promote long-term cooperation among its participants. At the same time it turned out to be also socially well organized.

The lectures and workshops held by the world most prominent doctors in the field of modern interventional cardiology entirely covered the full range topics and border disciplines. The International Convention Center in the heart of modern Jerusalem, where the meeting was held, give the opportunity for the 600 delegates from more than 30 different countries not only to choose among the various scientific topics of the presentations, but also to visit in the breaks the technical exhibition as well as to enjoy the calm atmosphere of the poster exhibition area. In the hall area of the center the lates products of nearly 40 outstanding companies from all over the world were to be found exhibited.

Almost all of the sessions were opened by a keynote lecture, which summoned the basic and global aspects in the topic of the panel. The following scientific session highlights were generated at this international meeting.

Percutaneous revascularization

All the various modern techniques for treatment of occluded, or stenosed coronary vessels were perfectly presented and deeply analyzed. The key points of the methods and the results compared with other small, or randomized studies were presented and served as a ground for numerous discussions. There were no only the "classic" methods (thrombolysis and percutaneous transluminal coronary angioplasty) demonstrated by the speakers but also data for trails with stenting and rotational atherectomy compared to success and patency rate. Initial results and the late follow up of the great variety of stents, in connection with technical details and complication occurrence were proposed to the attention of the audience.

The latest achievements with laser angioplasty were also the topic of the plenary session. Although it was suggested, after long experimental studies in the end of the 1980ies, that excimer laser light could precisely ablates biologic tissue without thermo injury, the current laser angioplasty, to the opinion of the speakers, was still not proposed as a routine procedure mainly because of not being one of the cheapest technologies.

A special interest was stressed on the revascularization in patients with acute myocardial infarct and emergency room intervention. Most of the studies connected to this topic concerned the problems of the significantly higher mortality of the patients. Difficulties and results of the interventional treatment of this part of the cases were compared to a similar group treated by the emergency bypass graft surgery. The questions emerging grom this comparison were opened for a discussion and it was obvious that numerous side factors were playing an important role. The Israel experience, where 80 % of the hospitals have cat labs (in USA 70 % of the hospitals do not have!) showed that time and available base were often the main factors responsible for the decisionmaking.

A local drug delivery alone, or as a part of the complex interventional treatment was presented as showing the best results for the reperfusion within the first 30 minutes. The jet spray local infusion pharmacomechanically destroying the thrombus was eliminated from the modern coronary thrombolysis, because of its intimal destructing effect and was replaced by a large scale of balloon combined infusion systems. Although many still in research phase, promising initial results and success rates were presented.

Imaging

Use and future of the intravascular ultrasound imaging! Criteria for optimal implantation, use in clinical decision-making, current skepticism! These were the main topics discussed widely during and after the sessions. The clinical importance, results and costs of intravascular US were compared with the other available diagnostic methods in order to determinate the exact indication area and the importance of this imaging method. Edging the contraversions brilliant presentations were made from different big cardiologic centers.

Research

Coronary physiology, molecular and vascular biology, histopathology were presented as being essential points in defining the choice of treatment and post-treatment management. Restenosis, its origin and the appropriate therapy as well as the adjunctive pharmacological therapy were the main topics in connection with the nowadays research work on interventional cardiology.

Working in the field of radiological intervention in the peripheral vessels and taking part in such an outstanding meeting was not only of great scientific value for me, but it also gave rise to some interesting thoughts. Participating in discussions and talks about the latest achievements not only in the narrow field of ones scientific work, but in some border discipline supplies an enormous amount of new and useful information and widens the know-how for the everyday routine work.

Dr. Janaki Hadijev
Medical University, Pécs, Hungary

Radiol Oncol 1997; 31: 390-3.

Prirojena vboklina lobanje. Prikaz primera

Giannakopoulou Ch, Hassan E, Hatzidaki E, Koumantakis E

Prirojene vbokline lobanje so redke. Običajno nastanejo zaradi mehanskih vzrokov ali dlje trajajočega pritiska na glavo pred ali med porodom. Opisan je primer 3200 g težke novorojenke, pri kateri je bil zaradi nevarnosti porodne stiske v 38. tednu gestacijske starosti narejen carski rez. Po porodu so s kliničnim pregledom ugotovili 5 cm veliko in 2 cm globoko uboklino, ki je ležala na zgornjem zadnjem delu temenice. Nevrološki pregled ni pokazal drugih simptomov, pravtako na CT slikah ni bilo videti zloma kosti. Ker niso odkrili nevroloških znakov bolezni, so novorojenko konzervativno zdravili. Pri 6 mesecih je bil otrok na pregledu normalno razvit, vboklina pa se je spontano zmanjšala.

Radiol Oncol 1997; 31: 345-7.

^{201}Tl SPECT za detekcijo viabilnega hiberniranega miokarda pri kronični zapori koronarnih arterij

Garcheva M, Piperkova E, Djorgova J, Petrov I

S perfuzijsko scintigrafijo miokarda s ^{201}Tl na SPECT in angiografijo smo preiskali dvanajst bolnikov s 17 kroničnimi okluzijami koronarnih arterij, nastalih 1-14 mesecev pred preiskavo. Zaradi ugotavljanja sprememb perfuzije in krčljivosti miokarda po zdravljenju, smo preiskave opravili pred revaskularizacijo (PTCA, CABG) in 2 meseca po njej. Ugotovljene spremembe so nam služile kot referenca za pozitivno ali negativno napovedno vrednost preiskave s SPECT pri ugotavljanju viabilnega hiberniranega miokarda. 52 (67 %) segmentov z znižanim kopičenjem talija je bilo v infarciranem predelu, viabilnih pa je bilo 44 (56 %). Angiografsko smo ocenili krčljivost 55 segmentov. Med segmenti z blago motnjo krčljivosti (19/55) je bilo 95 % (18/19) segmentov viabilnih, med segmenti s hudo motnjo krčljivosti (36/55) pa 39 % (14/55). Izraženost defektov na scintigramih se je dobro ujemala s stopnjo motnje krčljivosti. Pozitivna napovedna vrednost preiskave s SPECT je bila 87 % in negativna 84 %. Trajanje okluzije ni imelo vpliva na rezultate preiskav. Angiografsko dokazan kolateralni krvni obtok je bil povezan z višjim odstotkom viabilnih segmentov. Izboljšanje krčljivosti po PTCA smo ugotovili v 34 segmentih (16 oz. 84% iz skupine z blago motnjo krčljivosti in 16 oz. 45 % iz skupine s hudo motnjo krčljivosti). Izboljšanje funkcije je bilo izmerjeno pri 8 bolnikih. Porast iztisnega deleža levega prekata je bil 5,6 ± 4,6 %. Porast je bil znatnejši pri bolnikih z disfunkcijo levega prekata kot pri ostalih bolnikih (7,6 ± 4,8 % oz. 1,7 ± 1,08 $p < 0,01$).

Radiol Oncol 1997; 31: 348-52.

Radiosinoviektomija z itrijem 90 pri bolnikih z različnimi revmatskimi boleznimi: ugotavljanje trajanja terapevtskega učinka

Kos-Golja M, Budihna NV, Batagelj I

Cilj retrospektivne študije je bil oceniti učinek izotopske sinovektomije z itrijem 90 predvsem pri bolnikih z revmatoidnim artritisom in manj z nekaterimi drugimi revmatičnimi boleznimi. Bolnike smo opazovali v obdobju od pol do devet let. Poseg je bil napravljen pri 273 bolnikih (225 žensk, 48 moških) oziroma na 463 sklepih (402 na kolenih, 61 na ramenih in gležnjih). Učinek smo ocenjevali s spremembo stopnje jutranje

okorelosti, bolečine in otekline sklepa (od 0 do 9). Zelo dobre rezultate smo dosegli na 69 (15 %), dobre na 142 (30,5 %), srednje dobre na 197 sklepih (42,5 %), na 55 sklepih ni bilo učinka (12 %). Pol leta po posegu je bilo 38 sklepov (8 %) v remisiji, pol do dve leti 221 (48 %), po 3 do 4 letih 95 (20 %), po 5 do 6 letih je bilo 57 sklepov brez znakov vnetja (12 %), po 7 do 9 letih pa še 52 (11 %). Najpogostejši zapleti po sinovektomiji so bile bolečine in otekline sklepov (5,6 %). Pri dveh bolnicah, ki sta dobivali tudi imunomodulirajoča zdravila, smo odkrili kronično mieloično oziroma limfatično levkemijo. Izotopska sinovektomija je torej učinkovito in varno zdravljenje sinovitisa pri različnih revmatičnih boleznih.

Radiol Oncol 1997; 31: 353–7.

Vpliv izvora sevanja na kakovost transmisijskega scintigrama skeletnega fantoma

Será T, Mester J, Skretting A, Csernay L

Avtorji so za transmisijsko scintigrafijo na fantomu skeleta (Scanflex Transbone) uporabili gama kamero, ki je imela okrogli detektor s 37 fotopomnoževalkami, ali pa kamero SPECT s pravokotnimi detektorji. Pri tem so uporabljajli tri različne ploščate izvore sevanja: tehnecijev ploščinski izvor za večkratno polnjenje, ^{57}Co ploščinski izvor in pomični linijski izvor družbe Veenstra instruments B.V.. Proučevali so razlike v kakovosti nastalih scintigramov. Ti so bili posneti na rentgenski film v skladu z običajnim kliničnim protokolom (600 000–800 000 pulzov na sliko) in z velikim številom pulzov (2 milijona). Scintigrame so interpretirali trije neodvisni, izkušeni opazovalci. Iz doseženih rezultatov so ustvarili ROC (receiver operating charasteristic) krivuljo. Kakovost slik je bila sorazmerna površini pod ROC krivuljo. Med slikami posnetimi z istimi parametri ni bilo pomembnih razlik v površini pod ROC. Pomembno pa so se razlikovali rutinski scintigrami od tistih posnetih z velikim številom pulzov. Avtorji v sklepu navajajo, da so vsi navedeni ploščinski izvori primerni za snemanje transmisijskega skeletnega fantoma, ki služi kontroli kvalitete nuklearno medicinskih postopkov.

Radiol Oncol 1997; 31: 358-63.

Vinblastin poveča protitumorsko učinkovitost bleomicina

Čemažar M, Auersperg M, Serša G

V naši predhodni študiji smo ugotovili, da vinblastin poveča fluidnost plazemske membrane. S tem lahko povečamo vnos bleomcina, ki slabo prehaja preko plazemske membrane, a je zelo citotoksičen, če je prisoten v celici. Namen naše raziskave je bil na mišjih intraperitonealnih SA-1 tumorjih določiti, ali injiciranje vinblastina pred bleomicinom poveča učinkovitost bleomicina. Mišim smo injicirali samo vinblastin, samo bleomicin, vinblastin in bleomicin skupaj v različnih kombinacijah: vinblastin in bleomicin injicirana sočasno, bleomicin injiciran 24 h pred vinblastinom in vinblastin injiciran 24 h pred bleomicinom. Učinkovitost terapije smo ugotavljali s preživetjem živali. Zdravljenje z vinblastinom in bleomicinom je statistično značilno podaljšalo preživetje živali glede na kontrolno skupino. Vse tri kombinacije vinblastina in bleomicina so bile bolj učinkovite kot zdravljenje samo z enim kemoterapevtikom. Učinek terapije je bil enak, če smo sočasno injicirali vinblastin in bleomicin, ali če smo injicirali bleomicin 24 h pred vinblastinom. Najdaljše preživetje živali pa smo dobili, če smo injicirali vinblastin 24 h pred bleomicinom. Glede na naše rezultate lahko predpostavljamo, da sta za dobljeni učinek terapije odgovorna dva mehanizma delovanja vinblastina: povečanje fluidnosti membrane in verjetno celično kinetični efekt.

Radiol Oncol 1997; 31: 364-67.

Zahteve za klinični aparat za elektrokemoterapijo (elektroporator)

Puc M, Reberšek S in Miklavčič D

Članek opisuje zahteve za klinični aparat za elektrokemoterapijo. Zahteve so razdeljene glede na opremo, ki jo potrebujemo v elektrokemoterapiji. Opremo razdelimo na elektroporator in elektrode. Elektroporator je naprava, ki mora ustrezati električnim in varnostnim zahtevam. Pod električnimi zahtevami razumemo električne izhodne karakteristike, ki zagotavljajo učinkovitost terapije. Le-te morajo torej biti dosledno izpolnjene. Poleg tega mora biti naprava varna, ustrezati mora IEC standardom. Te zahteve ščitijo tako pacienta kot tudi operaterja naprave pred možnimi električnimi udari. Drug pomemben del opreme, ki jo potrebujemo za učinkovito elektrokemoterapijo, so elektrode. V času od pričetka uporabe elektrokemoterapije so raziskovalci razvili več tipov elektrod, ki jih v osnovi lahko razdelimo na elektrode za površinsko in za notranjo elektrokemoterapijo. Poleg pregleda parametrov je podan tudi pregled elektroporatorjev, ki jih danes uporabljamo v kliniki. Ne glede na to pa je potrebno poudariti, da pravih kliničnih elektroporatorjev zaenkrat še ni na tržišču.

Radiol Oncol 1997; 31: 368–73.

Vpliv spola na indukcijo debeločrevesnega karcinoma z 1,2-dimetilhidazinom (DMH) pri podganah Wistar

Breskvar L, Cerar A

Pri ljudeh je karcinom debelega črevesa pogostejši pri moških. Namen naše raziskave je oceniti vpliv spola na indukcijo debeločrevesnega karcinoma z 1,2-dimetilhidazinom (DMH) pri podganah Wistar.

Uporabili smo 60 podgan seva Wistar (30 samcev, 30 samic), ki smo jim 1-krat tedensko podkožno vbrizgali 20 mg DMH/kg telesne teže. Injicirali smo 15-krat. Po 25-ih tednih od začetka poskusa smo živali žrtvovali in jih obducirali. Vse makroskopske lezije smo histološko ovrednotili.

Indukcija debeločrevesnih tumorjev je uspela pri 37 % samcev in pri 17 % samic. Našli smo 21 tumorjev debelega črevesa in danke: 15 tumorjev pri samcih in 6 pri samicah. Histološko smo pri samcih našli 11 adenokarcinomov, 2 pečatnocelična karcinoma in 2 adenoma, pri samicah pa 4 pečatnocelične karcinome in 2 adenoma. Našli smo tudi tumorje izven debelega črevesa, predvsem tumorje tankega črevesa in Zymbalovih žlez.

Podgane seva Wistar so v primerjavi z nekaterimi drugimi sevi podgan kazale manjšo pojavnost kolorektalnih tumorjev po indukciji z DMH. Razlika med spoloma v pojavnosti tumorjev v debelem črevesu in danki se je pokazala kot statistično mejna ($p < 0,08$), statistično značilno razliko med spoloma pa smo ugotovili v pojavnosti vseh induciranih tumorjev ($p < 0,02$).

Samci so kazali večjo incidenco kolorektalnih tumorjev, ki so bili tudi histološko bolj podobni tumorjem pri človeku. Zato priporočamo za raziskovalno delo na kolorektalnih tumorjih Wistar samca.

Radiol Oncol 1997; 31: 374–79.

Citologija mediastinalnih tumorjev

Mermolja M, Kern I, Terčelj M, Jereb M

Avtorji predstavijo izkušnje Kliničnega oddelka za pljučne bolezni in alergična stanja Golnik s citološkimi pregledi mediastinalnih tumorjev. V retrospektivno študijo je bilo vključenih 117 bolnikov z mediastinalnim tumorjem. Najpogostejši so bili karcinomi (60,7%), sledijo limfomi (18,8%), drugi tumorji (15,4%) in timične neoplazme (5,1%).

Maligne ali sumljive celice so našli pri 77,4 % bolnikov s karcinomom. Celice, ki so dopuščale možnost ne-Hodgkinovega limfoma, so našli pri 9 od 14 bolnikov. Pri 5 od 6 primerov timičnih neoplazem je bila citološka slika skladna z diagnozo timične neoplazme. En primer timoma je bil citološko napačno opredeljen kot maligni limfom, en primer neurofibroma pa je bil napačno opredeljen kot adenokarcinom.

Senzitivnost citoloških pregledov je bila 67,5 %. Če bi 18 bolnikov, pri katerih dobljeni material ni bil ustrezen, izključili iz analize, bi senzitivnost zrasla na 80,8 %.

Ker so primarni in metastatski tumorji, ki se pojavljajo v mediastinumu zelo raznoliki, so za njihovo opredelitev poleg rutinskih citoloških tehnik potrebne tudi dodatne metode barvanja. Za končno citološko diagnozo je nujno poznati tudi klinične podatke in podatke slikovnih diagnostičnih metod. Glede na značilnosti dobljenega materiala in biološko obnašanje nekaterih mediastinalnih tumorjev vseh ni možno definitivno opredeliti na osnovi citološkega pregleda.

Radiol Oncol 1997; 31: 380-3.

Operacija zgodnjega raka piriformnega sinusa z vertikalno delno odstranitvijo žrela

Elő J, Balatoni Z, Tar T

V letih 1986 do 1995 so na kirurškem oddelku bolnice Uzsoki v Budimpešti operirali 179 bolnikov z rakom hipofarinksa. 35 bolnikom je bila narejena funkcionalna delna resekcija ter 13 od teh vertikalna delna odstranitev žrela in grla. Pristop do primarnega tumorja je potekal z lateralno faringektomijo. Dve leti po operaciji je 8 bolnikov od 13 brez znakov bolezni in z dobro funkcijo grla. Opazili so nekaj zapletov, peri- in postoperativnih smrti ni bilo.

Rak hipofarinksa uvrščamo med prognostične neugodne bolezeni. Kljub temu je v izbranih zgodnjih primerih bolezni indicirana ohranitvena operacija - delna odstranitev grla in žrela. S takšna operacija lahko ob primerni izbiri bolnikov ohranimo funkcijo organa in dosežemo sorazmerno veliko ozdravitev brez znakov bolezni.

Radiol oncol 1997; 31: 384-7.

Notices

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

Radiotherapy

February, 1998.

The ESTRO teaching course "Principles and Practice of Radiotherapy" will be offered in Rotterdam, The Netherland.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9340; or fax +32 16 7795 5494. E-mail: info@estro.be

Radiotherapy

February 8-12, 1998.

The ESTRO teaching course "Imaging for Target Volume Determination in Radiotherapy" will be offered in Bordeaux, France.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9340; or fax +32 16 7795 5494. E-mail: info@estro.be

Radiotherapy

March, 1998.

The ESTRO teaching course "Dose Calculations for high Energy Photon Beams" will be held in Greece.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9340; or fax +32 16 7795 5494.

Oncology

March 19-21, 1998.

The ESO advanced course "Improving the Quality of Life for Children with Cancer" will be held in Milan, Italy.

Contact European School of Oncology, Via Ripamonti 66, 20141 Milan, Italy; or call +39 2 57 305 416; or fax +39 2 57 307 143.

Gynecological cancer

March 22-27, 1998.

The ESO training course on gynecological cancer will be offered in Ankara, Turkey.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 loannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Gynecological oncology

March 24-25, 1998.

The ESO training course will be held in Cali, Colombia.

Contact ESO Latin America, Dr.G.Farante, Via Ripamonti 66, 20141 Milan, Italy; or call +39 2 57 305 416; or fax +39 2 57 307 143.

Urological cancer

March 26-27, 1998.

The ESO training course on urological cancer will take place in Nicosia, Cyprus.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 loannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695

Oncology

March 26-28, 1998.

The "1st Latin America ESO Conference on Cancer Management" will be held in Buenos Aires, Argentina.

Contact ESO Latin America, Dr.A.Rancati, Arenales 1826 (1o), 1124 Buenos Aires, Argentina; or call +54 1 814 2343; or fax +54 1 814 2343.

Breast cancer

March 29-30, 1998.

The ESO training course will take place in Porto Alegre, Brazil.

Contact ESO Latin America, Dr.A.Frasson, Ave. Ipiranga 6690, Porto Alegre, Brazil; or call +55 51 3392 709; or fax +55 51 3392 709.

Hodgkin's disease

March 28 - April 1, 1998.

The "4th International Symposium on Hodgkin's Lymphoma" will be offered in Koeln, Germany.

Contact Conference Secretariat IMEDEX, Bruistensingel 360, P.O.Box 3283, 5203 DG žs-Hertogenbosch, The Net-

As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please sent information to the Editorial office, Radiology and Oncology, Vrazov trg 4, SI-1105 Ljubljana, Slovenia.

herland; or call +3 7 3 642 9285; or fax +31 73 641 4766; e-mail: imedex@pi.net; internet: http://www.imedex.nl

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Lung cancer and head and neck cancer

April, 1998.

The ESO training course on Lung cancer including head and neck cancer will be offered in Hofburg Conference Center, Vienna, Austria.

Contact European School of Oncology, Office for Central and Eastern Europe, c/o Arztekammer fuer Wien, Mrs. Dagmar Just, Fortbildungsreferat, Weihburggasse 10-12, 1010 Vienna, Austria; or call +43 1 51 501 293; or fax +43 1 51 501 480.

Radiotherapy

April, 1998.

The ESTRO teaching course "Modern Brachytherapy Techniques" will take place in Berlin Germany.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9340; or fax +32 16 7795 5494.

Breast cancer

April, 1998.

The ESO multidisciplinary educational course on breast cancer will take place in Beirut, Lebanon.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Oncology

April, 1998.

The teaching course "Methodology of Clinical Research" will be organized by ESTRO.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9340; or fax +32 16 7795 5494.

Bone tumours

April or September, 1998.

The ESO training course on Surgical treatment of malignant bone tumours will take place in Hofburg Conference Center, Vienna, Austria.

Contact European School of Oncology, Office for Central and Eastern Europe, c/o Arztekammer fuer Wien, Mrs. Dagmar Just, Fortbildungsreferat, Weihburggasse 10-12, 1010 Vienna, Austria; or call +43 1 51 501 293; or fax +43 1 51 501 480.

Molecular Biology

April 5-8, 1998.

The ESO advanced course "Molecular Biology for Clinicians" will be offered in Cambridge, United Kingdom.

Contact European School of Oncology, Via Ripamonti 66, 20141 Milan, Italy; or call +39 2 57 305 416; or fax +39 2 57 307 143.

Chemotherapy

April 18-19, 1998.

The "4th International symposium on high-dose in Chemotherapy and stem cell transplantation in solid tumors will take place in Berlin, Germany.

Contact Prof. Dr. Wolfgang Siegert, Virchow Klinikum, Abt. Haematologie und Onkologie, Augustenburger Platz 1, 13353 Berlin, Germany.

Radiotherapy

May 13-17, 1998.

The "5th International meeting on Progress in Radio-Oncology ICRO/OGRO 6" will take place in Salzburg, Austria.

Contact Prof. Kogelnik, Institute of Radiotherapy, Muellner Hauptstr. 48, A-5020 Salzburg, Austria.

Surgical oncology

May 14-16, 1998.

The ESO advanced course "Breast Reconstructive and Cancer Surgery I" will be held in Duesseldorf, Germany.

Contact European School of Oncology, Via Ripamonti 66, 20141 Milan, Italy; or call +39 2 57 305 416; or fax +39 2 57 307 143.

Lung cancer

May 14-20, 1998.

The ESO training course "Lung Pathology -Oncology" will be offered in Ioannina, Greece.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Oncology

May 16-19, 1998.

The "ASCO Spring Meeting" will be offered in Los Angeles, CA, USA.

Contact ASCO Headquarters, 435 North Michigan Av., Suite 1717, Chicago, USA; or call +1 312 644 0828; or fax +1 312 644 8557.

Bladder cancer

May 22, 1998.

The ESO refresher day on bladder cancer will take place in University of Vienna, Vienna, Austria.

Contact European School of Oncology, Office for Central and Eastern Europe, c/o Arztekammer fuer Wien, Mrs. Dagmar Just, Fortbildungsreferat, Weihburggasse 10-12, 1010 Vienna, Austria; or call +43 1 51 501 293; or fax +43 1 51 501 480.

Oncology

May 28-30, 1998.

The 3rd ESO education convention will take place in Milan, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

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Clinical trials

June, 1998.

The EORTC course "Clinical Trials Statistics for non Statisticians" will be offered in Brussels, Belgium.

Contact EORTC Education office, Av. E. Mounier 83/11, 1200 Brussels, Belgium; or call +32 2 772 4621; or fax +32 2 772 6233. Internet: http/www.eortc.be

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Hepatology

June, 1998.

The "Postgraduate Course in Hepatology and Postgraduate Course in Hepatobiliary Surgery" organized by Clinical Centre Ljubljana, University of Ljubljana, Faculty of Medicine, Open society Institute and Hepato Pancreato Biliary Asociation Slovenia will be held in Ljubljana, Slovenia.

Contact Organizing Secretariat PRP d.o.o., Ljubljana, Miklošičeva 16, SI-1000 Ljubljana, Slovenia; or call +386 61 13032300; or fax +386 61 1303 23020; e-mail hbs@ prp.si

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Radiotherapy

June, 1998.

The ESTRO teaching course "Conformal Radiotherapy" will be offered in Rotterdam, the Netherland.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heeren@estro.be

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Oncology

June, 1998.

The ESO training course "From the Molecular to the Bedside Oncology" will be offered in Thessaloniki, Greece.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Radiotherapy

June, 1998.

The ESTRO teaching course "Molecular Oncology for Radiotherapy" will take place in Dublin, Ireland.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heeren@estro.be

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Computer tomography

June 4-6, 1998.

The postgraduate course "Spiral CT of the Thorax" will be offered in Lille, France.

Contact the Secretarial office, Department of Radiology, Pr Remy, Hospital Calmette, Boulevard Jules Leclerc, 59037 Lille Cedex, France; fax +33 3 2044 4720; e-mail mremy-jardin@chru-lille.fr

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Breast cancer

June 11-12, 1998.

The ESO advanced course "Breast Cancer" will take place in Milan, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

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Bronchology and Bronchoesophagology

June 14-17, 1998.

The "10th World Congress for Bronchology" and the "10th World Congress for Bronchoesophagology" will be offered in Budapest, Hungary.

Contact Conference Secretariat, Edit Vadkerty, Director, Coopcongress, Budapest, 1371 Bp. 5., P.O.Box 434, Hungary; or call +36 1 133 1086 / 134 2584; or fax +36 1 133 7969 / 114 0038.

Pneumology

June 18-21, 1998.

The "9th Czech and Slovak Pneumo-Phthisiologic Congress" with international participation will be held in Plzen, Czech Republic.

Contact Assoc. Prof. Dr. M. Pešek, Ph.D., Chest Dept., University Hospital, E. Beneše 13, 305 99 Plzen, Czech Republic.

Breast cancer

June 29-30, 1998.

The ESO training course will be held in Aruba.

Contact ESO Latin America, Dr. G.Farante, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtumŽbbs.infosquare.it

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Urology

August 12-13, 1998.

The ESO training course "Genito-urinary tract tumours" will take place in Sao Paulo, Brazil.

Contact ESO Latin America, Dr.A.Frasson, Ave. Ipiranga 6690, Porto Alegre, Brazil; or call +55 51 3392 709; or fax +55 51 3392 709.

Breast cancer

August 14, 1998.

The ESO training course "Breast Cancer, Diagnosis and Treatment" will be offered in Rio de Janeiro, Brazil.

Contact ESO Latin America, Dr.A.Frasson, Ave. Ipiranga 6690, Porto Alegre, Brazil; or call +55 51 3392 709; or fax +55 51 3392 709.

Radiotherapy

August 14, 1998.

The ESO training course on curiterapie will be offered as course pre-congress of the UICC in Rio de Janeiro, Brazil.

Contact ESO Latin America, Dr.A.Frasson, Ave. Ipiranga 6690, Porto Alegre, Brazil; or call +55 51 3392 709; or fax +55 51 3392 709.

Oncology

August 24-28, 1998.

The "17th UICC International Cancer Congress" will be held in Rio de Janeiro, Brazil.

Contact c/o Congrex do Brasil, Rua do Ouvidor, 60 grupo 413, 20010-030 Rio de Janeiro, RJ Brazil; or call +55 21 224 6080; or fax +55 21 231 1492.

Oncology

September, 1998.

The EORTC course "One Day Introduction to EORTC Trials" will be held in Brussels, Belgium.

Contact EORTC Education office, Av. E. Mounier 83/11, 1200 Brussels, Belgium; or call +32 2 772 4621; or fax +32 2 772 6233. Internet: http/www.eortc.be

Radiation Physics

September, 1998.

The ESTRO teaching course "Radiation Physics for Clinical Radiotherapy" will be offered in Leuven, Belgium.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heeren@estro.be

Haematology

September, 1998.

The ESO training course "Biology and Treatment of Plasma Cell Dyscrasias" will be offered in Athens, Greece.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Palliative care

September 8-9, 1998.

The ESO training course will be held in Costa Rica.

Contact ESO Latin America, Dr.G.Farante, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

Prostate cancer

September 10-12, 1998.

The ESO advanced course "Prostate Cancer" will be offered in Milan, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

Breast cancer

September 11-12, 1998.

The ESO training course will be held in Montevideo, Uruguay.

Contact ESO Latin America, Dr.G.Farante, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

Oncology

September 12-13, 1998.

The ESO training course "Sarcomas and Malignant Melanoma" will take place in Athens, Greece.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Breast cancer

September 14-15, 1998.

The ESO training course will be held in Santiago, Chile.

Contact ESO Latin America, Dr.G.Farante, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

Computer tomography

September 16-19, 1998.

The postgraduate course "Spiral CT of the Thorax" will be offered in Lille, France.

Contact the Secretarial office, Department of Radiology, Pr Remy, Hospital Calmette, Boulevard Jules Leclerc, 59037 Lille Cedex, France; fax +33 3 2044 4720; e-mail: mremy-jardin@chru-lille.fr

Radiotherapy and Oncology

September 19-24, 1998.

The "17th Annual ESTRO Meeting" will be offered in Edinburg, UK.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heeren@estro.be

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Radiotherapy

September 19-24, 1998.

The "4th Postgraduate Teaching Course", organised by ERTED (European Radiotherapy Technologist Education Development Group) will be held in Edinburg, UK, at the time of the 17th Annual ESTRO Meeting.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heeren@estro.be

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Medical oncology

September 24-26, 1998.

The ESO advanced course on medical oncology will be offered in Milan, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

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Radiotherapy and Oncology

September 25-28, 1998.

The "19th Annual ESTRO Meeting" will be held in Praha, Czech Republic.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heeren@estro.be

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Haematology

September 28-30, 1998.

The "3rd Educational Forum on Leukemia and Haematological Malignancies" will be held in Bergamo, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

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Radiotherapy

October, 1998.

The ESTRO teaching course "Evidence Based Radiation Oncology: Principles and Methods" will take place in Izmir, Turkey.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heeren@estro.be

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Radiobiology

October, 1998.

The ESTRO teaching course "Basic Clinical Radiobiology" will be held in Como, Italy.

Contact the ESTRO office, Av. E. Mounierlaan, 83/4, B-1200 Brussles, Belgium; or call +32 2 775 9344; or fax +32 2 779 5470. E-mail:germaine.heerenŽestro.be

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Surgical oncology

October 1-3, 1998.

The ESO advanced course "Breast Reconstructive and Cancer Surgery II" will take place in Milan, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

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Oncology

October 7-9, 1998.

The ESO training course "Innovation in Cancer Management" will be offered in Cairo, Egypt.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Oncology

October 8-9, 1998.

The ESO training course "Rare Tumours: Diagnosis and Treatment" will be held in Sofia, Bulgaria.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Oncology

October 15-21, 1998.

The ESO training course "Liver Pathology-Oncology" will be offered in Ioannina, Greece.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Radiation Oncology

October 19-22, 1998.

The "Annual Meeting of American Society for Therapeutic Radiology and Oncology ASTRO" will take place in Phoenix, Arizona, USA,

Contact Vicky Carroll, ASTRO office, 1891 Preston White Drive, Reston, VA 22091, USA; or call +1 703 716 7588; or fax +1 703 476 8167.

Colorectal cancer

October 22-24, 1998.

The ESO advanced course "Digestive Tract: Colorectal Cancer" will be held in Milan, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

Hematology and oncology

October 25-28, 1998.

The Annual Meeting of German and Austrian Association of Hematology and Oncology will be offered in Frankfurt, Germany.

Contact Prof.Dr. Dieter Hoelzer, Universitaetklinik Frankfurt, Medizinische Klinik III, Theodor Stern Kai 7, 60590 Frankfurt, Germany; or call +49 39 6301 5194; or fax +49 69 6301 7324; e-mail: hoelzer@em.uni-frankfurt.de

Pediatric Oncology

October 27-31, 1998.

The S.I.O.P. teaching course will take place in Moscow, Russia.

Call P.A. Voute +31 20 5665655 or fax +31 20 691 2231.

Clinical trials

November, 1998.

The EORTC course "Cancer Clinical Trials methods and practice" will be offered in Brussels, Belgium.

Contact EORTC Education office, Av. E. Mounier 83/11, 1200 Brussels, Belgium; or call +32 2 772 4621; or fax +32 2 772 6233. Internet: http/www.eortc.be

Breast cancer

November, 1998.

The ESO training course on breast cancer will take place in Thessaloniki, Greece.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Melanoma

November 12-14, 1998.

The ESO advanced course on Melanoma will take place in Milan, Italy.

Contact European School of Oncology, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 2 5831 7850; or fax +39 2 5832 1266. E-mail: comprevtum@bbs.infosquare.it

Breast Cancer

November 12-14, 1998.

The ESO advanced course on Breast cancer management will be offered in Hong Kong.

Contact Dr. Y. Lau, The Breast Centre, Department of Surgery, Kwong Wah Hospital, Waterloo Road, Kowloon, Hong Kong; or call +852 278 150 27 or 233 133 11; or fax +852 278 152 40.

Colorectal cancer

November 19-20, 1998.

The ESO training course on colorectal cancer will take place in Tirana, Albania.

Contact ESO Balkans and Middle East Office, Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

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Author Index 1997

Amichetti M: **2/109-11**
An DJ: 1/33-8
Andrejčič K: 2/238
Antonello M: 2/109-11
Anžič J: 2/134-6
Arcicasa M: 2/109-11
Ardizzoia A: 2/202-4
Auersperg M: 4/364-7

Bacci G: **2/125-6**
Baiocchi C: 2/215-7
Balatoni Zs: **2/186**, 2/187; 4/384-7
Balli M: 2/109-11
Barbara R: 2/168-70
Batagelj I: 4/353-7
Bebler B: 2/131-3, 2/134-6
Becner D: 2/195-8
Belehradek J, Jr: 1/33-8
Berti F: 2/215-7
Bérzinš A: 2/103-6
Birkenhake S: **2/149-50**
Bléry M: **3/322**
Bohuslavizki KH: **1/5-12**, 1/18-20, **1/21-6**; 3/279-85, 3/309-14
Borštnar S: 2/151-4; **3/298-304**
Bračko M: 2/134-6
Brenner W: 1/5-12, **1/18-20**, 1/21-6; 3/279-85, 3/309-14
Breskvar L: **4/374-9**
Brovet-Zupančič I: 2/238
Bruce R: 3/315-8
Buchert R: 1/21-6
Budach V: 2/219-26
Budihna M: 1/39-47; 2/95, 2/173-7
Budihna NV: **1/13-7**; 4/353-7
Burger J: 1/54-5

Caffo O: 2/109-11
Calzavara F: 2/215-7
Cerar A: 4/374-9
Cesaro MG: 2/215-7
Chiarion Sileni V: 2/168-70
Clausen M: 1/5-12, 1/21-6; 3/279-85
Coghetto F: 2/109-11
Colombo A: 2/202-4
Crispino S: **2/202-4**
Csernay L: 4/358-63
Cundrič F: 2/195-8
Czigner J: **2/192-4**, 2/199-201

Čemažar M: 1/33-8, **1/56-9; 4/364-7**
Červek J: 2/131-3, 2/134-6, **2/139-41**, 2/151-4
Čizmarević B: **2/195-8**
Čuček-Pleničar M: **2/131-3**, 2/134-6
Čufer T: **2/95, 2/151-4;** 3/298-304

Decker T: **2/112-6**
Delepine F: 2/144
Delepine G: 2/142, **2/143, 2/144**
Delepine N: **2/142**
Desbois J-C: 2/142
Didanović V: 2/195-8
Djorgova J: 4/348-52
Dobrowsky W: 2/211-4
Döker R: 2/219-26
Došen D: **2/181-5**
Druschke J: 2/219-26
Dvorak O: 2/219-26

Ebner F: 2/229-30
Élö J: 2/186, **2/187,** 2/209, 2/244-6, 2/252-4; **4/384-7**
Eržen D: 2/134-6

Fasan S: 2/109-11
Favretto S: 2/109-11
Fede A: 2/168-70
Fettich J: 1/27-32
Feyerabend B: 3/279-85
Fidler V: **1/27-32**
Fietkau R: 2/165-7, 2/188-9
Fock CM: 2/229-30
Fornasiero A: **2/215-7**
Friso LM: 2/168-70, **2/215-7**
Furlan L: 2/173-7

Gambaro G: 2/202-6
Garcheva M: **4/348-52**
Gennadi S. Moroz: **2/236-7**
Giannakopoulou Ch: **4/345-7**
Ghezzi P: 2/202
Golouh R: 2/139-41
Grabenbauer GG: **2/219-26**
Gramatzki M: 2/165-7, 2/188-9
Groen HJM: 2/233-5
Gruy B: 2/218

Hackl A: 2/229-30, 2/231-2
Hadjiev J: **4/388-9**

Hammer J: 2/218
Hassan EA: 4/345-7
Hatzidaki EG: 4/345-7
Henze E: 1/5-12, 1/18-20, 1/21-6; 3/279-85, 3/309-14
Ho AK: **3/315-8**
Hočevar-Boltežar I: **2/247-51**
Hojker S: 1/27-32
Horváth E: **2/252-4**
Huber K: 2/219-26
Hutter M: 2/219-26
Hübner R-H: **3/279-85**
Hültenschmidt B: 2/219-26
Iro H: **2/165-7,** 2/178-80, **2/188-9,** 2/190-1

Jančar B: **2/238**
Janušić R: 2/181-5
Jarm T: **1/33-8**
Jassen J: **2/163-4**
Jereb B: **1/48-53; 3/305-8**
Jereb M: 4/380-3
Jevtić V: **3/320-1**

Kalina S: 1/5-12
Karashmalukov A: 2/210
Kern I: 4/380-3
Kettritz U: 2/112-6
Kiebert GM: **2/239-43**
Klančič M: **3/286-90**
Kleina A: 2/112-6
Klocker J: 2/119-21, **2/171-2**
Klutmann S: 1/18-20, 1/21-6, 3/279-85, **3/309-14**
Kos-Golja M: **4/353-7**
Kótai Zs: 2/186, **2/244-6**
Kotnik T: 1/33-8
Koumantakis EE: 4/345-7
Kragelj B: 2/151-4
Krajina Z: 2/181-5
Krengli M: 2/202-4
Kuhelj J: **1/54-6**
Kuhne-Velte H-J: 2/219-26

Labeck W: 2/118
Lamovec J: 2/131-3
Lassmann S: 1/5-12
Lastrucci L: 2/202-4
Leja D: 2/103-6
Lešnicar H: **1/39-47;** 2/173-7, **2/205-8**
Logar P: 2/238
Lora O: 2/109-11, 2/168-70
Lorregian L: **2/168-70,** 2/115-7
Lovey K: 2/123-4
Lüttges J: 3/279-85

Majdič E: **2/122**
Maluta S: 2/109-11
Di Marco A: 2/109-11
Martus P: 2/149-50
Mayer A: 2/123-4
Mayer R: **2/229-30,** 2/231-2
Mazzarotto R: 2/215-7
Mermolja M: **4/380-3**
Mester J: 1/5-12, 1/21-6; 3/279-85; 4/358-63
Meyer M: 2/219-26
Miklavčič D: **1/33-8;** 3/291-7; 4/368-73
Milan V: 2/107-8
Milčinski M: 3/286-90
Mir LM: 1/33-8
Morack G: 2/112-6
Moroz GS: **2/236-7**
Mršić-Krmpotić Z: 2/181-5
Muggio A: 2/107-8
Munda A: 2/195-8
Mustacchi G: 2/107-8

Nagykálnai T: **2/123-4**
Nemeskéri Cs: 2/123-4
Neri S: 2/109-11
Novak Janez: 2/131-3, **2/134-6,** 2/139-41
Novak Janko: **2/227-8**

Obenaus R: 2/112-6
Orešić V: **2/100-2**

Pacagnella A: 2/168-70
Panizzon G: 2/109-11
Panzer M: 2/219-26
Parmigiani F: 2/202-4
Péntek Z: 2/117-8
Petrinec Z: 2/100-2
Petrov I: 4/348-52
Petrovic G: 2/119-21
Piperkova E: 4/348-52
Pogačnik A: **2/155-7**
Pohar-Marinšek Ž: 2/134-6
Ponticelli P: 2/202-4
Porenta M: 1/13-7
Pötter R: **2/211-4**
Preidler KW: 2/231-2
Prepadnik M: 1/27-32
Prettenhofer U: 2/229-30, 2/231-2
Puc M: **4/368-73**
Pummer K: 2/231-2
Purkalne G: 2/103-6

Puskás T: **3/277-8**
Pušenjak J: 1/33-8; **3/291-7**
Putz E: 2/218

Raben A: **2/127-30**
Rác S: 3/277-8
Rahóty P: **2/137-8**
Ramalho VM: 3/322
Ranner G: 2/229-30
Ratchkov I: 2/210
Raunik W: **2/119-21,** 2/171-2
Reberšek S: 4/368-73
Ribecco A: 2/202-4
Richetti A: 2/109-11
Riddi F: 2/168-70
Rigon A: 2/109-11
Roncadin M: 2/109-11
Rovó L: **2/199-201**
Rubinić M: **3/273-6**
Rudolf Z: 2/298-304
Rühl U: 2/219-26
Ruhnke M: 2/112-6

Sabitzer H: 2/119-21, 2/171-2
Sandri P: 2/107-8
Sauer R: 2/149-50, 2/219-26
Sávay L: 2/199-201
Seewald DH: **2/218**
Senčar M: 2/134-6
Séra T: **4/358-63**
Serša G: 1/33-8, 4 364-7
Shomov G: 2/210
Sibata CH: 3/315-8
Sileni VC: 2/168-70
Simbrunner J: 2/229-30
Simeone F: 2/202-4
Skretting A: 4/358-63
Slavtchev R: **2/210**
Snoj M: **3/319**
Srakar F: 2/134-6
Stanec M: 2/100-2
Steinhart H: **2/190-1**
Stranzl H: **2/231-2**
Strojan P: 1/54-5
Stuecklschweiger GF: 2/229-30, 2/231-2
Svastics E: **2/117-8**
Szaba Weniger: 1/60-1
Szendröi M: 2/137-8
Szerján E: 2/117-8
Szolar D: 2/229-30

Schneider IHF: 2/219-26
Schneider W: 2/112-6
Schumer J: 2/171-2

Šmalcelj J: 2/181-5
Šmid L: 2/173-7
Šoba E: 2/173-7
Špiler M: 2/131-3
Šurlan M: 2/139-41

Taino R: 2/202-4
Tar T: 2/187, **2/209;** 4/384-7
Teodorani S: 2/109-11
Terčelj M: 4/380-3
Tester W: **2/145-8**
Thomadsen BR: 3/315-8
Tinnemeyer S: 1/5-12; 3/279-85
Track C: 2/218
Turić M: 2/181-5

Us-Krašovec M: 2/155-7

Valdagni R: 2/109-11
Veronesi U: **2/97-9**
Vidali C: **2/107-8**
Vikmanis U: **2/103-6**
Vodnik A: 2/134-6
Vraspir-Porenta O: 1/13-7
Vrdoljak DV: 2/100-2
Vujasković Z: **2/233-5**

Waldfahrer F: 2/165-7, **2/178-80,** 2/188-9
Weidenbecher M: 2/165-7
Wendt TG: 2/219-26
Weniger Szaba: **1/60-1**
Wieser S: 2/171-2
Willfurth P: 2/131-2

Zakotnik B: 2/139-41, 2/151-4, **2/173-7,** 2/205-8
Zámbó O: 2/244-6
Zini G: 2/109-11
Zoidl JP: 2/218
Zorat P: 109-11
Zorc-Plesković R: 1/13-7
Zorman D: 3/286-90
Zupanc M: 1/13-7

Žargi M: **2/158-62,** 2/173-7, 2/247-51
Žumer-Pregelj M: 2/151-4

Subject Index 1997

advanced tumors: 1/39-47
aged: 2/168-70
amifostine: 3/279-85
amputation: 2/131-3
antineoplastic agents, combined: 4/364-7
arthritis rheumatoid: 4/353-7

bioeffects algorithm, radiotherapy planning, radiation therapy, dose response relationship: 3/315-8
biopsy, needle: 4/380-3
bladder neoplasms: 2/145-8, 2/151-4
– bladder neoplasms – pathology: 2/155-7
– bladder neoplasms – radiotherapy – chemotherapy: 2/149-50
bleomycin: 2/173-7, 4/364-7
bone and bones – radionuclide imaging: 4/358-63
bone neoplasms: 2/131-3, 2/134-6, 2/137-8
– bone neoplasms – surgery: 2/125-6, 2/144
bone sarcomas: 2/142
brachytherapy – methods: 1/54-5
breast cancer: 2/112-6
breast conserving surgery: 2/123-4
breast conserving therapy: 2/112-6, 2/119-21
breast neoplasms: 2/97-9, 2/100-2, 2/103-6, 2/107-8, 2/109-11, 2/117-8, 2/119-21, 2/122, 2/123-4

cephalometry: 4/345-7
chemotherapy: 2/218, 2/219-26
– chemotherapy, adjuvant: 2/125-6
children: 2/142
choroid neoplasms, brachytherapy, melanoma: 2/238
chronic disease: 3/273-6
cisplatin: 2/139-41, 2/171-2
clinical results: 1/39-47
colorectal neoplasms – chemically induced: 4/374-9
combined modality therapy: 2/145-8, 2/151-4, 2/158-62, 2/178-80
combined modality treatment: 2/211-4
computer assisted: 3/315-8
conservation surgery: 2/122
conservative surgery: 2/117-8
coronary disease: 4/348-52
– coronary disease – diagnosis: 3/286-90
craniofacial abnormalities: 4/345-7
cytophotometry: 1/13-7

dimethylhydrazines: 4/374-9
direct current electrotherapy: 1/33-8
DNA: 1/13-7
dose response relationship: 3/315-8
ductal carcinoma in sity: 2/107-8

electroporation – instrumentation: 4/368-73
endorectal magnetic resonance imaging: 2/229-30
epiglottis: 2/209
extracellular space: 3/291-7
extremities: 2/125-6, 2/131-3, 2/139-41
FDG-PET – diagnostic value: 1/21-6
fibrosarcoma electric stimulation therapy: 1/33-8
flow cytometry: 2/155-7
function of the limb: 2/142

gastrointestinal hemorrhage – diagnosis: 3/277-8
glottis: 2/205-8, 2/247-51

head and neck dissection: 2/244-6
head and neck neoplasms: 2/158-62
– head and neck neoplasms – drug therapy – radiotherapy: 2/163-4, 2/168-70
– head and neck neoplasms – therapy: 2/165-7, 2/171-2, 2/173-7
heart – radionuclide imaging: 3/286-90
hemipelvectomy: 2/134-6, 2/137-8
hyaluronidase: 2/171-2
hyperthermice, induced: 1/39-47
hyperthyroidism – radionuclide imaging: 1/13-7
hypopharyngeal neoplasms: 2/190-1
– hypopharyngeal neoplasms – drug therapy: 2/188-9
– hypopharyngeal neoplasms – surgery: 2/187; 4/384-7

image processing, computer assisted: 1/27-32
impalpable lessions: 2/117-8
interferon – alpha: 3/305-8
interstitial brachytherapy: 1/54-5
intraductal carcinoma: 2/109-11

laryngeal neoplasms: 2/252-4
– laryngeal neoplasms – drug therapy: 2/202-4
– laryngeal neoplasms – radiotherapy: 2/247-51
– laryngeal neoplasms – surgery: 2/192-4, 2/195-8, 2/199-201, 2/209
– laryngeal neoplasms – surgery – radiotherapy: 2/105-8
laryngectomy: 2/202-4

– laryngectomy – methods: 2/192-4, 2/195-8, 2/252-4
laser surgery: 2/199-201, 2/209
local control: 2/122, 2/231-2
– local control rate: 2/218
local recurrence: 2/123-4
local thermoradiotherapy: 1/39-47
lung neoplasms – lobectomy: 2/236-7
lung neoplasms – radiotherapy: 2/233-5
alignant bone tumors: 2/143
manometry: 3/291-7
margin investigation: 2/112-6
mastectomy – methods: 2/100-2, 2/103-6
mastectomy, segmental resection: 2/97-9
mediastinal neoplasms – pathology: 4/380-3
mitomycin C: 2/173-7
mixed tumor, malignant: 2/210
mouth neoplasms – therapy: 2/178-80
multicenter studies: 2/109-11
myocardial stunning: 4/348-52

nasopharyngeal neoplasms – drug therapy – radiotherapy: 2/181-5
neoplasm recurrence, local: 2/210
neoplasms: 2/239-43; 3/298-304
– neoplasms – drug therapy: 3/305-8; 4/368-73
– neoplasms – radiotherapy: 1/39-47; 3/315-8
– neoplasms – therapy: 3/291-7
nephroblastoma – radiotherapy: 1/48-53
nuclear medicine: 1/27-32

oropharyngeal neoplasms – surgery: 2/186
osteosarcoma: 2/125-6

palatal neoplasms: 2/210
pancreatic – neoplasms – radionuclide imaging: 1/21-6
pancreatitis – diagnosis: 3/277-8
– pancreatitis – diagnosis, cholangiopancreatography, endoscopic retrograde: 3/273-6
parietal bone – abnormalities: 4/345-7
partial pharyngolaryngectomy: 4/384-7
pelvic bones resection: 2/134-6
pelvic bones – surgery: 2/137-8, 2/143
phantoms; imaging: 4/358-63
pharyngectomy: 2/190-1; 4/384-7
– pharyngectomy – methods: 2/187
plasminogen inactivators: 3/298-304
pneumonectomy: 2/236-7
preoperative chemotherapy: 2/139-41
prognosis: 2/103-6; 3/298-304
prognostic factors: 2/122
prognostic parameters: 1/39-47
prostatic cancer: 2/229-30
prostatic neoplasms: 2/231-2
prosthesis: 2/142
prosthesis reconstruction: 2/143
prosthetic reconstruction: 2/144

quality control: 4/358-63
quality of life: 2/239-43, 2/244-6

rabbits: 2/279-85
radiation injuries – diagnosis – therapy: 3/309-14
radiation pneumonitis: 2/233-5
radiation – protective agents: 3/279-85
radiation therapy: 3/315-8
radiographic image enhancement: 3/277-8
radionuclide imaging: 1/27-32
radiotherapy: 2/119-21, 2/122, 2/123-4, 2/171-2, 2/173-7, 2/188-9, 2/219-26, 2/231-2
– radiotherapy – adverse effects: 3/279-85
– radiotherapy planning: 3/315-8
rats: 4/374-9
rectal adenoma: 2/227-8
rectal neoplasms: 2/211-4, 2/219-26
– rectal neoplasms – radiotherapy: 2/218
– rectal neoplasms – radiotherapy – drug therapy: 2/215-7
regional blood flow: 1/33-8
risk factors: 2/123-4

salivary glands – radiation effects: 3/279-85
salivary glands – radionuclide imaging – iodine radioisotopes – adverse effects: 1/5-12
sarcoma: 2/127-30
– sarcoma experimental – drug therapy: 4/364-7
serine proteinases: 3/298-304
skull – abnormalities: 4/345-7
soft tissue sarcomas: 2/139-41
software: 1/27-32
speech therapy: 2/252-4
surgery: 2/227-8
– surgery – radiotherapy: 2/127-30
survival rate: 2/122, 2/131-3, 2/151-4, 2/187, 2/218, 2/231-2, 2/236-7
synovial membrane – surgery: 4/353-7

thallium radioisotopes: 4/348-52
thyroglobulin – calcitonin – carcinoembryonic antigen – tissue polypeptide antigen – neuron-specific enolase: 1/18-20
thyroid neoplasms – diagnosis: 1/18-20
tibia – surgery: 2/144

tomography, emission – computed – methods, fenorine radioisotopes: 1/21-6
tomography, emission-computed, single-photon: 4/348-52
tomography, x-ray computed: 3/277-8
transforming growth factor beta: 2/233-5
transperineal template: 1/54-5
treatment options: 2/107-8, 2/109-11
treatment outcome: 2/100-2, 2/107-8, 2/109-11, 2/112-6, 2/119-21, 2/125-6, 2/127-30, 2/139-41, 2/145-8, 2/149-50, 2/151-4, 2/163-4, 2/171-2, 2/173-7, 2/181-5, 2/186, 2/188-9, 2/192-4, 2/195-8, 2/215-7, 2/219-26
tumor growth retardation, blood perfusion: 1/33-8
tumor markers, biological: 1/18-20

urine – cytology: 2/155-7
urokinase: 3/298-304

vinblastine: 4/364-7
vindesine: 2/171-2
vocal cords: 2/199-201
voice quality: 2/247-51, 2/252-4

yttrium radioisotopes: 4/353-7

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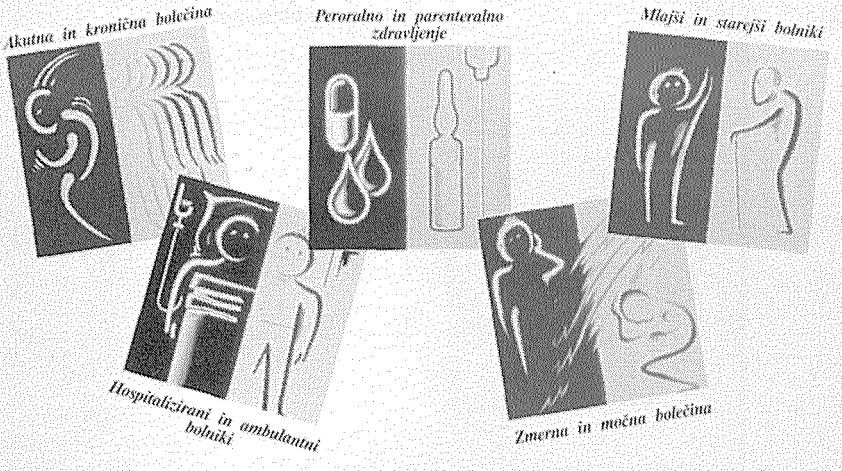

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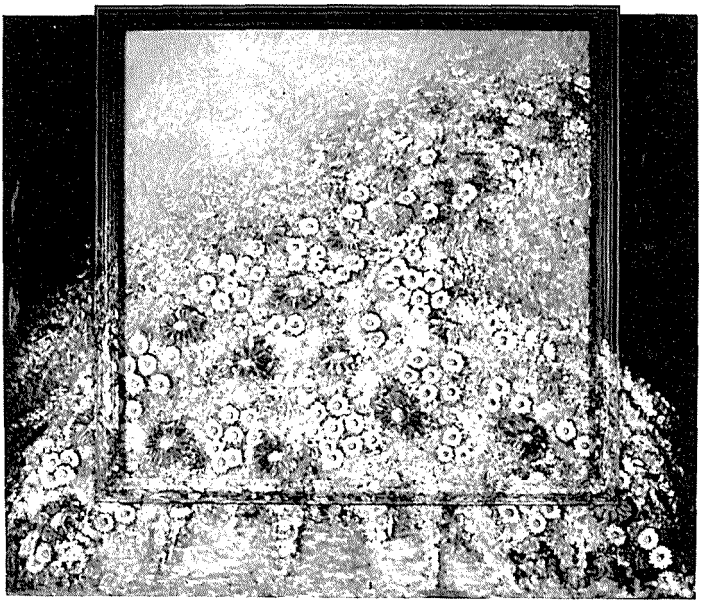

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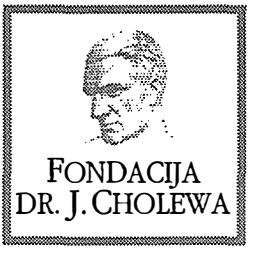

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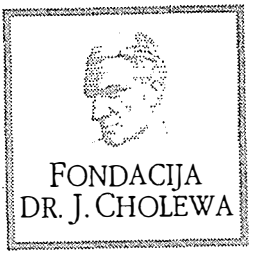

Activity of "Dr. J. Cholewa" Foundation for cancer research and education – a report for the final quarter of 1997

As the 1997 comes to its end it can be regarded as one of the more successful years since the "Dr. J. Cholewa" foundation for cancer research and education was formed. It continues to provide research and educational grants to those aplicants interested in the problems of oncology in Republic of Slovenia that fulfilled its strict criteria. Collaboration with the European School of Oncology from Milan proceeded smoothly, although it is still to be intensified and extended. Several steps were taken by the members of the Foundation to initiate and extend the collaboration and to ensure better coordination with other foundations and some state institutions in Slovenia, as not to double all the efforts unnecessary. Further steps in this direction will be taken in 1998.

The Foundation continues to support regular publication of "Radiology and Oncology" international scientific journal that is being edited and published in Ljubljana, Slovenia. In the same way, it also supports the regular publication of the "ESO Challenge", the newsletter of the European School of Oncology. The publication of this newsletter forms a part of a broader international initiative that was in detail outlined in the Djerba statement (ESO Challenge 1996; 1/6:1). This statement forms the basis for many initiatives in the fostering of better prevention, detection and therapy for cancer in countries and regions which for the moment cannot yet afford solutions proposed in the developed world (Aapro MS. Limited resources: unlimited possibilities. ESO Challenge 1997; 1/9: 2–6). On the other hand, the Foundation continues to support an important and already traditional local educational activity in the form of "Oncological weekend" meetings, that is primarily intended to all in the medical profession interested in problems connected with oncology.

It is with great sadness that the members learned of the untimely death of (the) Right Rev. Friderik Kolšek, one of the founding and most active members of the " Dr. J. Cholewa" foundation for cancer research and education. As a man of boundless energy he was dedicated to the activity of the Foundation until his very end. His kindness, his wit, together with his clear and incisive intelligence, will be greatly missed by all the remaining members of the Foundation.

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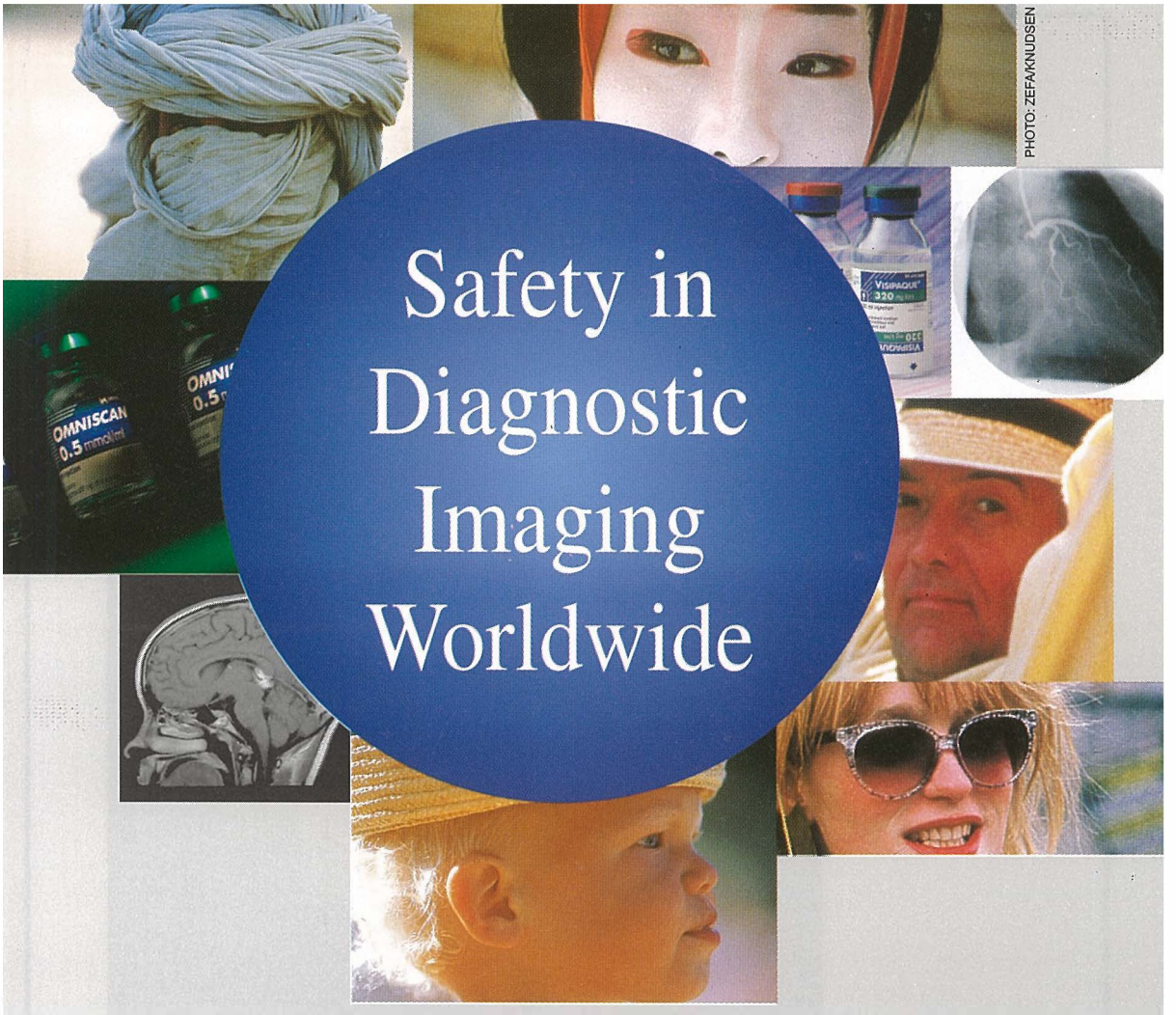

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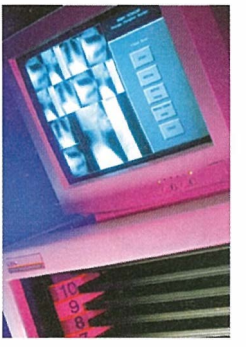

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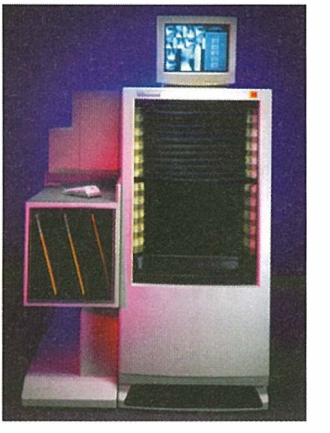

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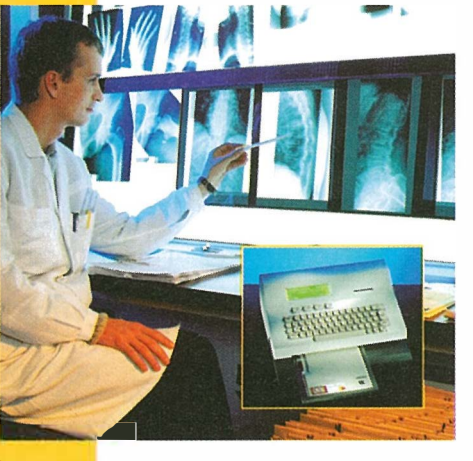

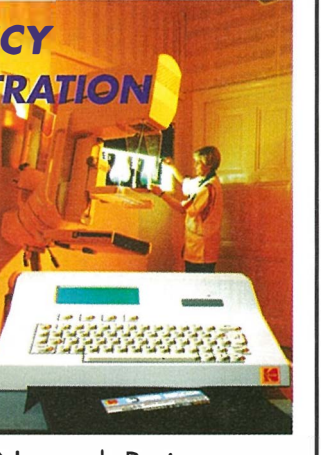

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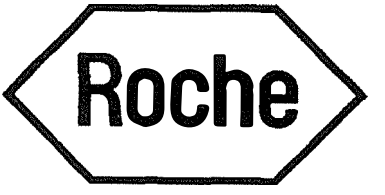

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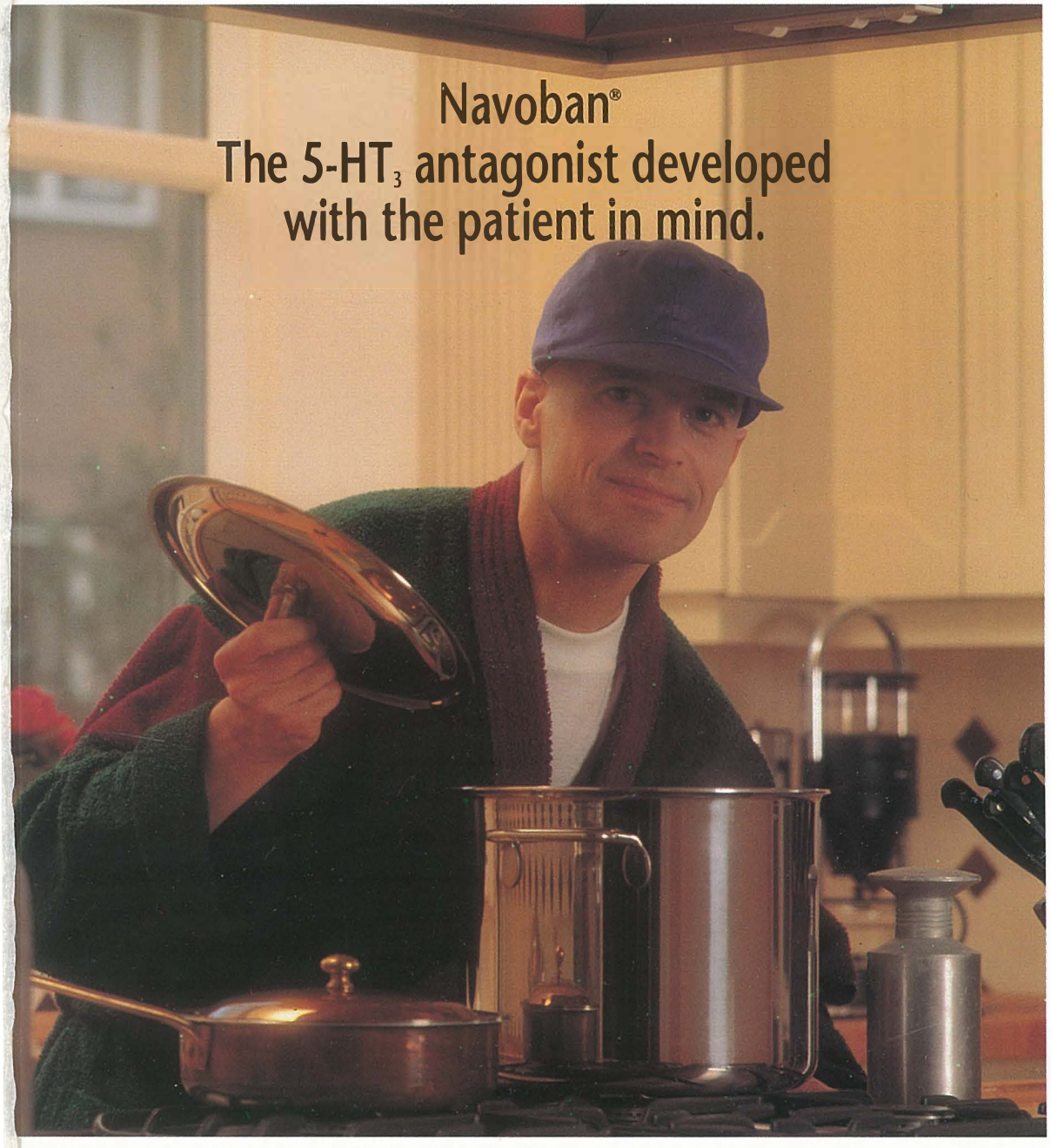

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