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Nepotrebno je, da bolezen spremlja bolečina

Moč opioidnega analgetika brez opioidnih stranskih učinkov

- centralno delujoči analgetik za lajšanje zmernih in hudih bolečin
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Indikacije: Srednje močne do močne akutne ali kronične bolečine. ***Po tristopenjski shemi Svetovne zdravstvene organizacije za lajšanje bolečin pri bolnikih z rakavim obolenjem tramadol odpravlja srednje hudo bolečino ali bolečino druge stopnje.*** **Kontraindikacije:** Zdravila ne smemo dajati otrokom, mlajšim od 1 leta. Tramadola ne smemo uporabljati pri akutni zastrupitvi z alkoholom, uspavali, analgetiki in drugimi zdravili, ki delujejo na osrednje živčevje. Med nosečnostjo predpišemo tramadol le pri nujni indikaciji. Pri zdravljenju med dojenjem moramo upoštevati, da 0,1 % zdravila prehaja v materino mleko. Pri bolnikih z zvečano občutljivostjo za opiate moramo tramadol uporabljati zelo previdno. Bolnike s krči centralnega izvora moramo med zdravljenjem skrbno nadzorovati. **Interakcije:** Tramadola ne smemo uporabljati skupaj z inhibitorji MAO. Pri sočasni uporabi zdravil, ki delujejo na osrednje živčevje, je možno sinergistično delovanje v obliki povečane sedacije, pa tudi ugodnejšega analgetičnega delovanja. **Opozorila:** Pri predoziranju lahko pride do depresije dihanja. Previdnost je potrebna pri bolnikih, ki so preobčutljivi za opiate, pri starejših osebah, pri miksedemu in hipotiroidizmu. Pri okvari jeter in ledvic je potrebno odmerek zmanjšati. Bolniki med zdravljenjem ne smejo upravljati strojev in motornih vozil. **Doziranje in način uporabe:** *Odrasli in otroci, starejši od 14 let:* Injekcije: 50 do 100 mg i.v.,i.m.,s.c.; intravensko injiciramo počasi ali infundiramo razredčeno v infuzijski raztopini. Kapsule: 1 kapsula z malo tekočine. Kapljice: 20 kapljic z malo tekočine ali na kocki sladkorja; če ni zadovoljivega učinka, dozo ponovimo čez 30 do 60 minut. Svečke: 1 svečka; če ni učinka, dozo ponovimo po 3 do 5 urah. ***Otroci od 1 do 14 let:*** 1 do 2 mg na kg telesne mase. Dnevna doza pri vseh oblikah ne bi smela biti višja od 400 mg. **Stranski učinki:** Znojenje, vrtoglavica, slabost, bruhanje, suha usta in utrujenost. Redko lahko pride do palpitacij, ortostatske hipotenzije ali kardiovaskularnega kolapsa. Izjemoma se lahko pojavijo konvulzije. **Oprema:** 5 ampul po 1 ml (50 mg/ml), **5 ampul po 2 ml (100 mg/2 ml)**, 10 ml raztopine (100 mg/ml), 20 kapsul po 50 mg, 5 svečk po 100 mg.

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Correspondence address
Radiology and Oncology
Institute of Oncology
Vrazov trg 4
61000 Ljubljana
Slovenia
Phone: + 386 61 1320 068
Fax: + 386 61 1314 180

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Milica Harisch
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Transesophageal echocardiography – a new diagnostic method in cardiology

Mirta Koželj

Department of Cardiovascular Disease, University Medical Centre, Ljubljana, Slovenia

Transesophageal echocardiography (TEE) is a rapidly expanding diagnostic procedure in cardiology. Limitations of transthoracic approach caused by pulmonary emphysema, obesity, thoracic deformation and dyspnea have been overcome by using the transesophageal approach. TEE has a higher resolution, because higher frequency transducers can be used and there is no thorax interposition between the heart and transducer. There are strong and relative indications for this procedure. The TEE examination is a safe method and has very limited contraindications.

Key words: echocardiography transesophageal, diagnostic method, cardiology

Introduction

After the introduction of echocardiography, it soon became apparent that scanning of the heart is sometimes hindered by inadequate penetration of ultrasound through the thoracic wall and ribcage. This stimulated many investigators to search for alternative approach. Within only a few years, transesophageal echocardiography (TEE) has become established as an important new imaging technique in cardiology. TEE has opened a unique »new window« to the heart. The immediate proximity of oesophagus and the posterior heart permits exceptionally high resolution images, particularly of the left atrium, mitral valve, and interatrial septum, and thoracic aorta. Additionally, from the stomach, the ventricles can be dependably imaged.

Correspondence to: Mirta Koželj, MD, PhD, Department of Cardiovascular Disease, University Medical Centre, Zaloška 7, 61000 Ljubljana, Slovenia. Phone: + 386 61 317 057. Fax: + 386 302 455.

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Technological developments and current TEE probes

The technique of TEE imaging was first introduced on an experimental basis in the late 1970s.[1] Since then, rapid advances in ultrasound technology have greatly changed the practice of TEE imaging. Miniaturisation of transducers size, the development of phased array systems housed in flexible endoscopes, and the ability to perform pulsed and colour Doppler flow imaging have made TEE a valuable diagnostic tool.[2, 3] Until recently, transesophageal endoscopes have had a single set of transducer orments attached to the probe tip. Using this transducer, images are acquired in serial transverse imaging planes. Recently Omoto et al.[4] have introduced a biplane transesophageal pro-

be. Two phased-array transducers, one imaging in transverse and one in longitudinal planes, are mounted side-by-side at the tip of the gastroscope. This additional sagittal plane transducer allow imaging of the heart in two orthogonal planes, and enable a more complete biplane examination of cardiac and aortic anatomy. Much more sophisticated systems operate with multiplane probes, which allow to observe the heart in even multiple sections.

The basic construction of all transesophageal transducers is similar. A commercially available gastroscope is adapted by fitting a phased-array transducer at its tip for imaging in the transverse axis. The fiberoptics, together with the channels used for suction and biopsy, are removed to provide space for electronic connections for the transducer, but normal guidance controls are retained (Figure 1). The probes have the capacity for two-dimensional imaging at 5 to 7 MHz and 3.5 MHz for Doppler sampling.

TEE echocardiography is presently utilised in two environments: intraoperatively and for outpatient examinations. Intraoperatively, TEE is utilised to monitor cardiac function and detect intracardiac air or debris, to diagnose or quantitate cardiac pathology and to assess operative results.

Patient preparation for TEE examination

TEE is unpleasant for most patients. Prior to the TEE examination, the possibility of gastroesophageal disease must be excluded, specifically oesophageal varices, diverticula, spasm and strictures, and intraesophageal masses. To prevent aspiration the patient should abstain from all oral intake for at least 4 hours, and during the introduction and examination the patient lies in the left decubitus position. Antibiotic prophylaxis is recommended only for a group of patients at high risk of infectious endocarditis such as those with prosthetic heart valves, severe native mitral regurgitation, and congenital heart disease.[5] Choice of anti microbial agent is made in accordance with the guidelines of the American Heart Association.[6] Lidocain spray is given for local anaesthesia to all patients. In our experience other premedication is not necessary. We perform TEE with sedatives and spasmolytics only in patients, in whom the aortic dissection is suspected. The patient is asked to swallow and the probe is advanced into the oesophagus with the aid of gentle pressure. Under no circumstances should oesophageal intubation be attempted against resistance. For the unconscious for example at intraoperative TEE, anaesthetised patients, no preparations are needed other than those for the operative procedure itself. The TEE probe is introduced into the oesophagus following of anaesthesia.

TEE: anatomic correlations

A comprehensive transesophageal examination entails a sequence of transducer positions and tomographic planes of sections. A step-by step approach that can be altered on the basis of the clinical situation is suggested. During TEE, two distinct tomographic examinations are performed – namely, that of the heart and that of the thoracic aorta.

Complete TEE imaging of the heart is performed from transducer locations in the stomach and various levels of the oesophagus. Views from the distal and proximal fundus of the stomach, gastroesophageal junction, lower and

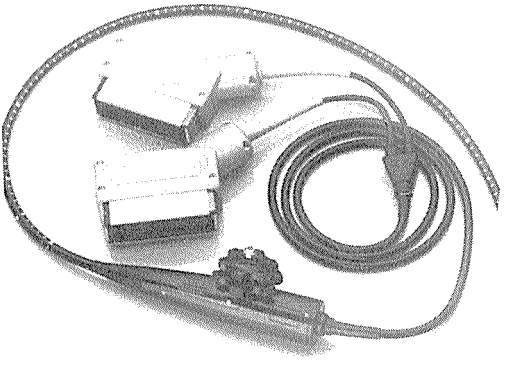

Figure 1. Biplane probe (5 MHz). Note dual cables and connectors ("vertical, horizontal") for two transducers.

middle oesophagus, and upper oesophagus are included in a standard TEE study of the heart. Although these locations serve as a general guide, the exact location of the transducer should be guided by the acquired image and not by the position in the stomach or oesophagus. If the probe is rotated anticlockwise, all of the thoracic descending aorta can be visualised adjacent to the transducer.[7]

The main clinical indications for a TEE study in adults

The oesophagus is adjacent to the left atrium and descending aorta. The high resolution and the shorter distance to the transducer make possible high quality images of the left atrium, mitral valve, interatrial septum and aortic valve. Flow patterns in the heart can be studied in detail. With transthoracic echocardiography, shielding of the left atrium by prosthetic valves often prevents evaluations of insufficiencies. TEE with colour flow Doppler provides magnificent evaluation of (para) valvular mitral insufficiency. Biplane TEE provides better evaluation of all cardiac valves and of valve insufficiencies in the longitudinal sections. Longitudinal sections are superior for the evaluation of the right ventricular outflow tract. With TEE, the interatrial septum is about perpendicular to the transducer and also the detection of a very small atrial septal defect is easy now. A different and often better evaluation of the aortic valve and right atrium is possible with TEE.

Major indications for ambulatory (outpatient and inpatient) TEE include defining the aetiology and severity of native valve disease, especially mitral regurgitation; detecting vegetations and other sequels of endocarditis (Figure 2); assessing prosthetic valve function and regurgitation; and identifying a potential cardiac embolic source (Figure 3). TEE has been shown to be an excellent method for detecting atrial septal defects, atrial septal aneurysm (Figure 4), and patent foramen ovale. In regard to cardiac tumours, although the data are preliminary, certain tumour locations and morphologic aspects are better evaluated with TEE than with other techniques. Important advantages of TEE over transthoracic echocardiography are the high resolution images of cardiac cavities for tumour location and the visualisation of the

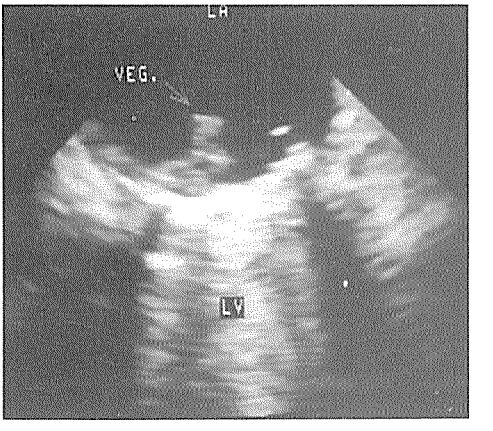

Figure 2. Transesophageal echocardiogram at the level of the left atrioventricular junction. A bileaflet prosthetic valve is in mitral position, which casts a shadow within the left ventricle (LV). There is a vegetation (arrow) of the left atrial side of the prosthesis. LA = left atrium. The vegetation was not seen at transthoracis study because of shadowing of mitral prosthesis in the left atrium.

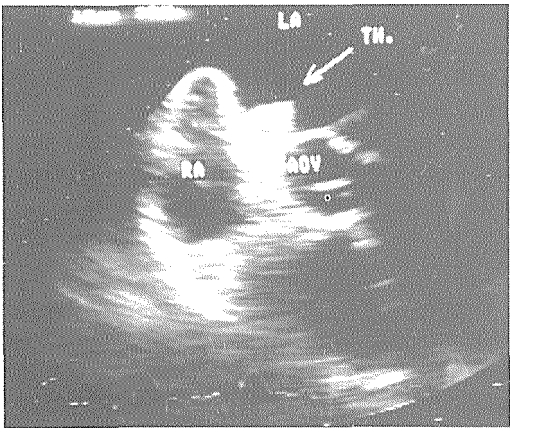

Figure 3. Transesophageal transverse-axis image in a patient with dilative cardiomyopathy. A large thrombus (TH) attached at interatrial septum is clearly visible (arrow). On the precordial image no definite structure could be visualised. LA = left atrium, RA = right atrium, AOV = aortic valve.

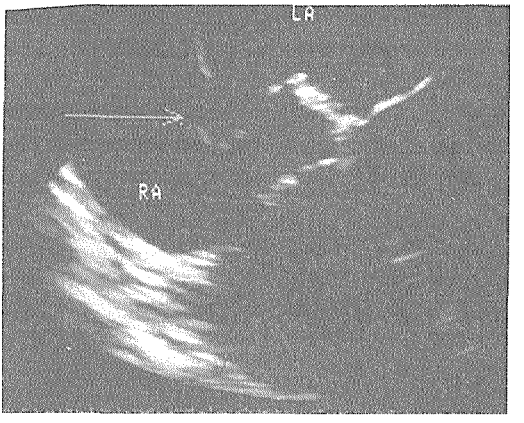

Figure 4. Transesophageal image of an atrial septal aneurysm (arrow). LA = left atrium, RA = right atrium.

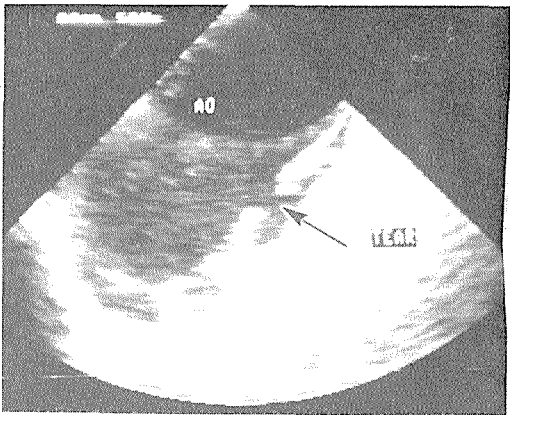

Figure 5. Cross-sectional transesophageal image of the aortic arch (AO) in a patient with acute dissection. The arrow shows the intimal tear. The color flow Doppler study confirms the flow at this site. Subsequent surgical inspection confirmed that this was the site of an intimal tear.

myocardial wall and great veins for recognition of impingement, containment, migration and infiltration of diverse tumours types.[8]

A new field in ultrasound diagnosis is the thoracic aorta. Good information about the presence of dissection and plaques can be obtained (Figure 5). The true and false lumen can be distinguished with colour flow Doppler. The aortic arch and ascending aorta are not always visible because of interposition of trachea.

TEE is of limited value in the evaluation of lesions within the coronary arteries. Even where the quality of the images is excellent, only limited segments of the proximal vessels can be visualised. It is our opinion that the only practical value is in the idenfication of left main coronary stenosis or the involment of coronary arteries in dissection of ascending aorta.

Safety and complications of TEE

Clear indications for TEE are necessary because side effects are rare but can be harmful. The complications include intolerance of the procedure, bronchospasm, spasm of oesophagus, vomiting, cardiac rhythm disturbances, angina, pharyngeal bleeding. The ECG monitoring is mandatory during the procedure. Nevertheless a careful history concerning upper gastrointestinal problems should be taken before TEE study.[9]

Conclusion

TEE has indeed opened a new and exciting window to the heart. TEE has now become a logical extension of a complete transthoracic echocardiographic examination. Predictable high-quality images obtained from the transesophageal examination have fostered wide application of this new technology. With newer multiplanar scanning devices becoming available, whole sets or families of short- and long-axis and four chamber views of the heart will be obtained.

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Age-related changes of renal vascular resistance in normal native kidneys: color duplex Doppler ultrasound assessment

Boris Brkljačić,[1] Ivan Drinković,[1] Diana Delić-Brkljačić,[2] Andrija Hebrang[1]

[1] Department of Radiology, Ultrasonic Center, University Hospital "Merkur" and [2] Department of Medicine, University Hospital "Sestre Milosrdnice", Croatia.

Purpose: To evaluate age-related changes of renal vascular resistance (RVR) in normal native kidneys. Materials and methods. Intrarenal arteries were insonated in 180 kidneys of 90 examinees and Doppler sonographic resistive indexes (RIs) were measured. Examinees were classified into three age groups: the first consisted of subjects < = 30 years old, the second of subjects between 31 and 54 years and the third of subjects 55 years of age and older.
Results: Mean RIs were 0.57 in the first group, 0.598 in the second group, and 0.621 in the third group. RIs were found to be age dependent, with significant elevation observed with increasing age (group I vs. group II, P < .01; group II vs. group III, P = .03; group I vs. group III, P < .01).
Conclusion: Doppler sonographic resistive indexes reflect elevation of RVR with aging.

Key words: kidney, blood, renal artery-ultrasonography; ultrasonography, supply, Doppler, color; age factors.

Introduction

Extensive research has been performed during the last decade in Doppler assessment of intrarenal blood flow in transplanted kidneys.[1–3] In the last few years Doppler studies were performed in native kidneys, as well.[4–6] Normal values have been established in a few studies and Doppler indexes have been correlated with renal functional tests and blood pressure values in several renal diseases.[7–13] In most of these studies age-dependent changes of renal vascular resistance were neglected, although some authors referred to age-related changes of Doppler inexes in large series of patients.[10] The purpose of this study was to evaluate age-related changed of renal vascular resistance, reflected in values of Doppler sonographic resistive indexes (RIs), in normal native kidneys.

Correspondence to: Boris Brkljačić, M. D., Ph. D., Department of Radiology, Ultrasonic Center, University Hospital "Merkur", Zajčeva 19, Zagreb, Croatia. Phone/Fax: + 385-1-2331440.

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Materials and methods

Between November 1991 and November 1994 color-duplex Doppler sonography of intrarenal arteries was performed in 180 kidneys of 90

subjects without renal impairment. There were 39 men, and 51 women, aged 18–55 years (mean 44.6 ± 14.6 years). Twenty six were healthy volunteers and 64 were studied in the course of nonrenal abdominal, thyroid or breast US examinations. The inclusion criteria for the examination were abscence of a history of kidney disease; absence of systemic, chronic or malignant diseases that might affect renal function; absence of hypertension; absence of history of congenital or acquired heart disease; normal conventional US finding of kidneys; and normal urinalyisis findings prior to Doppler US examination. Twenty eight subjects had findings of normal serum creatinine, tested within 30 days prior to Doppler US examination. Informed consent was obtained from all examinees. All subjects were older than 18 years, to avoid variations in RIs values noted in childhood.[14,15] The examinees were arbitrarily classified into three age groups (< = 30 years old, 31–54 years, > = 55 years) to evaluate age dependence of RI values in healthy adult subjects.

Real-time and color duplex-Doppler US examinations were performed with a Radius CF color Doppler scanner (GE-CGR, Buc, France), with a curved-array 3.75-MHz transducer. After color-Doppler identified flow in intrarenal vessels, a sample-volume was positioned in segmental, interlobar and arcuate arteries in their typical positions. Spectral analysis was performed and RIs measured using existing software capabilities of the scanner. Mean RI values for each kidney were calculated from all measurements. Wall-filter of 50 Hz and minimal PRFs were used to obtain optimal spectral waveforms in all cases. Sample-volume was set at 2–4 mm. Examination was technically successful and adequate spectra obtained in all subjects. The RI was measured with the formula (peak systolic frequency shift – minimum diastolic frequency shift)/mean frequency shift during the cardiac cycle.[16] Subjects were examined in supine and decubitus positions; the duration of the examination per person was 30–40 minutes. All the examinations were performed by the first author (B. B).

Mean RI values were compared between different age groups of examines. "Goodness-of-fit test" (Kolmogornov-Smirnov) was used to test whether the distribution of RI values was normal. The statistical significance of observed differences was calculated with the Mann-Whitney U test. The Pearson method was used to estimate the correlation between RIs and age of the age of the whole group of examinees.

Results

The mean RI ± SD in 180 kidneys of 90 subjects with normal native kidneys was 0.596 ± 0.038 (range 0.535 – 0.685). All RIs were below 0.70.

There were 23 examinees 30 years old or younger (group I), 46 subjects were in the range of 31 – 54 years of age (group II), and 21 examinees were 55 years old or older (group III). The distribution of RIs by these three age groups is shown in Figure 1.

The age distribution, as well as distribution of RIs within each age group was normal. Statistical significance of differences of RIs between different age groups (Mann-Whitney U-test) was observed between the age groups I and II ($P < .01$), between the age groups II and III ($P = .03$; 95 % confidence level), and between the age groups I and III ($P < .01$).

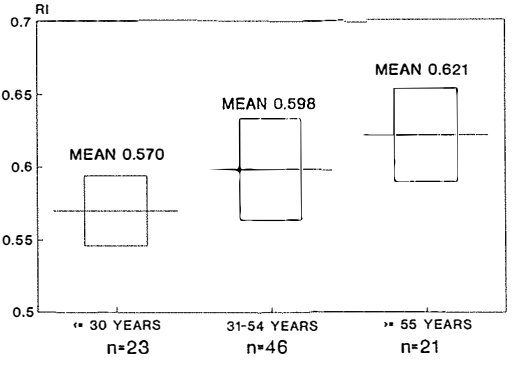

Figure 1. The distribution of mean RI values and 1 S. D. in three age-groups of examinees with normal native kidneys. n = number of patients within the particular age-group.

The typical Doppler spectra from intrarenal arteries with high continuous diastolic flow and low resistive index are shown in the Figure 2.

The Pearson lienar correlation method showed high and statistically significant correlation between RIs and age of the whole group of examinees with normal native kidneys. The Pearson correlation coefficient (r) between age of examinees and RI was 0.5172 ($P < .001$).

The Pearson method showed lack of correlation between RIs and renal length and between RIs and renal parenchymal thickness in subjects with normal native kidneys. Correlation coefficients between RIs and renal lenght were: $r = -0.053$ for the right kidney ($P = NS$) and $r = -0.061$ for the left kidney ($P = NS$). Coefficients between RIs and renal parenchymal thickness were: $r = -0.078$ for the right kidney and $r = -0.086$ ($P = NS$) for the left kidney ($P = NS$).

Discussion

Doppler sonographic studies of renal vascular resistance in renal parenchymal diseases have shown complex interrelations of several parameters affecting values of Doppler sonographic indexes.[10,17] A few studies have analyzed relation between RI and renal biopsy findings. It appears that the site of the pathologic alterations within the kidney is very important in measurement and interpretation of Doppler sonographic indexes.[13,18] Doppler analysis seems to be particularly useful in disease affecting tubulointerstitial and vascular compartments of kidneys. In diabetic nepropathy Doppler indexes reflect elevated renal vascular resistance.[10,17] In unilateral pyelocalicectasis Doppler seems to be very accurate in distinguishing between obstructive and non-obstructive collecting system dilatation.[11,12] In addition to pathologic alterations within the kidney and hypertension, age has emerged in large studies as a significant covariable, affecting RVR and Doppler indexes values.[10,17] The present study has shown a high and significant correlation of Doppler sonographic resistive index and age of examinees with normal native kidneys. It has also shown age-dependance of RIs values, which tend to increase with aging.

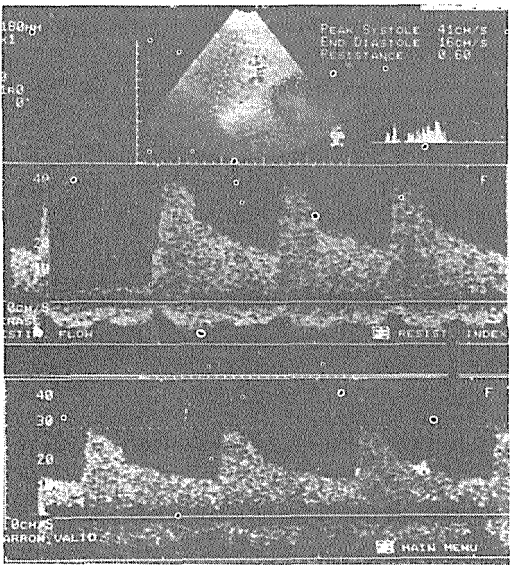

Figure 2. The normal spectral waveforms of intrarenal arteries in normal native kidney; continuous high diastolic flow with low resistive index.

In a literature a RI value of 0.70 has been generally accepted as a threshold value for pathological renal vascular resistance, and RIs of 0.70 and higher are considered abnormally elevated. This threshold RI value has been introduced by Platt[5,17,18] and other groups of investigators have accepted it.[10–13] This study has shown that it is reasonable to take into account age-related dependence of Doppler indexes in interpretation of their values and in comparison with the control groups.

Statistically significant differences of RIs values were observed in the present study between arbitrarily chosen age-groups of examinees. It was noted that all the examinees had RIs below 0.70, and even in the oldest age-group the mean RI of 0.621 was far below the threshold value of 0.70. The mean RI value of 0.596 ± 0.038 observed in this study was similar to other studies where mean intrarenal RIs in normal native kidneys ranged from 0.58 to 0.64.[5,7,9,10]

There are several limitations in the golden standard reference method for normal renal

status. It is known that serum creatinine levels may be normal while even a 50% decrease in renal function may exist simultaneously.[19] Therefore, it is hard to prove normal renal status when a study is performed in a usual clinical setting. An analysis of creatinine clearance rates has to take in account potential error from inaccurate urine collection.[19] In the present study, small proportion of control subjects had serum creatinine levels tested and we had to rely in the majority of subjects on absence of history of renal disease, normal conventional US findings and urin analysis findings for inclusion of examinees in the control group. Although some persons with renal functional impairment may have been included in the control group using such criteria, we believe that the relevance of obatined data is not essentially decreased.

This study shows that elevation of RIs with aging does not represent false variations or variability of these values. A few studies about physiology of aging suggest that the loss of renal function related with aging is hemodinamically mediated (elevated renal vascular resistance).[20–23] The present study confirms those results. Some authors think that elevation of Doppler indexes that occurs with aging reflects the loss of functioning nephrons, observed in the senescent kidney, that is not reflected by serum creatinine elevation.[5,19,24] In pediatric population higher RIs were observed in comparison with adults.[14,5] Only subjects older than 18 years were included in the present study, so the changes of RIs in childhood need not to be accounted for. RIs values did not show significant correlation with renal length and parenchymal thickness of our examinees, which is not surprising for normally functioning kidneys.

Doppler US imaging has the most important potential for the diagnosis of parenchymal renal diseases in the longitudinal follow-up of patients with renal disease to provide predictive clinical information on the recovery of renal function or the progression of renal disease. Results of the present study indicate that elevation of RIs with increasing age has to be taken into account in such longitudinal studies, and that it is acceptable to consider RI of 0.70 as a threshold value for pathologic elevation of renal vascular resistance.

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Color-Doppler ultrasound evaluation of renal cell carcinomas

Ivan Drinković, Boris Brkljačić, Žarko Zeljko[1]

Department of Radiology, Ultrasonic Center and Department of Surgery, Division of Urology, [1] University Hospital "Merkur", Medical School, University of Zagreb, Croatia

Color-duplex Doppler US (CDDUS) evaluation was performed in 39 patients with renal cell carcinomas (RCC). Intrarenal arteries within the tumor, on the margin of the tumor, and in the unaffected part of the kidney were insonated. Spectral analysis was performed, peak-systolic frequencies recorded, and Doppler-sonographic resistance-indices (RIs) calculated. Intrarenal arteries of 44 normal examinees were studied as a control group, in which a mean RI of 0.597 ± 0.035 (1 SD) was found. Spectral features of vessels on the margin of the malignant tumor consisted mostly of high frequency Doppler shifts (mean systolic peak 3.89 ± 1.06 kHz), while vessels within the tumor had very low vascular resistance, with low RI values (mean RI 0.498 ± 0.059), which were significantly lower in comparison with the control group ($P < .01$). These features are similar in RCC regardless of their size. The overall sensitivity of CDD US in detection of at least one of abnormal flow features in RCC was 92.3%, while the specificity was 93.2%. CDD US can aid significantly in the noninvasive diagnosis of RCC, with exception of relatively rare hypovascular and avascular tumor types.

Key words: kidney neoplasms-ultrasonography; carcinoma, renal cell; ultrasonography, Doppler, color

Introduction

Malignant renal tumors make up to 3% of all human malignant tumors and renal cell carcinoma (RCC) is the most common primary malignancy of the kidney. These are generally tumors with the slow growh rate, late manifestation of clinical symptoms and, consequently, often late discovery. Despite the slow growth rate the prognosis is poor, with an overall survival rate of 20–25% 10 years after nephrectomy. However, if the carcinoma is confined to the kidney there is a 50% 10-year survival. Therefore, the early diagnosis of this lesion is very important.[1,2]

The widespread use of ultrasound and CT has increased the detection of small renal neoplasms, often found incidentally in patients without renal simptoms. Still, diagnostic difficulties are often encountered with excretory urography, CT, conventional US and renal angiography in the diagnosis of small renal tumors.[3,4]

Correspondence to: Doc. Dr. Ivan Drinković, Department of Radiology, Ultrasonic Center, University Hospital "Merkur", Zajčeva 19, Zagreb, Croatia.

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The introduction of color-Doppler US has enabled the visualisation of intrarenal vascularization and has considerably facilitated the quantification of Doppler signals from intrarenal arteries and arteries within various pathological lesions.[5,6] The purpose of this study was to evaluate the color-Doppler US in the detection of renal cell carcinomas, particularly of smaller tumors which are more difficult to be diagnosed with conventional US and other imaging modalities.

Patients and methods

Between December 1991 and June 1994, CD US and spectral analysis was performed in 39 patients with RCC. 26 patients were referred from the Divisions of Urology and Nephrology with the suspicion for renal tumor, and 13 tumors were discovered incidentally in asymptomatic patients on conventional US examinations. Twenty seven patients were male and 12 female. They were aged 45–79 years (mean, 58.1 years). Intrarenal arteries of 44 normal examinees (mean age 49.5 years) were studied as a control group. All the subjects were examined in the morning, usually after an eight hour fast. In all patients urography, CT and selective DSA were also performed. Doppler study was performed after conventional US in 17 patients, after urography and conventional US in 11 patients, after CT and conventional US in 8 patients, after CT and selective DSA in 2 patients and after DSA in 1 patient. Pathohystologic findings produced definite diagnosis in 34 patients who were operated and fine-needle biopsy specimens analysis in 5 patients who were not subjected to operation because of poor general condition, disseminated disease and high surgical risk. On the conventional US examinations the largest diameter of tumors was 6.2 ± 3.3 cm (mean $\pm$ 1 SD). Fourteen tumors were up to 4 cm large in the largest diameter, while 25 tumors were larger than 4 cm.

Conventional and CD US examinations were performed with a color-Doppler scanner (Radius CF, GE-CGR, Buc, France) with a curved array 3.75 MHz transducer. All patients and control subjects were examined in supine and semioblique positions by two experienced radiologists. The duration of examination per patient was 30–45 minutes. In patients with renal masses, vessels were as a rule insonated in at least 3 spots in the kidney – arteries within the tumor, arteries on the margin of the tumor, and at least one artery in the morphologically normal part of the kidney, unaffected by the tumor. Intrarenal arteries (interlobar and arcuate) of the opposite kidney were studied in all patients and in the control subjects in 2–3 different parts of the kidney. In all insonated arteries spectral systolic frequency peaks were recorded (in kHz), and resistance indices (RIs) calculated with the following formula: (peak systolic frequency shift – minimum diastolic frequency shift / peak systolic frequency shift). Mean RIs were calculated for normal kidneys from multiple measurements from different intrarenal arteries. The wall filter was set usually at 50 Hz, and the sample volume was 2–4 mm. Only optimal spectral waveforms were used for all measurements.

The statistical significance of observed differences was calculated with the Mann-Whitney U test. Descriptive statistical parameters were also used.

Results

CD US showed prominent vascularization within the tumor and on the margin of the tumor in 34 patients and adequate spectral waveforms were obtained in these spots in all of these patients. Vascularization was not observed within the tumor in 5 patients and spectral waveforms could not have been obtained from these tumors. All these patients had hypovascular or avascular types of renal cell carcinomas, as shown by selective DSA. However, in 3 of these 5 patients clearly visible vessels on the margin of the renal mass were observed by color-Doppler and in 2 cases high systolic spectral peaks (> 3 kHz) typical for tumor neovascu-

larization were obtained from these arteries. Sensitivity of color-Doppler US for obtaining adequate signals from arteries within the tumor was 87.2% and for obtaining signals from arteries on the tumor margin 94.9%. Spectral systolic frequency peaks in arteries on the margin of the tumor, obtained in 37 patients, were ranging from 2.1 kHz to 6 kHz (mean 3.89 ± 1.06). In 4 of 37 patients spectral peaks in these arteries were below 3 kHz (which corresponds to velocity of cca. 80 cm/s for our transducer of 3.75 MHz). Spectral systolic peaks in all intrarenal arcuate, interlobar and segmental arteries in normal kidneys (control group) and contralateral normal kidneys of patients with renal tumors were below 2.5 kHz. Systolic peaks were below 3 kHz in all main renal arteries in the control group. If systolic peak of 3 kHz for our transducer is used as a cutoff value for abnormally high frequency shifts in the artery on the margin of the tumor, indicative of malignant neovascularization, the sensitivity of CD US and spectral analysis for detecting pathologic vessels in RCC was 89.2% (33 of 37 patients). If all 39 patients with renal carcinoma are taken into account, including those 2 with completely avascular malignancies, the sensitivity of CD US and spectral analysis in the detection of abnormally high frequency shifts indicative of A–V shunts in vessels on the tumor margin was 84.6% (33 of 39 patients). The specificity of 3 kHz cutoff value for our scanner was 100%.

Mean RI in intrarenal arteries in the control group of examinees was 0.597 ± 0.035 (mean ± SD). Mean RI measured in arteries within the tumor obtained in 34 patients was 0.498 ± 0.059, with the range from 0.38 to 0.65. The difference betwen RI values in these 34 patients and RI values in intrarenal arteries of normal examinees was statistically significant (Mann-Whitney U-test, $P < 0.01$). We propose mean RI value ± 1 SD as a cutoff value for abnormally low RI value. In our study it would be RI value below 0.56. Out of 34 patients with RCC who had flow detectable by CD US in arteries within the tumor, 31 patients had RI values below 0.56. Therefore, the sensitivity of spectral analysis for detecting abnormally low renal vascular resistance characteristic for malignant neovascularization in those patients was 91.2% (31 of 34 patients). When all patients are taken into account, including those where arteries within the tumor could not have been visualized by CD US, the overall sensitivity of RI value below 0.56 in detecting malignant neovascularization within the tumor was 79.5% (31 of 39 patients).

The proportions of patients with vascularization observed on the margin of the tumor and within the tumor, as well as proportions of observed pathological frequency peaks (> 3kHz) in marginal vessels and RIs < 0.56 in vessels within the RCC are presented in Table 1.

Table 1. Proportions of patients with vascularization on the margin of the tumor and within the tumor, and proportions of pathological frequency peaks (> 3 kHz) in marginal vessels and RIs < 0.56 in vessels within the RCC.

	PTS with RCC N = 39	%
vascularization on TM margin	37/39	94.9
peaks > 3 kHz in vessel on TM margin	33/39	84.6
vascularization within tumor	34/39	87.2
RI < 0.56 within tumor	31/39	79.5

The mean RI values ± 1 SD in vessels within tumors and in the intrarenal arteries of control subjects are shown in Figure 1.

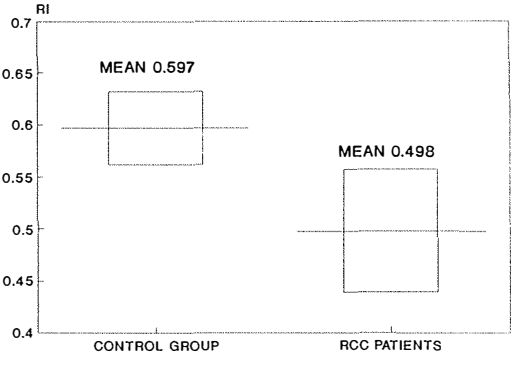

Figure 1. Mean RIs ± 1 SD in vessels within RCC and in control group of normal examinees.

In the intact part of the kidney with the tumor we did not observe any differences of RIs in comparison with the control group. The mean RI value below 0.56 was observed in 3 young patients (mean age 23.2 years) in the control group. So, this cutoff value has the theoretical specificity for detecting malignant neovascularization of 93.2%. However, since generally no abnormalities can be seen in the normal subjects on conventional US, the CD US findings have to be evaluated together with conventional US findings. Therefore, the specificity of low RIs associated with abnormal conventional US finding indicative of renal mass is in practice 100%.

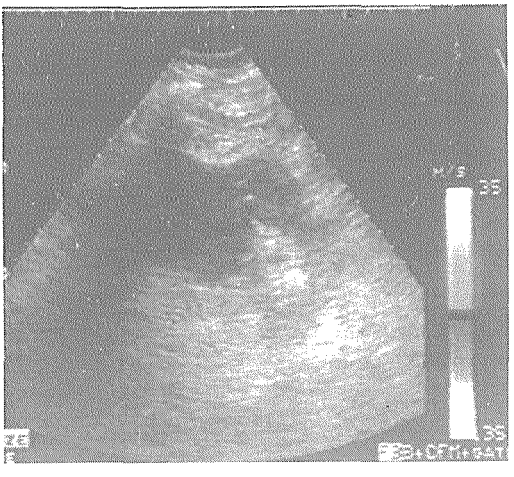

Figure 2. Conventional US finding of hypoechoic, solid, exophytic renal mass – renal cell carcinoma.

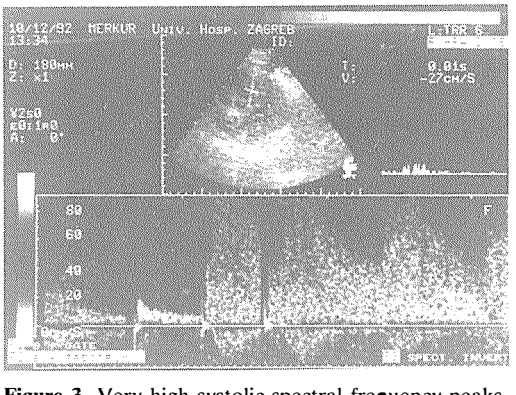

Figure 3. Very high systolic spectral frequency peaks, higher than 3 kHz, with phenomenom of aliasing, obtained in the vessel on the margin of a renal cell carcinoma.

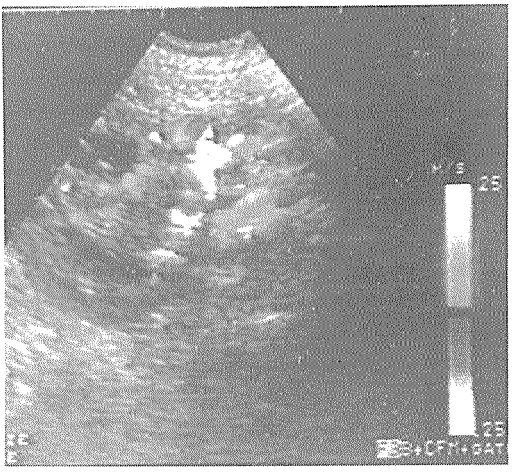

Figure 4. Color-Doppler US image of abundant vascularization within and on the margin of the renal mass – renal cell carcinoma.

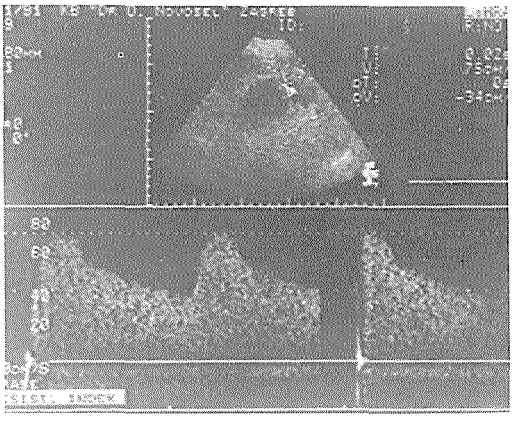

Figure 5. Spectral analysis of the vessel within the RCC – low pulsatility waveform, with high diastolic flow and low resistance index (RI = 0.47).

Thirty-six out of 39 patients had at least one abnormal Doppler finding, either peak systolic shift in the artery on the margin of the tumor higher than 3 kHz or the RI of 0.55 or lower in the artery within the tumor. Therefore, the overall sensitivity of CD US and spectral analysis in the detection of pathologic flow in RCC, using one of two proposed criteria was found to be 92.3%.

Fourteen patients with small renal tumors with the largest diameter below 4 cm were analyzed as a separate group, using two proposed

criteria for abnormality. At least one of two abnormal Doppler findings were observed in 13 patients. Therefore, the sensitivity of CD US and spectral analysis for detection of pathological flow characteristic for RCC was 92.9% in patients with small renal tumors. In one case without detectable abnormality the tumor was avascular on selective DSA examination.

Discussion

RCC is most commonly seen in the sixth and seventh decades of life, with a 3 to 1 male to female ratio. Patients most frequently present with hematuria, palpable mass and flank pain. Widespread metastases are also common, especially to lungs, bones, lymph nodes, liver, adrenal glands and brain.[7]

RCC presents with a wide spectrum of US findings that range from a predominantly cystic to a solid mass. The most common sonographic pattern is echo-complex. However, approximately 30% of RCC appear as hypoechoic lesions and there is possibility of mistaking carcinoma for a benign cyst.[8] When a lesion is big and has infiltrated renal vein, IVC or lymph nodes, conventional US diagnosis of malignancy is relatively simple. However, small RCC are often difficult to diagnose and differentiate from benign lesions (hypertrophied column of Bertin, angiomyolipoma, oncocytoma, inflammatory mass, complex cyst) with conventional US, as well as other imaging modalities.[9–11]

Doppler US of intrarenal arteries has been extensively used for analysis of flow in transplanted kidneys and in native kidneys, for diagnosis of renal artery stenosis, renal obstruction and parenchymal kidney diseases.[5,12–15] Doppler US has been also suggested as a way of further chraracterizing malignant from benign lesions.[16] The advent of color-Doppler, in our experience, further enhances the value of Doppler in evaluating malignant neovascularization.

A few studies have shown high Doppler shift frequencies in vessels along the margin of renal tumors.[17–19] Our results confirm these findings. The recorded peak frequencies are dependent on the transducer frequencies and cannot be compared between scanners with different transducers. The cutoff value of 3 kHz that we have used in this study is equivalent to the velocity of 80 cm/s, which is higher value than in normal intrarenal arteries and main renal arteries. The usage of even higher cutoff value of 4 kHz would have reduced our sensitivity for approximately 20%, without increase in specificity when normal examinees from the control group are considered. High frequency shifts in arteries along the tumor margins have been generally attributed to arteriovenous shunts, found in hypervascularized RCCs.[17–19] Our results confirm these findings. In addition, we have observed very low vascular resistance in arteries within the tumor itself, and we were able to visualize these vessels in very high proportion of patients. RI index values reflect renal vascular resistance and RIs were statistically significantly lower in arteries within the tumor (mean 0.498) in comparison with intrarenal arteries of normal examinees (mean 0.597). These pathological vessels in RCC lack muscular elements in their walls, which is the presumed cause of low resistance.[20] However, there is a relatively small, but significant proportion of hypovascular or avascular RCCs (cca 15%) and in these tumors CD US signals could not have been found. However, it is hard to diagnose these tumors with CT and DSA, as well.

With continuous improvements in US, CT and MRI the dilemma of what to do with the small, less than 3 cm, renal parenchymal lesion has become prevalent. Frequently, a small renal mass is discovered incidentally during routine US or CT abdominal examination. These lesions are frequently of indeterminate nature, as they are hypoechoic on US and measure 25 HU or more on CT.[21] Bosniak suggested that in the elderly or those with terminal disease, these small lesions can be ignored.[22] However, in others the use of a multimodality approach including gadolinium-enhanced MRI may be indicated. We have shown that CD US and spectral analysis yield high sensitivity and specificity in the diagnosis of pathological vasculari-

zation in the RCC smaller than 4 cm in size.

With the exception of avascular or hypovascular RCC, CD US and spectral analysis have high sensitivity and specificity in detecting pathologic vascularization of RCC, regardless of its size. Since it is a noninvasive and relatively simple method we believe it should be included in the diagnostic algorithm as a first method for suspected renal mass after conventional US. This method has same or higher sensitivity and specificity in detecting pathologic vascularization in RCC in comparison with conventional CT and selective DSA.[23,24]

We are conducting further investigation for differentiation of benign and malignant renal masses with CD US. It seems that angiomyolipoma and oncocytoma lack Doppler spectral findings observed in RCC. Also, the differentiation of column of Bertin from hypervascularized tumor is quite straightforward. The problem in differential diagnosis are inflammatory masses that may also have abnormal vascularity along the margin of the mass. In these cases fine-needle aspiration biopsy is very useful in the differentiation of these conditions. Also, some other malignancies that are not hypervascularized, like transitional-cell tumors of renal pyelon seem to be hard to diagnose with CD US and spectral analysis.

Although further studies are necessary to assess the clinical usefulness of this method in differentiating benign and malignant renal masses, it is obvious that CD US has a very high sensitivity in detecting pathologic vascularization in RCC, since these tumors are in the majority of cases hypervascular. Regardless of possibility of false-positive diagnosis in the case of inflammatory mass, Doppler findings of high frequency shifts along the kidney mass margin and/or low resistance in arteries within the mass should alert the clinician for a very high probability of RCC.

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Role of CT guidance in the biopsy of the spine and paravertebral soft tissue

Tamás Puskás

Department of Radiology, Markusovszky Teaching Hospital, Szombathely, Hungary

CT is the only imaging system which can visualise the vertebral bodies and the adjacent soft tissues at the same time. Contrary to conventional fluoroscopy-guided skeletal biopsy, CT guidance results in more accurate and safer performance of the intervention. Thereby, the complication rate of these procedures can be diminished.

Key words: spinal diseases – radiography; biopsy; computed tomography, x-ray

Introduction

Earlier two-directional radiography and conventional tomography were the only possible imaging modalities in the diseases of the vertebrae. In this way the paravertebral soft tissues could not be identified with safety. Among the modern imaging systems, CT and MR can visualise the vertebrae and the adjacent soft tissues at the same time. Representing the axial plane, CT scans have defined the exact position of the lesion, resulting in better guidance of diagnostical approach.

Materials and methods

The first paper about CT-guided intervention was issued in 1976.[1] From that time on a lot of publications have emphasised the advantages of CT guidance, and development of interventional procedures.[2,3] We have performed CT examinations in our hospital by a 3rd generation Siemens Somatom DRH equipment since 1989. The CT-guided intervention was introduced in 1991. The total number of procedures in the last 3 years have amounted to 136, including 16 biopsies in patients affected by diseases of vertebrae and paravertebral soft tissue. We are the first among Hungarian radiologists who have performed CT-guided biopsies in vertebral and paravertebral diseases. For the biopsy of bone structures we use a Jamshidi needle, in case of soft tissue biopsy, it is carried out by a 14 G Uro-cut needle. Before intervention the position and extent of the lesion, and the exact point of biopsy are determined. The patient is in prone position. We use local anaesthesia in adults, a short general anaesthesia is needed in children.

Correspondence to: Tamás Puskás MD, Department of Radiology, Markusovszky Teaching Hospital, Szombathely, Hungary, H-9701.

UDC: 616.711-073.756.8

Results

As to the site of 16 interventions we performed the biopsy of soft tissue in 7, and of vertebral

body in 9 patients. We had to repeat the intervention in 2 patients, because the specimens were not sufficient for histology. In all other cases the first procedure proved to be successful. We present the patients, the types of biopsy and the final diagnosis in Table 1. We marked the repeated biopsies with an asterisk (*).

Case reports

1. A 56-year-old female patient suffered from lumboischialgia. On myelography the contrast material stopped at the level of LIII-IV. The emergent CT examination revealed a large soft tissue mass at the level of LIV, destroying the vertebral arch, and invading to the spinal canal. The CT-guided biopsy verified a metastatic lesion of a malignant thyroid tumour (Figure 1).

2. A 55-year-old female patient was admitted to our hospital because of weight loss and abdominal pain. In her history an ovarian tumour and a gynaecological surgery were mentioned. Ultrasonography showed a large cystic

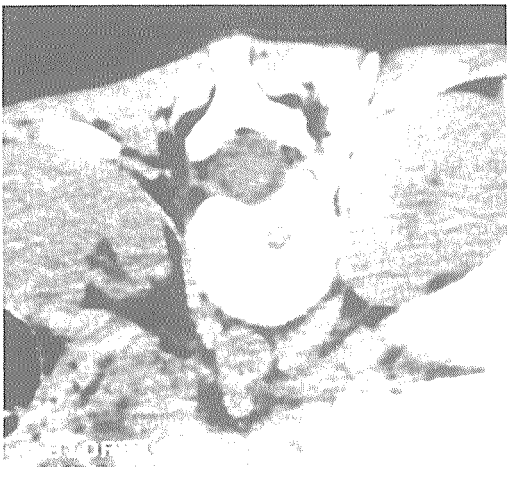

Figure 1. Biopsy of a large soft tissue mass invading the spinal canal at the level of L IV.

Table 1. Types of biopsy and final diagnosis.

Number	sex	age	Site of biopsy	Result
1	F	50	body of LIV	unsuccessful
2	F	56	paravertebral soft tissue	metastatic thyroid tumour
3*	F	50	body of LIV	tuberculous inflammation
4	M	45	body of LII	metastatic testicular tumour
5	F	57	body of LIV	metastatic breast tumour
6	M	53	paravertebral soft tissue	sarcoma
7	F	81	paravertebral soft tissue	unsuccessful
8*	F	81	paravertebral soft tissue	inflammation-abscess
9	F	55	paravertebral soft tissue	metastatic ovarian tumour
10	F	11	body of ThXII	tuberculous inflammation
11	F	54	body of ThX	metastatic breast tumour
12	M	45	paravertebral soft tissue	metastatic testicular tumour
13	M	72	body of CVII	metastatic colon tumour
14	F	64	body of LI	metastatic lung tumour
15	M	38	body of ThXI	tuberculous inflammation
16	M	71	paravertebral soft tissue	metastatic pancreas tumour

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Evaluation of hypertrophic pulmonary osteoarthropathy by bone scintigraphy in patient with carcinoma of the lung

Dražen Huić,[1] Damir Dodig,[1] Mirjana Huić,[2] Ivan Škorak,[2] Mirjana Poropat[1]

[1]Department of Nuclear Medicine and Radiation Protection, [2]Department of Internal Medicine, University Hospital Rebro, Zagreb, Croatia

The authors described a case of a 61-year-old heavy smoker with some symptoms of hypertrophic pulmonary osteoarthropathy (HPO) and suspected pulmonary malignancy.
The bone scan demonstrated diffuse bony involvement of the long bones of the lower limbs raising question about possible metastatic bone disease. The knees and ankles were not affected.
The plain radiographs of the bones were normal but the chest radiograph showed right hilus deformation. Transpleural biopsy revealed a bronchogenic adenocarcinoma. Typical radionuclide finding of HPO without bone destruction on radiographs ruled out metastatic bone disease.

Key words: secondary hypertrophic osteoarthropathy, radionuclide imaging, bronchogenic carcinoma, bone scintigraphy

Case report

The 61-year-old man was admitted complaining of worsening cough, rapid weight loss, digital clubbing, but without joint swelling or tenderness. The terminal phalanges were enlarged, and there was loss of the normal nail-to-cuticle angle (Figure 1). The sedimentation rate, white blood cell count and alkaline phosphatase level were slightly elevated.

The whole body scintigraphy was performed because of suspected metastatic malignant disease. Scans, obtained 3 hours after injection of 740 MBq of Tc-99m pyrophosphate, showed

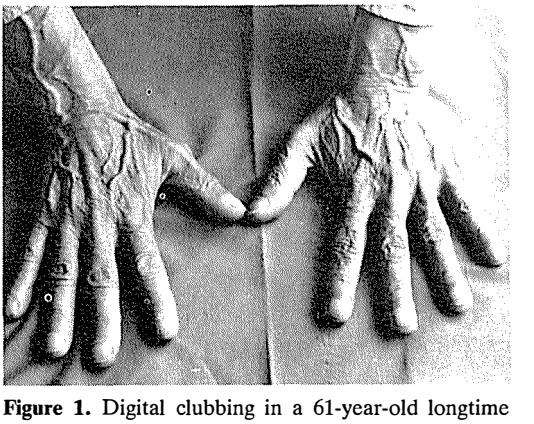

Figure 1. Digital clubbing in a 61-year-old longtime smoker. The terminal phalanges are enlarged, and there is loss of the normal nail-to-cuticle angle.

Correspondence to: Dražen Huić, M.D., Department of Nuclear Medicine and Radiation Protection, University Hospital – Rebro, Kišpatićeva 12, 41000 Zagreb, Croatia. Fax: +385 41 23 57 85.

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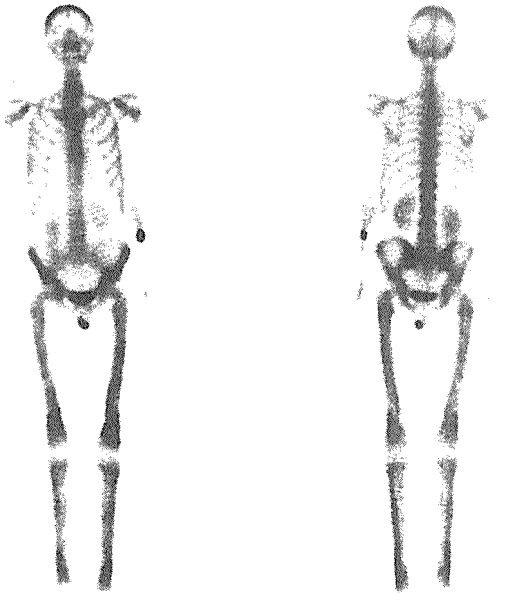


Figure 2a. The whole body scan, obtained 3 hours after radionuclide injection, shows diffuse increased radiotracer uptake in all long bones of the lower limbs.

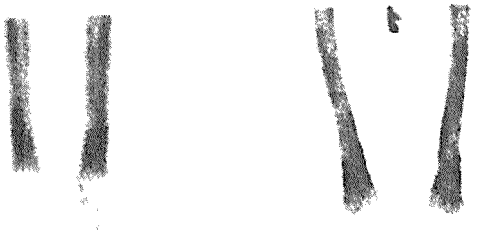


Figure 2b. The delayed static images of both lower extremities reveal prominent uptake pericorticaly in the distal parts of the long bones, which is typical for hypertrophic osteoarthropathy and differentiates it from metastatic bone disease.[1, 2]

diffuse increased radiotracer uptake in all long bones of the lower limbs (Figure 2a). The knees and ankles were not affected.

The detailed static images of both lower extremities revealed most prominent uptake pericorticaly in the distal parts of the long bones (Figure 2b).

The radiographs of the lower limbs did not demonstrate any bone destruction or abnormalities suggestive of hypertrophic pulmonary osteoarthropathy (HPO) (Figure 3a, b).

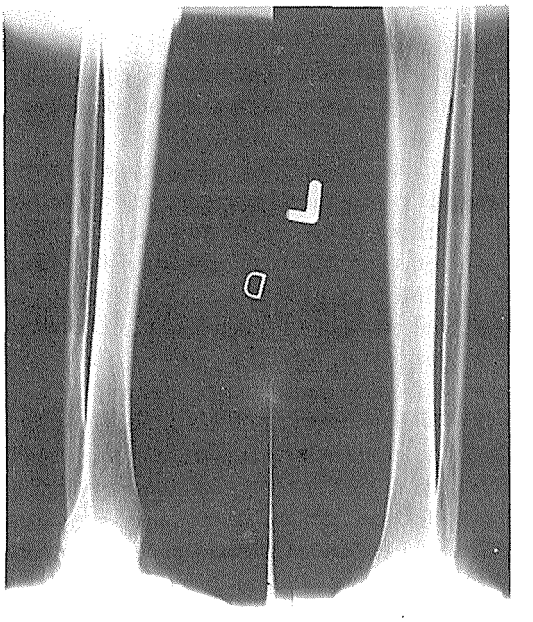
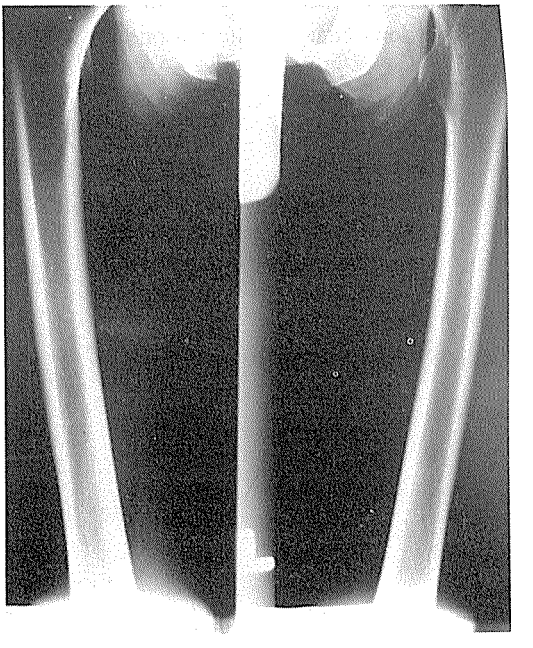


Figure 3a, b. The radiographs of the lower limbs do not show the characteristic periosteal elevation of hypertrophic osteoarthropathy.[3]



The chest radiograph revealed right hilus deformation and a lesion in right upper lobe was suspected. Finally, transpleural biopsy revealed a bronchial adenocarcinoma.

Discussion

Detection of HPO with 99 m-Tc-phosphate complexes has been often reported in the past.[1–5]

The incidence of HPO in patients with bronchogenic carcinoma is approximately 10 % and it is particularly important to distinguish HPO and metastatic bone disease in radionuclide images. Most prominent uptake pericorticaly in the distal parts of the long bones, as obtained in our patient, is typical for HPO and differentiates it from metastatic bone disease.[4]

The radiographs of the lower limbs did not show the characteristic periosteal elevation of HPO,[6] not either bone destruction, what is typical for metastases.

Unusual radionuclide scans of HPO are not uncommon,[3] but we found our patient interesting because of non-affected joints, which are almost always affected. Probably we can say this is the case of hypertrophic osteopathy.

Unfortunately, patient had metastases in a few other organs and he was not suitable for an operation. That was the reason why a bone biopsy was not performed, but the typical radionuclide finding without bone destruction on radiographs ruled out metastatic bone disease.

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Improved therapeutic effect of electrochemotherapy with cisplatin by intratumoral drug administration and changing of electrode orientation for electropermeabilization on EAT tumor model in mice

Maja Čemažar,[1] Damijan Miklavčič,[2] Lojze Vodovnik,[2] Tomaž Jarm,[2] Zvonimir Rudolf,[1] Borut Štabuc,[1] Tanja Čufer[1] and Gregor Serša[1]

[1] Institute of Oncology, Ljubljana, [2] University of Ljubljana, Faculty of Electrical and Computing Engineering, Laboratory of Biocybernetics, Ljubljana, Slovenia.

Antitumor effectiveness of cisplatin can be improved either by intratumoral administration of the agent or by increased drug delivery into the cells by exposing the tumor to short intense electric pulses. Electric pulses increase plasma membrane permeability (electropermeabilization) of tumor cells and thus allow the chemotherapeutic agent intracellular access. This combined use of electric pulses and chemotherapy is termed electrochemotherapy. Also, we recently demonstrated that efficacy of electrochemotherapy can be improved by changing of electrode orientation for electropermeabilization. Therefore, the aim of this preliminary study was to determine whether intratumoral cisplatin administration and changing of electrode orientation for electropermeabilization can improve therapeutic effect of electrochemotherapy. For this purpose electrochemotherapy with intratumoral versus intravenous cisplatin administration and electrochemotherapy with train of 8 electric pulses versus two trains of 4 pulses, given perpendicularly to each other (4 + 4 pulses), were tested on EAT subcutaneous tumors in mice. Electrochemotherapy with intratumoral cisplatin administration was more effective than electrochemotherapy with intravenous cisplatin administration. In addition, antitumor effectiveness of electrochemotherapy with intratumoral cisplatin administration was improved with changing of electrode orientation (4 + 4 pulses), since with this treatment 18 % of mice were cured in contrast to other treatment combinations tested, where only some partial responses were observed.

Key words: neoplasms, experimental-therapy; cisplatin; electric stimulation therapy; cell membrane permeability

Correspondence to: Gregor Serša, Ph.D., Institute of Oncology, Department of Tumor Biology, Zaloška 2, 61105 Ljubljana, Slovenia. Tel.: + 386 61 323 063 ext. 2933; fax.: + 386 61 131 41 80; E-mail: gsersa@mail.onko-i.si

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Introduction

Cisplatin is chemotherapeutic agent widely used against variety of malignancies. Like all chemotherapeutic agents, its effectiveness is limited by normal tissue toxicity.[1] One of the ways to reduce toxicity to normal tissues is local, intratumoral (i.t.) cisplatin administration. By this

route of administration higher cisplatin concentration in the tumor and lower concentration in the organism is achieved, and thus therapeutic gain is increased.[2]

Also, one of the ways of potentiating cytotoxic action of chemotherapeutic drugs is increased drug delivery into the tumor cells. This can be done by use of short intense electric pulses, which nonselectively increase plasma membrane permeability (electropermeabilization), without impairing cell viability and thus allowing chemotherapeutic drugs to diffuse into the cells and act on their intracellular targets.[3–10] This principle of increased drug delivery was termed electrochemotherapy. Electrochemotherapy with bleomycin and cisplatin was elaborated *in vitro, in vivo* and in clinical trials.[8, 11–22]

In all of the studies on electrochemotherapy reported electric pulses were delivered in one direction.[11, 12, 14–17, 19, 21, 22] However, according to our observations on electrochemotherapy with bleomycin, therapeutic response to treatment can be improved if train of 8 electric pulses used for electropermeabilization is split into two and the second train given perpendicularly to the first one (4 + 4 pulses).[23] By this changing of electrode orientation whole tumor mass is encompassed by electrodes and more tumor cells are exposed to electric field over critical threshold value for effective electropermeabilization.

The aim of this preliminary study was to determine whether intratumoral administration of cisplatin and changing of electrode orientation for electropermeabilization can improve therapeutic effect of electrochemotherapy with cisplatin on EAT tumor model in mice. For this purpose we compared electrochemotherapy with i.t. versus intravenous (i.v.) cisplatin administration and electrochemotherapy with train of 8 electric pulses given in one direction versus two trains of 4 pulses given perpendicular to each other for electropermeabilization. Tumor response to electrochemotherapy was assessed by tumor growth delay and therapeutic responses to treatment.

Materials and methods

Drug formulations

Cisplatin (Platimit) was obtained from Pliva (Zagreb, Croatia) as crystalline powder and dissolved in sterile H_2O at a concentration 1 mg/ml. The final cisplatin dose (1 mg/kg) was prepared in 0.9 % NaCl solution. The cisplatin solutions were injected systemically, i.v. into the lateral tail vein of the mice or locally, i.t.. Injection volume was 0.02 ml/g body weight for i.v. administration and 0.1 ml/tumor for i.t. administration. For i.t. cisplatin administration "fan" pattern was used which facilitates drug distribution throughout the tumor.[2] Cisplatin solution was injected while the needle was slowly withdrawn. For each experiment fresh cisplatin solution was prepared.

Animals

In the experiments CBA mice of both sexes, 8–12 weeks old, weighing 20–30 g, in good condition, without fungal or other infections were used. Mice were purchased from the Institute of Pathology, University of Ljubljana and were kept at constant room temperature (24 °C) under natural day/night light cycle, fed with standard mouse chow and tap water *ad libitum*.

Tumor model

Ehrlich ascites tumor (EAT) cell suspension, syngeneic to CBA mice was prepared from ascitic form of the tumor. Solid subcutaneous tumors were initiated in the right flank of the mice by injection of 5×10^6 EAT cells. The viability of the cells injected was over 95 % as determined by trypan dye exclusion assay. After 6–8 days when the tumors reached approximately 40 mm^3, mice were randomly divided into experimental groups comprising 5–11 mice and subjected to specific treatment protocol.

Electrochemotherapy protocol

Electric pulses were delivered through two parallel plate electrodes 8 mm apart (two stainless

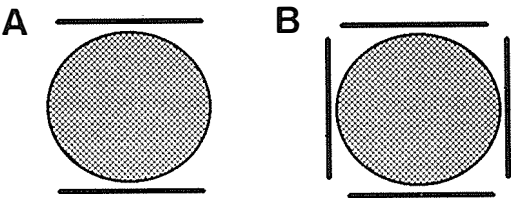

Figure 1. Schematic presentation of the electrode orientation at the two electric pulses treatment protocols. A. Electric pulses were given by two electrodes positioned on the two opposite margins of the tumor in the train of 8 consecutive pulses; B. In the protocol B the 8 pulses were split into two trains of 4 pulses with one second interval (4 + 4 pulses). Each train of 4 pulses was given to the tumor by the placement of the electrodes at the opposite margins of the tumor in the two perpendicular directions.

steel strips with rounded corners, 7 mm in width) placed at the opposite margins of the tumor. Conductive gel was used to assure good contact between electrodes and the skin. Eight square wave pulses; 100 μs pulse width, repetition frequency 1 Hz and 1040 V amplitude were generated by electropulsator Jouan GHT 1287 (St. Herblaine, France). Tumor bearing mice were treated either with 8 square wave pulses given in one direction or with 8 pulses split into two train of 4 pulses. In this experimental group second train of 4 pulses was given perpendicularly to the first one (Figure 1). Cisplatin was injected either i.v. or i.t. In electrochemotherapy with i.v. cisplatin administration mice were treated with electric pulses 3 min after cisplatin injection and in electrochemotherapy with i.t. injection mice were treated with electric pulses 10 min after i.t. cisplatin injection. Mice in control group and in electric pulses groups were injected with 0.9 % NaCl solution instead of cisplatin solution.

Tumor response and statistical analysis

Tumor growth was followed every 2 days by measuring three mutually orthogonal diameters (e_1, e_2, e_3) with vernier calliper and tumor volume calculated by the formula $e_1 \times e_2 \times e_3 \times \pi/6$. From the measurements, the arithmetic mean (AM) and standard error of the mean (SE) were calculated for each experimental group, pooled from two separate experiments. Tumor doubling time (DT) was determined as time in days for tumors to double their volume from the beginning of the treatment. For each individual tumor in all experimental groups DT and tumor growth delay from the DT of each individual tumor in experimental groups minus mean DT of control group were calculated.

Therapeutic response was scored according to WHO guidelines as progressive disease (PD) if tumor volume increased, no change (NC) if tumor volume reduced less than 50 %, partial response (PR) if tumor volume reduced more than 50 % and complete response (CR) if tumor became unpalpable. Mice, tumor free 100 days after the treatment, were termed as cured and were not included in tumor growth curves and tumor growth delay calculations.

The significance of the differences between the mean DT and tumor growth delay of the experimental groups was evaluated with Newman-Keuls method for multiple comparison after one way analysis of variance was performed and fulfilled. Levels of P less than 0.005 were taken as statistically significant.

Results

In this study electrochemotherapy with i.t. cisplatin administration was compared to electrochemotherapy with i.v. administration. In addition, electrochemotherapy with train of 8 electric pulses given in one direction was compared to electrochemotherapy with two trains of 4 pulses given perpendicularly to each other (4 + 4 pulses).

Cisplatin treatment alone as single treatment was more effective after i.t. administration than after i.v. administration. Intratumoral cisplatin administration had marked antitumor effect, tumor growth delay was significantly prolonged compared to i.v. cisplatin treated group (Table 1, Figure 2).

Electric pulses treatment alone as single treatment, in both orientations (8 pulses and 4 + 4

Table 1. Antitumor effectiveness of electrochemotherapy with 1 mg/kg cisplatin. Comparison of i.t. versus i.v. cisplatin administration and train of 8 pulses given in one direction versus two times of 4 pulses (4 + 4 pulses) given perpendicularly to each other for electropermeabilization.

Experimental groups	n	DT[2] (days)	Tumor growth delay[3] (days)	Therapeutic response[4] (n)	Cures (n, %)
Control	21	4.1 ± 0.3			0
Cisplatin i.v.	14	5.1 ± 0.3	1.0 ± 0.3	PD(14)	0
Cisplatin i.t.	10	13.5 ± 1.6	9.4 ± 1.6	PD(8)/NC(2)	0
Electric pulses 8 p.	15	6.5 ± 0.5	2.4±0.5	PD(15)	0
Electric pulses 4+4 p.	10	6.4 ± 0.8	2.3 ± 0.8	PD(10)	0
ECT[1] 8p.-i.v. cisplatin	16	8.1 ± 0.6	4.0 ± 0.6	PD(14)/NC(2)	0
ECT 4+4p.-i.v. cisplatin	10	10.4 ± 1.0	6.3 ± 0.8	PD(4)/NC(6)	0
ECT 8p.-i.t. cisplatin	11	17.8 ± 1.4	13.7 ± 1.4	NC(7)/PR(4)	0
ECT 4+4p.-i.t. cisplatin	11	20.5 ± 1.1	16.4 ± 1.1	NC(4)/PR(5)/CR(2)	2 (18 %)

[1] ECT – electrochemotherapy
[2] DT – tumor doubling time (AM ± SE)
[3] Tumor growth delay compared to control group (AM ± SE).
[4] Therapeutic response to treatment was scored according to the WHO guidelines as PD-progressive disease; NC – no change; PR – partial response; CR – complete response.

pulses), was equally effective and had moderate effect on tumor growth (Table 1, Figure 2).

Electrochemotherapy treatment with i.v. cisplatin administration was more effective than treatment with i.v. cisplatin alone as single treatment, demonstrated by significantly prolonged tumor growth delay (Table 1, Figure 2). Changing of electrode orientation (4 + 4 pulses) for electropermeabilization did not potentiate antitumor effectiveness of i.v. cisplatin administration compared to treatment with 8 electric pulses given in one direction. The small difference between the two electrochemotherapy treatment protocols with i.v. cisplatin administration was observed only in the first 4 days after the treatment. Electrochemotherapy with i.v. cisplatin administration and 4 + 4 pulses arrested tumor growth in the first 4 days after the treatment, while after electrochemotherapy with i.v. cisplatin administration and 8 pulses no arrest of the tumor growth was observed.

Electrochemotherapy with i.t cisplatin administration was more effective than treatment with i.t. cisplatin treatment alone as single treatment, demonstrated by significantly prolonged tumor growth delay (Table 1, Figure 2). Changing of electrode orientation for electropermeabilization (4 + 4 pulses) was more effective than treatment with 8 pulses in one direction. Electrochemotherapy with 8 pulses resulted in 36 % of PR, whereas changing of electrode orientation (4 + 4 pulses) resulted in higher percentage of PR (45 %) and also in 18 % of cured mice.

Electrochemotherapy with i.t. cisplatin administration was more effective than electrochemotherapy with i.v. cisplatin administration (Table 1, Figure 2). Specifically, tumor growth delay after electrochemotherapy with i.t. cisplatin administration was significantly prolonged compared to tumor growth delay after electrochemotherapy with i.v. cisplatin administration. Also, electrochemotherapy with i.t. cisplatin administration resulted in high percentage of PR and CR, in contrast to electrochemotherapy with i.v. cisplatin administration where only NC therapeutic response was recorded.

Discussion

This study shows that i.t. cisplatin administration and 4 + 4 pulses given perpendicularly to each other for electropermeabilization improve therapeutic effect of electrochemotherapy with 1 mg/kg cisplatin on EAT tumor model in mice.

In our previous study on three different tumor models in mice (EAT, SA-1 fibrosarcoma and B 16 melanoma) antitumor effectiveness of electrochemotherapy with i.v. cisplatin administration was tested with respect to electric pulses amplitude, cisplatin dose and sequencing and timing of cisplatin administration relative to electric pulses application.[22] In that study

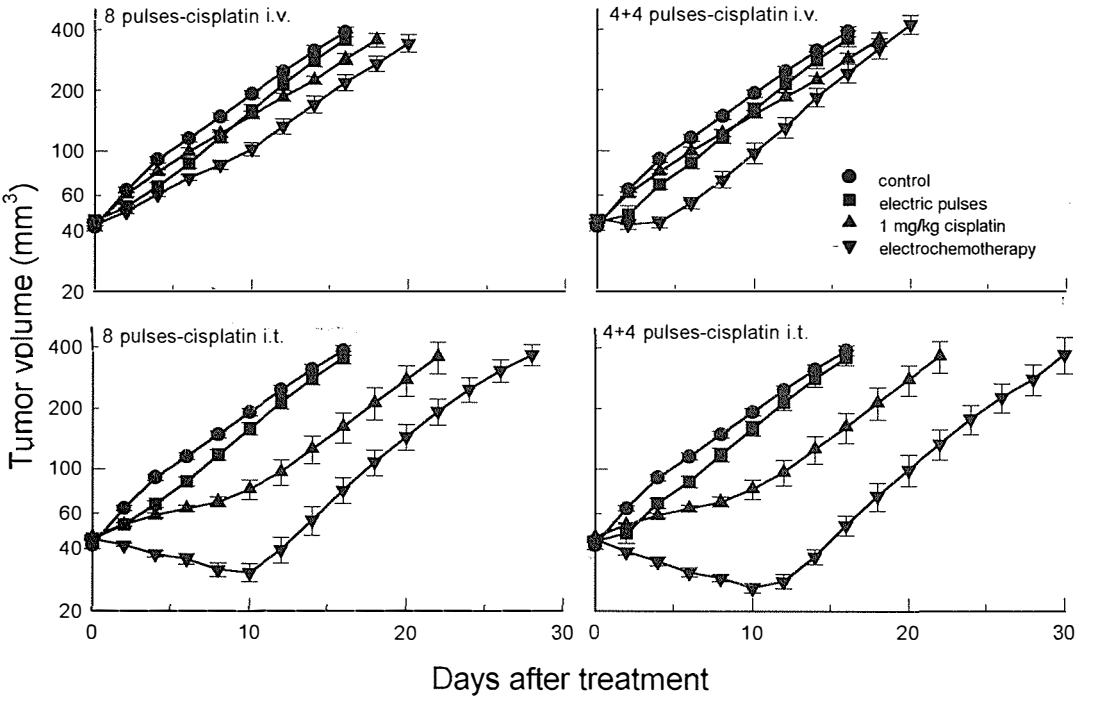

Figure 2. Growth curves of EAT tumors after treatment with 1 mg/kg cisplatin administered either i.v. or i.t. and/or electric pulses (8 pulses or 4 + 4 pulses; pulse length 100 μs, repetition frequency 1 Hz, pulse amplitude 1040 V, electrode distance 8 mm). In electrochemotherapy group with i.v. cisplatin administration mice were treated with cisplatin 3 minutes before electric pulses application and in electrochemotherapy with i.t. cisplatin administration 10 minutes before electric pulses. Values are AM ± SE for 9–21 mice.

antitumor effectiveness of electrochemotherapy with i.v. cisplatin administration was demonstrated by prolonged tumor growth delay compared to cisplatin treatment alone. Also, electrochemotherapy with 8 mg/kg (the highest dose tested) resulted in 14% of cured mice bearing B 16 melanoma tumors. However, no mice bearing EAT or SA-1 tumors were cured. In addition, in our previous study on EAT tumor model we have demonstrated that changing of electrode orientation for electropermeabilization improves therapeutic effect of electrochemotherapy with bleomycin.[23] Therefore, in this preliminary study both i.t. cisplatin administration and changing of electrode orientation for electropermeabilization were tested for ability to improve therapeutic effect of electrochemotherapy with cisplatin.

For electrochemotherapy with i.v. cisplatin administration 3 minute time interval between the cisplatin administration and electric pulses application was chosen. In our previous study we demonstrated that at this time interval the most pronounced antitumor effect of electrochemotherapy with cisplatin is achieved.[22] Also, for electrochemotherapy with i.v. bleomycin it was demonstrated that the best antitumor effect is achieved when bleomycin is injected 3 minutes before electric pulses application.[21] Therefore, it seems that both chemotherapeutic drugs have similar accumulation properties in tumors of mice. According to the experiments performed on electrochemotherapy with i.t. bleomycin administration, where the best antitumor effect was achieved with 10 minute interval (Heller, personal communication), the same time interval (10 minutes) was used for electrochemotherapy with i.t. cisplatin administration. However, a time response relationship studies for electrochemotherapy with i.t. cisplatin administration need to be performed to confirm the choice of timing.

The dose of cisplatin used in our preliminary study was a subtoxic dose (toxic dose 10-15 mg/kg), well tolerated by the animals, which injected systemically did not induce significant antitumor effect. The results demonstrate that electrochemotherapy with i.v. cisplatin administration was moderately effective and suggest that cisplatin concentration achieved in the tumor is not sufficient for pronounced antitumor effect. However, electrochemotherapy with i.t. cisplatin administration was more effective than electrochemotherapy with i.v. cisplatin administration at the same dose of the drug. Antitumor effectiveness of electrochemotherapy with i.t. administration is comparable to electrochemotherapy with i.v. administration, but in 8-fold higher dose.[22] In addition, electrochemotherapy with i.t. cisplatin administration and 4 + 4 pulses for electropermeabilization resulted in some cured mice with long lasting CR (18 %), indicating that with increased cisplatin concentration in the tumor and changing of electrode orientation more clonogenic tumor cells are electropermeabilized and thus also sterilized by the chemotherapeutic drug.

In conclusion, electrochemotherapy with i.t. cisplatin administration and 4 + 4 pulses given perpendicularly to each other for electropermeabilization improves therapeutic effect of electrochemotherapy on EAT tumors in mice. Therefore, electrochemotherapy with i.v. cisplatin administration can be used as adjunct to ongoing cisplatin-based chemotherapy in patients who have tumor lesions accessible to application of short intense electric pulses, so that antitumor effectiveness of chemotherapy is potentiated locally. On the other hand, since electrochemotherapy with i.t. cisplatin administration is more effective than electrochemotherapy with i.v. cisplatin administration, it could be used as a single treatment modality.

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Radiol Oncol 1995; 29: 128-41.

Early stage Hodgkin's disease: the remaining challenge after a "success story" An overview of the thirty years' experience of the Florence Radiotherapy Department

Stefano M. Magrini,[1] Enrico Cellai,[1] Maria G. Papi,[1] Pietro Ponticelli,[2] Susanna Sulprizio,[1] Maurizio Pertici,[1] Rita Bagnoli,[1] Gianpaolo Biti[1]

[1]Radiotherapy Unit of the Clinical Physiopathology Department of the University of Florence, Italy
[2]Radiotherapy Department, Arezzo, Italy

The experience of the Florence Radiotherapy Department with early stage Hodgkin's disease (HD) is reviewed, along with an analysis of the literature on this subject. In particular, the issue of the reduction of the diagnostic and therapeutic "burden" in the more favourable cases and of the identification of "high risk" cases, to be submitted to more aggressive treatment, is discussed.

Key words: Hodgkin's disease-radiotherapy

Introduction

Even if the impact of the present time oncology on cancer mortality in adults is rather unsatisfactory for the majority of malignant neoplasms, including the more frequent ones, clear-cut progresses have been made as far as Hodgkin's disease is concerned.[1, 2] The cause specific survival rate for all the patients with Hodgkin's disease (HD) treated in Florence after 1970 is much higher than that, relative to patients treated before 1970 (20-year survival: 74 % vs 46 %). Similar gains in survival have been obtained in almost all major Institutions and have been attributed to a better understanding of the natural history of the disease, to a more accurate staging (lymphangiography, laparotomy, with splenectomy) and to rational use of radiotherapy and chemotherapy.

On the other hand, many patients have been exposed to a variety of possible long term complications of the treatment given, *even if they were cured of their disease.* The data collected by the International Database on Hodgkin's Disease (IDHD), regarding over 14000 patients treated in many Institutions, show that about 6 % of the deaths are directly attributable to the complications of the treatment. Moreover, some of the deaths caused by other diseases

Correspondence to: Stefano M. Magrini, M.D., Radiotherapy Unit of the Clinical Physiopathology, Department of the University of Florence, Policlinico di Careggi, Viale Morgagni 85, 50134 Florence, Italy.

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(24 % of the total number of deaths) might also be linked with the therapy given for HD (e.g., second neoplasms, cardiovascular events).[2] Therefore, a remarkable effort has been devoted, in the last years, to the study of the late effects of the treatment; as a consequence of these studies, some major Institutions are presently aiming at a reduction in the "therapeutic burden", whenever possible without hampering the good survival results already obtained.

However, the IDHD data also show that almost 70 % of the deaths after the treatment of HD are caused by the disease itself. Therefore, an effort is also needed to identify the subsets of patients to be treated more aggressively to obtain the cure of the disease. The attempts to reach this second goal are based on the study of "old" and "new" prognostic factors and also on the research on new therapeutic tools.

Along with an analysis of the literature, we will present in this review data derived from the Florence Radiotherapy Department experience, regarding about 1300 HD patients, consecutively treated with radical aim since 1960. Long term data coming from a single Institution may help to clarify the questions how to successfully address the ultimate challenge: to increase the *overall* survival rates of patients treated for HD. A reduction in the incidence of treatment related deaths and an increase in the proportion of the "high risk" patients who can be cured are, in fact, two faces of the same problem.

Questions regarding prognostic factors, staging procedures and therapy: tailoring the diagnostic and therapeutic "burden" according to the different clinical features of the disease

Sixty to seventy per cent of the patients with HD are defined, after a thorough clinical staging, as having Stage I and II disease. The proportion of Clinical Stage (CS) I and II patients in different hospital series is shown in Table 1.[2–5]

The majority of these patients are treated with radiotherapy (RT) alone. However, different treatment philosophies stand behind this fact. The choice of the treatment modality depends also from the staging procedures adopted.

Table 1. Proportion of patients with Clinical Stage I–II disease in different series from the literature.

Institution, Ref.	N. of patients	N. with CS I–II disease	%
Stanford,[3]	1660	1014	61 %
Princess Margaret,[4]	790	466	60 %
Royal Marsden,[5]	732	455	61 %
IDHD,[2]	14225	9041	64 %
Florence	1121*	743	66 %

* treated 1960–88

In fact, some Institutions submit all the CS I–II patients to surgical staging, then treating with RT alone those without occult abdominal involvement and, in some cases, those with only splenic and/or upper paraaortic nodes involvement (pathological stage IIII). For example, Mauch and co-workers reported the experience of the Joint Center for Radiation Therapy in Boston with 315 Pathological Stage (PS) IA and IIA HD patients: overall cause specific survival at 14 years was 93 %, primary treatment having been mantle (M) plus lumbar bar (LA) radiotherapy alone.[6] Similar results have been observed in 232 PS I–IIA patients treated at our Institution approximately in the same period (1970–1988) and with the same modality (M + LA radiotherapy): actuarial overall cause specific survival was 88 % at ten years and 85 % at 20 years.

Others prefer to rely on the identification of different prognostic groups to select patients to be treated with RT alone, thus avoiding laparotomy with splenectomy. For example, the Princess Margaret Hospital group suggested that the proportion of CS I–II patients given radiotherapy alone (about 80 %) will not change by selecting patients for this treatment according to a prognostic grouping in three categories rather than with laparotomy and splenectomy. The clinical factors defining the three groups include clinical stage, presence or absence of general symptoms, histology, age.[4] These clini-

cal investigators observed that their results are in line with those one could expect from a policy of surgical staging followed by the appropriate therapeutic choice; they report a 78% ten-year overall cause specific survival for a group of 252 CS I–IIA patients treated with radiation alone over a decade (1968–77).

A third option is based on the combination of radiotherapy and chemotherapy for all CS I–II patients, again avoiding surgical staging, in the belief that chemotherapy will obviate for the need of treating with radiotherapy the abdominal sites of disease, if present. Survival figures do not seem to be different from those reported for patients treated with radiation alone. In fact, randomized studies comparing patients treated with RT alone with those treated with RT plus chemotherapy, evidenced often better relapse free survival rates for patients treated with the addition of chemotherapy (CT), but overall cause specific survival was never significantly different. For example, the Manchester group (Anderson, Crowther et al.) randomized patients with PS I–IIA *and* I–II B to RT or Rt plus CT;[7] the overall 10-year survival, after correction for intercurrent deaths, was 90% for the RT alone group (n = 56), as opposed to 95% for the RT plus CT group (n = 59). An attempt has been recently made to analyse togheter all the numerous randomized clinical studies comparing radiation alone vs radiation and chemotherapy for early stage HD. The results of this meta-analysis showed, again, that the addition of chemotherapy produces higher relapse free survival rates, but no significant advantage in terms of cause specific survival.[8]

No randomized clinical trial is available to give a definitive answer about the possible superiority of one of these three approaches the others. Therefore to some authors conclude that there is not a "treatment of choice", but "a choice of treatments" for early stage Hodgkin's disease.[9]

Our policy largely depends from surgical staging of CS I–II patients, because:

1. it allows the use of RT alone in a large proportion of early stage patients, selection being based on the most important prognostic factor (presence or absence, and extent, of abdominal disease);

2. it obviates the need for splenic irradiation and might result in a further reduction of the treated volumes, according to other prognostic factors, in PS I–IIA cases;

3. it entitles to a clear distinction between III1 and III2 substages, thus allowing treatment with RT alone of the III1 cases (or of part of them);

4. it clearly defines the subdiaphragmatic extent of the disease, and therefore the sites to be treated with radiotherapy, also in cases submitted to combined modality treatment.

Furthermore, we prefer the use of RT alone for early stage patients, because it reduces the "therapeutic burden", combined modality treatment being the only viable alternative. In fact, CT alone has proved inferior to RT alone in the randomised trial we conducted, with the Hematology and Radiotherapy Departments of the Universities of Florence and Rome, comparing M + LA radiotherapy with MOPP chemotherapy in the treatment of PS I–IIA patients.[10] With a median follow up in excess of 9 years, overall cause specific survival resulted in 93% in the RT alone group (n = 45) and in 56% in the MOPP group (n = 44). The difference in overall survival was mainly due to a more difficult rescue of relapsed patients treated initially with CT, whose survival probability 80 months after relapse was of 15%, the corresponding figure for patients relapsed after RT alone being 85%. The percentage of "true" relapses (occurring at initially involved sites) was much higher (8/12 vs 1/12, $p < 0.001$) in the MOPP group; which underscores the need for adequate radiotherapy of initially involved sites also in the context of combined modality treatment. It should be mentioned that a similar study of early stage HD, conducted in the United States by the National Cancer Institute on 136 patients, yielded somewhat different results, the difference between the MOPP and the RT arms being not significant, when the 13 PS IIIA1 cases, also randomised, were excluded from the analysis. It should be noticed, howe-

Table 2. Incidence of cases with CNHD in some reported series.

Institution, Ref.	N. with CS I–II HD	Period of accrual	N. with CS I	N. with CS II
Royal Marsden,[12]	225	1970–79	78 (34.6%)	25 (11.6%)
Stanford,[3]	915	1968–86	104 (11.3%)	52 (5.7%)
Florence	703	1960–88	77 (10.9%)	21 (3.0%)
Joint Center,[13]	552	1969–86	108 (19.5%)	N.R.

N.R. = Not reported; *only patients with supradiaphragmatic HD considered.* The Royal Marsden series includes only patients subsequently submitted to staging laparotomy; all the other series consider all the CS I–II patients.

ver, that in this study 30 cases with "favourable" presentations, out of 34 with PS IA, were treated with radiotherapy alone, but not randomized; conversely, 22 patients with PS I–IIB were randomised and evaluated.[11] Moreover, in the NCI study, higher proportion of the relapses observed after RT alone were "true" (in field) relapses (7/17, 41.2%, vs 1/12, 8.3%, as observed in the Italian study).

The retrospective analysis of our results with Clinical Stage I–II patients (743 cases treated 1960–1988) seems to confirm the general statement that, for early stage HD, radiotherapy alone is as effective as combined modality treatment. Five-, ten- and fifteen-year disease specific survival rates are respectively of 85%, 77% and 74% for the 578 cases treated with radiotherapy alone; the corresponding figures for the 129 cases treated with RT and CT are respectively 84%, 78% and 78%. However, some clinical presentations of the disease could not be easily forced in a schematic subdivision by clinical or pathological stage only. These presentations should be analysed separately.

Clinical stage I–II Hodgkin's disease involving cervical nodes only (*CNHD*) should be considered as a rather uncommon presentation of this neoplasm, accounting for an average of 20% of the supradiaphragmatic CS I–II patients (Table 2).[3,12,13]

Distinctive clinical, pathologic and biologic features are reported for this subset. Firstly, an excess of cases with a histologic diagnosis of lymphocytic predominance HD (LPHD) has been observed (in comparison with the much larger group of the other stage I-II patients). Therefore, the peculiar clinical characteristics linked with this hystological subtype are frequently present among CNHD patients: male preponderance, an age peak in the fourth decade, a single site of disease, a long time lapse between the appearance of a cervical adenopathy and the definitive diagnosis, a chronic relapsing course, an excess of second tumors and an allegedly better prognosis.[14,15] Secondly, the entire group of cases with CNHD has been studied in detail, as far as the results of laparosplenectomy are concerned, aiming at the avoidance of surgical staging, at least in some patients. The high incidence of cases with LPHD among CNHD patients is confirmed also in our series: 33% of the 98 cases with CNHD treated between 1960 and 1988 show this histologic subtype, as opposed to only 12% of the remaining supradiaphragmatic CS I–II patients ($P = 0.001$). A higher proportion of male patients among cases with LPHD histology has been observed in our CNHD series (M/F = 3.0). The age at diagnosis peaks in the fourth decade for the LPHD patients of the CNHD group. More than 10% of our CNHD cases (13/98) had a long history (>2 years, 4.5 years on average) of adenopathy in the same site subsequently biopsied, reaching the diagnosis of HD.

Forty-four out of the 98 patients studied have been submitted to staging laparotomy with splenectomy. The overall incidence of occult abdo-

Table 3. Incidence of splenic involvement in CNHD patients, according to different clinical features.

Clinical feature	N. with spleen involved	%
Males	2/24	8.3%
Females	0/20	–
Clinical Stage I	1/38	2.6%
Clinical Stage II	1/6	16.6%
High neck disease	0/15	–
Low neck disease	2/32	6.3%
Bulky nodal masses	1/8	12.5%
No bulky nodal masses	1/36	2.7%

minal involvement is low (4.5%). Factors apparently related with a higher frequency of splenic involvement are shown in Table 3.

Therefore, the need for surgical staging may be questioned in a fraction of the patients with CNHD (namely, female patients with high neck disease, CS I, without bulky nodal masses).

In our series, all patients were treated with RT alone. Cause specific survival is very good (87%); disease free survival is in the region of 80%. Therefore, other therapeutic modalities do not appear to be a viable alternative. Instead, an attempt should be made to identify the cost/benefit ratio for the use or different treated volumes. Waldeyer's ring (WR) involvement has been frequently detected in these patients (17/98, 24%), but prophylactical irradiation of this anatomic region does not seem warranted. According to our experience, in fact, biopsy of clinically negative WR always gave negative results.[16] Not surprisingly, the use of wide field radiotherapy determines an increase in relapse free survival when compared with that of involved field (IF) irradiation. Taking into account the types of relapse observed in the group of patients treated with IF and their treatment, we judge that the use of "mini mantle", avoiding the irradiation of the mediastinum, would be the best choice for many CNHD patients. In our series, the use of "mini mantle" would have probably avoided 3 of the 7 relapses observed in the IF treated group (the marginal ones). Appropriate salvage chemotherapy (and the possibility of cure) is now available, but could not be offered to 3 of the 4 remaining patients, with other types of relapse, at the time when they were treated.

Patients with subdiaphragmatic presentations of HD (SDHD) represent a small fraction of the cases with Stage I–II A disease (5–10%, in the more relevant series of the literature; 5% in our series). They also have distinctive clinical-pathological features, shared in part with CNHD patients. Among our 41 cases (treated 1960–1990) we observed a relatively high M/F ratio (3.1), a high proportion of cases with the LP histotype (25%), an older median age at presentation (46 years). However, it is possible to subdivide this small group of cases: those with "central" (abdominal) presentation have more often systemic symptoms, a mixed cellularity (MC) histotype, Stage II disease and a worse prognosis. On the contrary, those with "peripheral" (inguinal) presentation have more often a LP histotype, no systemic symptoms, Stage I disease and a better prognosis. For Stage IA patients, lymphangiography is 100% accurate and the results after radiotherapy only (the treated volume being almost always the "inverted Y") are very good (100% cause specific survival in our series). As far as IIA cases are concerned, laparotomy with splenectomy identifies a subset with pathological Stage I disease, and therefore could not be omitted, to avoid "overtreatment" of the downstaged cases (Table 4). In fact, pathologically staged IIA cases and all the IIB cases should be treated more aggressively, because the relapse rate is otherwise unacceptably high.

In conclusion, CNHD and SDHD cases account for about a quarter of our series of CS I–II patients; in a not negligible fraction of them, laparotomy with splenectomy could be

Table 4. Stage variations among 27 SDHD patients after laparotomy with splenectomy.

Clinical Stage / Pathologic al Stage	CS IA	CS IIA	CS IIB
PS IA	6	8	–
PS IIA	–	7	–
PS IIAS	–	2	–
PS IIB	–	–	–
PS IIBS	–	–	4

Table 5. Prognostic factors and actuarial 5,10- and 15-year disease specific (DS) and relapse-free survival (RFS). 743 Clinical Stage I–II HD patients treated 1960–1988.

Factor (n. of cases)	5-year DS	10-year DS	15-year DS	5-year RFS	10-year RFS	15-year RFS
ALL CASES (743)	85 %	77 %	74 %	64 %	58 %	56 %
Clin. Stage II (582)	84 %	75 %	73 %	60 %	54 %	51 %
Clin. Stage I (161)	89 %	86 %	82 %	79 %	74 %	71 %
"B" symptoms (105)	70 %	65 %	65 %	45 %	38 %	36 %
No "B" symptoms (638)	87 %	80 %	76 %	67 %	61 %	59 %

avoided and/or the treated volumes reduced, apparently without hampering the good results obtained with radiation alone.

Another group of patients with CS I–II HD seems, conversely, to have a worse prognosis after treatment with radiation alone.

According to our data and to the results from the literature, advanced age and male sex are significantly related with a worse prognosis.[17] In addition, the effect of the "biologic" prognostic factors outweights that of the factors linked with the so called "tumor burden".

Among the 743 Clinical Stage I and II HD patients treated at our Institution (1960–88), the presence of "B" symptoms confers an unfavorable prognosis (univariate analysis, $p < 0.001$, Table 5). Among the different prognosticators linked with the "tumor burden", only stage seems to be equally relevant (Table V), mostly however, as far as relapse free survival is concerned. In line with these remarks, it is of some interest that in our experience, the presence of a "bulky" mediastinal mass (transverse mediastinal diameter larger than one third of the thoracic diameter) is not linked with a significantly worse prognosis.

The subset of patients with "B" symptoms is in fact the only one seemingly deriving survival advantage from the addition of chemotherapy to radiotherapy as primary treatment (Table 6). Therefore, our treatment policy for I–IIB patients (representing about 15 % of the CS I–II cases of our series) is different from that, adopted for the other CS I–II HD patients and the primary treatment includes chemotherapy. The addition of chemotherapy to radiotherapy seems to eliminate the prognostic disadvantage of the "B" cases.

Questions regarding long term, treatment related damage: tailoring the diagnostic and therapeutic "burden" according to the risk of sequelae

The fact that a large fraction of patients cured of HD has been already exposed to a variety of long term sequelae of the treatment attracted the interest of many clinical investigators.

A relatively high incidence of second malignant neoplasms, the occurrence of cardiac or pulmonary damage and of infections and the

Table 6. Disease specific (DS) and relapse free survival (RFS) after different treatment types for CS I–II B patients (105 cases, 1960–1988, Florence Radiotherapy Departement).

Treatment modality (n)	5-year DS	10-year DS	15-year DS	P	5-year RFS	10-year RFS	15-year RFS
ALL "B"	70 %	65 %	65 %		45 %	38 %	36 %
RT ALONE (n = 61)	60 %	56 %	56 %		33 %	29 %	26 %
RT + CT (n = 39)	85 %	76 %	76 %		63 %	49 %	49 %
CT (n = 5)	–	–	–	–	–	–	–

P (Logrank) = 0.03 for DS and 0.006 for RFS

risk of infertility are among the most feared "consequences of survival".

We studied extensively the problem of *second malignancies* (SM).

It is known from the literature and from our own data that the risk of SM and of acute leukemia in particular, is higher among patients treated for Hodgkin's disease than in the general population.[18] Among our patients (1121 cases treated 1960–88), the observed/expected (O/E) ratio for SM resulted to be 2.27 (95% confidence intervals, C.I., 1.8–2.9) with respect to a comparable sample of the general population (data from the Tuscan Tumor Registry). For acute leukemia, the O/E ratio resulted to be 30.3 (C.I. 14.5–55.8). We therefore studied the cumulative probability of having a SM in different clinical and therapeutic subgroups of our series.

The 15-year cumulative probability of acute leukemia (AL) is equal to 1.6%; the risk of AL resulted to be much higher after chemotherapy, alone or in combination with radiotherapy, than after radiotherapy alone (Table 7).

Another interesting remark is that the risk of acute leukemia (AL) is apparently higher when chemotherapy and radiotherapy are given togheter, at presentation, than when radiotherapy is given at presentation and chemotherapy for relapse (4/185 cases vs 0/142, RR = 10, P = 0.03).

In our experience, splenectomy does not increase the risk of AL.

Overall cumulative probability of second solid tumors (SST) is higher than that of AL (9% at 15 years). The risk of SST is linked mainly with age at diagnosis of HD. However, chemotherapy, alone or associated with extended field radiotherapy, seems to be linked also with an increased incidence of SST (Table 8).

While a remarkable excess of cases of AL in HD patients treated with chemotherapy has been observed also in the large majority of the other published series, an excess of second solid tumors in the same group of HD patients has been less frequently reported. However, two large recent studies, from the M.D. Anderson Cancer Center and from the British National Lymphoma Investigation Group, reached conclusions very similar to ours.[19,20] In conclu-

Table 8. Relative risks of second solid tumors (SST) in different age classes and therapeutic subgroups (Multivariate analysis, Cox model, 1121 patients treated in Florence 1960–1988, relapsed patients censored at relapse).

Factor	RR of SST	P
Age at diagnosis		
< 20	1	–
20-40	3.7	0.075
40-60	8.2	0.006
> 60	27.9	< 0.001
Treatment intensity		
IF/M	1	–
STNI/TNI	1.9	0.12
IF/M + CT	1.5	0.49
STNI/TNI + CT	4.4	0.01
CT	3.9	0.03

IF = Involved field; M = Mantle; STNI, TNI = Subtotal- and Total nodal irradiation; CT = Chemotherapy. RR = relative risk. Likelihood ratio statistics, P< 0.001.

Table 7. 15-year cumulative probability and relative risks (RR) of acute leukemia (AL) in 1121 patients treated in Florence (1960–88), according to the therapy given at presentation (relapsed patients have been censored at relapse; comparisons of different Kaplan Meier cumulative probability curves have been made with the Logrank test).

Therapy at presentation	N. cases	15-year AL cumulative probability	RR	P
Radiation alone	745	0.2%	1	–
Radiation + Chemotherapy	272	4.3%	13.4	0.02
Chemotherapy alone	104	11.1%	9.9	0.10

Table 9. Relative risk (RR) of respiratory complications according to age groups and radiation dose levels to mediastinum: multivariate analysis, Cox model, 1060 patients treated in Florence until 1986.

Factor	RR	P
Dose to mediastinum		
<20 Gy	1	<0.001
20–30 Gy	7.3	
>30 Gy	18.0	
Age		
<20	1	<0.001
20–60	1.9	
>60	<1	
Extent of Mediastinal Involvement		
None	1	<0.005
Nonbulky	1.6	
Bulky	2.8	
Nonbulky and hylum	2.3	
Bulky and hylum	2.1	

sion, the risk of developing a SM is not negligible and seems to be at least in part treatment-related: therefore, it should be taken into account when choosing primary treatment for early stage HD.

According to an analysis conducted on a series of 1060 cases treated at our Institution until 1986, about one third (34%) of the *complications* observed are *respiratory;* however, mild paramediastinal fibrosis (rarely accompanied by mild symptoms) account for about 90% of the episodes; in the remaining 10% symptoms were more severe or protracted. Multivariate analysis shows that the age of the patients and the dose to the mediastinal structures are directly related to the incidence of respiratory complications (Table 9), along with the extent of the mediastinal mass (and therefore of the lung volume exposed to radiation). To perspectively evaluate these data, however, functional evaluation of radiation damage to the lung should be considered.

In a series of 43 patients consecutively treated at our Institution with radiotherapy alone between 1978 and 1980, respiratory function tests (RFT) were performed before mantle irradiation and 6, 9, 15 or more months thereafter. Small variations in the different functional parameters explored were observed 3 to 6 months after radiotherapy, with complete recovery thereafter; in patients with abnormal RFT before therapy (with large mediastinal adenopathies), all parameters improved after mantle irradiation.[21] Similar results have been reported by other investigators.[22]

Treatment with chemotherapy by itself may produce respiratory damage; however, the addition of regimens containing bleomycin or adriamycin to mediastinal irradiation greatly increases the risk of severe respiratory impairment. In particular, a significant increase in the proportion of patients experiencing moderate to severe respiratory toxicity and two lethal pulmonary insufficiencies have been observed in patients enrolled in the H6F trial of the European Organization for Research and Treatment of Cancer and randomized to treatment with the ABVD regimen plus mantle and lumbar bar radiotherapy, when compared with those treated with radiation and MOPP chemotherapy.[23] A recent pilot study of the British National Lymphoma Investigation testing the value of involved field radiotherapy plus a chemotherapy regimen including vinblastine, methotrexate and bleomycin (VBM) in early stage HD was prematurely discontinued also because of severe pulmonary toxicity.[24]

Age and dose to mediastinum (Table 10) appear to be the factors more directly related also to the occurence of *cardiac complications*, that are much less frequent of the respiratory ones (5% of the total number of complications observed in our series). Of the various types of cardiac damage we observed, ischemic heart

Table 10. Relative risk (RR) of cardiac complications according to age groups and radiation dose levels to mediastinum: multivariate analysis, Cox model, 1060 patients treated in Florence until 1986.

Factor	RR	P
Age (years)		
<30	1	<0.01
30–50	1.22	
>50	3.65	
Dose to mediastinum		
<30 Gy	1	<0.05
>30 Gy	2.3	

disease is the prevailing one (60 % of the cases). Cardiac damage has been studied only recently also in comparison with adequate control groups of the general population. Glanzmann and colleagues identified 6 patients with fatal coronary heart disease (CAD) in a series of 339 HD cases who received mediastinal radiotherapy, with or without chemotherapy.[25] The cases with fatal CAD were equally distributed in the groups treated with or without chemotherapy. Standardised mortality rate in comparison with the general population resulted to be 5.6 (C.I. 2.6–10.7.). However, the excess risk was limited to HD patients with known risk factors for CAD (high cholesterol levels, smoking, hypertension).

On the whole, *infectious complications* account for about one third of the episodes of iatrogenic damage observed in our series (30 %). According to our experience, zoster infections represent more than two thirds of the infectious episodes and their occurrence appears to be related with splenectomy, with the extent of the treated volume and with the combination of radiotherapy and chemotherapy (Table 11).

Similar relationships have not been observed for bacterial infections and for the other viral infections. We observed two cases of sepsis, but only one following splenectomy.

Table 11. Relative risk (RR) of zoster infections according to the use of splenectomy, to the extent of the treated volume and to the treatment modality: multivariate analysis, Cox model, 1060 patients treated in Florence until 1986.

Factor	RR	P
Splenectomy		
No	1	<0.01
Yes	2.4	
Treated volume		
IF	1	<0.05
M – STNI	1.6	
TNI	2.6	
Treatment Modality		
Radiation alone	1	<0.05
Radiochemotherapy	1.9	
Chemotherapy alone	1	

IF = Involved field; M = Mantle; STNI, TNI = Subtotal- and Total nodal irradiation.

More aggressive chemotherapy regimens may result in prolonged neutropenic episodes, occasional septic deaths having been reported.

In conclusion, respiratory and cardiac complications appear to be related to the age of the patient and to mediastinal irradiation.

Radiation pneumopathy is relatively frequent, but rarely symptomatic. It may be more severe and occasionally fatal when chemotherapy (especially with drugs as bleomycin or adriamycin) is added to radiotherapy.

Cardiac damage is much less frequent, but more often severe; it is linked also with the other well known risk factors.

Infections caused by the herpes zoster virus are the most frequent; their incidence is increased among patient submitted to splenectomy and in those treated with radiation (especially on larger volumes) and chemotherapy. Other viral or bacterial infections are less frequent; their incidence is increased after combined modality treatment. Infections in patients rendered neutropenic by combination chemotherapy may be occasionally fatal.

The risk of *gonadal damage* is particularly worrying, owing to the young mean age of the HD patients. Consequences of the treatment given of fertility are particularly difficult to "measure"; psychosocial problems in HD survivors may in fact alter the sexual behaviour (and therefore fertility) even more than the physical damage from radiation and/or chemotherapy. Moreover, in 30–70 % of HD male patients, defects in spermatogenesis are present before any treatment. Finally, the fact that 30–50 % of HD patients already had a child before the diagnosis of HD may well influence their behaviour after treatment. In a recent paper from the Memorial Sloan Kettering Cancer Center, Kornblith and coworkers[26] reported the results of a comparison of psychosocial adaptation and sexual function in 150 long term survivors of advanced HD treated with three different, chemotherapy regimens (MOPP, ABVD and MOPP/ABVD). They conclude that there are no differences between the different treatments as far as the measured outcomes are concerned, even though differences among the "physical"

effects of MOPP and ABVD on gonadal function may well exist. Therefore, other factors, unrelated to therapy (as the perceived negative effect of having had a cancer on the socioeconomic status of the patient or on his sexual life) may exert a profound influence on the probability of having children of HD survivors.

For male patients, the use of total nodal irradiation (TNI) might produce long lasting azoospermia, because of the scattered radiation to the testes; also very low fractional doses seem effective in damaging spermatogenesis. The irradiation of less extended volumes is much less dangerous in this respect. The scattered dose to the testes has been determined by researchers at the National Cancer Institute and resulted to be between 0.2% and 1% of a midline dose of 40 Gy for mantle or paraaortic fields; when a pelvic field is added, the total dose to the testes rises up to 140–300 cGy.[27] In fact, the scarce clinical data on this subject seem to confirm that male HD patients treated on volumes smaller than TNI can preserve their fertility, if not already compromised before treatment. In our series, TNI was included in the primary tratment mostly until 1980, while it was very rarely used thereafter (139/776 cases -18%- vs 26/500 -0.5%-); this is particularly true for early stage disease.

Chemotherapy induced gonadal damage is very frequent in male patients treated with the MOPP regimen: after such treatment infertility is the rule. Apparently, the ABVD regimen seems to exert a less pronounced effect on spermatogenesis. Thirty-six per cent of 25 male patients treated by Santoro and colleagues in Milan with ABVD plus radiotherapy (STNI) had azoospermia and 20% oligospermia after chemotherapy; full recovery of spermatogenesis was evident in the 13 patients who had a repeated sperm count within 18 months.[28] Alternating regimens (like the MOPP/ABVD or the COPP/ABVD ones) seem to affect fertility in a percentage of male patients similar to that observed after MOPP chemotherapy.[29]

For female patients, another critical factor is age; women younger than 20–30 years have a higher probability of preserving fertility both after radiotherapy and after chemotherapy. Radiotherapy to mantle and lumbar bar seems to be relatively "safe"; on the contrary, when radiation to pelvis (TNI) is necessary, many authors suggest to perform an oophoropexy along with staging laparotomy and splenectomy. In this way, a central pelvic shield may protect ovaries and more than 70% of the treated women continue to have or resume, shortly after treatments normal menses. As far as chemotherapy is concerned, the Milan group claims that also for females the ABVD regimen is less toxic for gonadal function than the MOPP one. Out of 24 females treated with STNI and ABVD, none had "prolonged" amenorrhea as opposed to 5/10 of those over thirty years of age treated with MOPP and STNI.[28] As for the effect of alternating regimens, the same observations reported for males apply also to female patients.

In conclusion, the issue of gonadal damage is complicated by the effect of various psychologic and social factors; however, chemotherapy with the MOPP regimen seems to produce sterility in nearly all the male patients and in a substantial number of the female ones; similar conclusions can be drawn for other MOPP-like regimens (as the MVPP one). Even if long term data with ABVD are more scarce, it seems that gonadal damage is less frequent after treatment with this regimen. For both male and female patients, radiotherapy seems to be much less damaging for the gonads than chemotherapy (with the possible exception of total nodal irradiation in males, nowadays rarely used).

Discussion and concluding remarks

The evidence from the literature and our own data show that the knowledge of a few easily identifiable prognostic factors, coupled with the awareness of the potential risks of each therapeutic modality, may allow to design a reasonable treatment strategy for early stage HD. The Florence Radiotherapy Department policy of treatment has been built on the "gold standard" represented by subtotal nodal irradiation in

laparotomy staged patients. This choice granted both acceptable survival rates and a sufficiently low cumulative probability of major complications. High, and reproducible, cause specific survival rates are reported after STNI in laparotomy staged patients, no significant survival differences having been reported in comparison with patients treated with radiation and chemotherapy; the cumulative probability of second malignancies (acute leukemia in particular) is lower for these radiotherapy treated patients than for those treated with chemotherapy, particularly of the MOPP type, alone or combined with radiation. After radiotherapy alone, gonadal function appears to be preserved in a much higher proportion of cases.

The fact that about 30% of the patients treated with radiotherapy alone will relapse (therefore requiring salvage chemotherapy) does not seem to obscure the picture. The majority of the relapsed patients will be cured; moreover, the risk of leukemia does not seem to be raised in this subgroup; in fact, the risk of AL is much higher when chemotherapy and radiation are given concurrently rather than separately, one (RT) at presentation and the other (CT) at relapse.

Cardiac and respiratory sequelae seem, however, mainly linked with age and with the radiation dose to the mediastinum. Unfortunately, this form of iatrogenic damage cannot be eliminated with combined modality treatment (because of the need of treating with radiotherapy the initially involved sites, that most often include the mediastinal nodes); moreover, the addition of chemotherapy regimens containing bleomycin or adriamycin may significantly increase the frequency and severity of radiation related lung damage.

From the large group of CS I–II patients, two groups can be identified, requiring a different therapeutical approach.

For the "favourable", or "peripheral", cases (with high neck disease, or with limited subdiaphragmatic disease), the use of less extended treated volumes (avoiding mediastinal irradiation in a not negligible fraction of cases) and a less frequent recourse to staging laparotomy with splenectomy do not seem to hamper the excellent survival figures previously reported. Conversely, patients with "B" symptoms should be treated with combined modality treatment, that seems to produce better survival results when compared with radiation alone.

While this is a reasonable state-of-the-art policy, ongoing studies aim at two major end results:

1. The *further reduction of the therapeutic burden*, mainly attempting the combination of the irradiation of less extended volumes with novel chemotherapeutic regimens, presumably less leukemogenic and/or less toxic to lung and gonads, in clinically staged patients; or the reduction in the treated volume in a fraction of the laparotomy-staged cases;

2. The *identification of "very high risk" cases* (both at diagnosis and after relapse) to be submitted to very aggressive treatment (for example, "supramaximal" chemotherapy with or without different types of radiation therapy and with some from of bone marrow support).

As far as the use of new, less toxic, chemotherapy regimens associated with small field radiotherapy is concerned, the more relevant example of this strategy is represented by the use of the VBM schema (vinblastine, 6 mg/m^2, bleomycin, 10 mg/m^2, methotrexate, 30 mg/m^2, given i.v. on days 1 and 8 of a 28-day cycle for 6 cycles) plus involved field radiotherapy, as proposed by the Stanford group and tested by American and British investigators.[24,30] In the Stanford experience, survival results were substantially the same with this treatment protocol and with extended field radiotherapy alone, in early stage patients.[30] Gonadal toxicity was very low after VBM; moreover, the individual drugs of the schema have been selected for their allegedly lower carcinogenicity. However, a relatively higher incidence of abnormal pulmonary function test was recorded in these VBM-treated patients. A more recent paper from the British National Lymphoma Investigation group reports that 47% of the 30 patients treated with the VBM schema suffered from pulmonary toxicity (as opposed to 31% of the patients treated at Stanford), defined as "unex-

pectedly severe". Moreover, a septic death was recorded. Therefore, the BNLI group prematurely interrupted the study.

Of course, the search for new effective chemotherapy regimens for HD continues, and probably some of them will be tested also in this clinical setting.

Considering the issue of the reduction of the treated volume in surgically staged patients, the EORTC experience should be mentioned. Treated volume was limited to the "mantle" in the PS I–II patients with favourable prognostic factors enrolled in the H6F EORTC trial.[19] Patients were characterized by the absence of bulky mediastinal masses, less than 3 involved sites, absence of B symptoms with an ESR lower than 50 or B symptoms, but with an ESR lower than 30. Six year cause specific and relapse-free survival higher than 90% and 80% – respectively – have been reported.

In this very favourable subset of patients, therefore, a strategy of laparotomy followed by radiotherapy limited to "mantle" alone in PS I–II cases might be justified. A retrospect analysis of the 439 cases with CS I–II treated in Florence 1975 through 1988 showed that 93 of the PS I–II patients treated with radiotherapy alone presented with the same features of the H6F patients. For this subset, overall 6-year cause specific (CSS) and relapse free survival (RFS) rates were respectively of 94% and 85%. Patients treated with mantle radiotherapy alone (n = 19) fared as well as those treated on larger volumes (n = 74): CSS and RFS rates in the two groups were respectively 93% vs 94% and 85% vs 86%. However, the Physician Data Query information sheet, released by the National Cancer Institute, in its July 1994 update, recommends strict follow up, including careful surveillance of abdominal nodes, for the favourable PS I–II cases treated with mantle radiotherapy only.

As far as the treatment of high risk cases is concerned, the presence of B symptoms and advanced stage correlate with a worse prognosis in patients failed after radiation therapy alone for early stage HD, for example in the Stanford experience.[31] Patients not responding, progressing or relapsing after primary treatment and belonging to one of the unfavourable prognostic groups listed above have been relatively often submitted to "supramaximal" chemotherapy with marrow support.[32,33] However, even this very aggressive therapeutic effort will obtain acceptable survival results only if there is residual sensitivity of the disease to the therapeutic modalities already used during primary treatment. This is the main reason of the somewhat deluding results obtained. Mature data on allogeneic, syngeneic and autologous marrow transplantation after "supramaximal" therapy for HD come from the Seattle group.[28] These investigators report an overall 5-year survival probability of 21%, with a median follow up of two years; 40% of the patients died for causes unrelated to active HD (pulmonary or multiorgan failure being the prevailing ones). The proportion of patients with less advanced disease treated according to such (or similar) policy has been relatively higher in some other reported series: the results have been in some cases better (survival rates up to 30–40%, but generally after a much shorter median follow up period).

The Transplant Unit of the Hematology Department of the University of Florence, a Center collaborating with our Institution as far as the care of HD patients is concerned, performed about 200 autologous bone marrow transplants since 1988. Nineteen of these transplants (2 allogeneic, 17 autologous) have been performed in HD patients, all but two treated initially with chemotherapy for advanced disease. Eleven of these cases had refractory disease (mainly relapsing HD, a few with primarily refractory disease). Eight cases had partial responses after primary treatment (3 cases) or after treatment for first (4 cases) or second (1 case) relapse. All the patients were submitted to supramaximal chemotherapy only before the transplant. Until now, five patients relapsed after transplant, 5 died because of progressing disease, 3 for treatment-related causes. Six cases have been followed for less than one year. Our excperience, therefore, seem to be aligned with the results obtained elsewhere.[32,33]

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Postoperative adjuvant chemotherapy with 5-fluorouracyl, adriamycin and cisplatin (FAP) in resectable gastric cancer

Saša Markovič, Zvezdana Hlebanja, Borut Štabuc

Institute of Oncology, Department of Medical Oncology, Ljubljana, Slovenia

The effectiveness of combined chemotherapy FAP as an adjunct to surgery was investigated in resected gastric cancer patients. Of 40 pts, 33 were evaluable. All patients were randomly assigned to surgery plus adjuvant FAP or surgery alone. The results have shown no benefit of adjuvant FAP in overall and disease free survival of patients with resectable gastric cancer. In addition, gastrointestinal intolerance presented a severe drawback and compromised the patients' quality of life.

Key words: stomach neoplasms – drug therapy; postoperative period

Introduction

Gastric cancer remains a major health problem in Slovenia, despite its decrease during the last decades. The prognosis in patients is poor; the overall five year survival rates are modest and have not increased over 5 % to 12 %.[1] The only chance of cure is still offered by surgery, although at the time of diagnosis only 20–30 % of patients will be amenable to operation.[1,2] Up to two thirds of patients, who have undergone curative resection, present with a recurence and die due to locoregional failure or metastatic disease. In the Western countries there has been no improvement in the prognosis over the past 40 years. The Japanese have however documented both better resectability and improved survival rates during the past 30 years. Extended lymphadenectomy has been reported to modify the survival in Stage II gastric cancer, while in stage III only 15 % patients can be cured by surgery alone.[3–5]

The failure of surgery to control the disease has led to several trials on adjuvant therapy.[5–14] The combination of the drugs used is often the one that has shown satisfactory results in the treatment of advanced gastric cancer. The combination of 5 FU, adriamycin and cisplatinum (FAP) is one of the several chemotherapeutic regimens that have proved active against advanced disease and have yielded 50 % response rate.[15] This paper, presents the results of a prospective randomized controlled study of adjuvant chemotherapy using FAP combination in operable gastric cancer.

Correspondence to: Assist. Prof. Saša Markovič, M. D., Ph. D., Institute of Oncology, Zaloška 2, 61105 Ljubljana, Slovenia.

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Materials and methods

Patients included in the study had undergone resection for histologically proven gastric adenocarcinoma. The UICC TNM classification

was used to define the stage of the disease. Histological subtyping of tumors was done by means of Lauren classification. The patients were randomized either to surgery plus chemotherapy or to surgery alone. Chemotherapy was started within 6 weeks following surgery. The chemotherapy consisted of 5 fluorouracil (5-FU) 500 mg/m^2 by rapid i.v. infusion on day 1 through day 5, doxorubicin 30 mg/m^2 i.v. on day 1, CDDP 20 mg/m^2 in 1500 ml of 0.5 normal saline i.v. over 2 hours on day 1 through day 5. The cycle was repeated every 4 weeks. Six consecutive cycles were planned to be given to each patient. Antiemetic therapy was administered routinely. Chemotherapy related toxicity was evaluated using WHO score. Appropriate dose adjustment or discontinuation of therapy was made if extensive toxicity was experienced during the proceeding course or if the patient refused further treatment. In addition, any histologically proven evidence of local recurrence or metastatic disease necessitated cessation of FAP treatment. Criteria for recurrence were histological proof or X-ray evidence of metastases.

Before entry to trial and after completed chemotherapy staging was carried out using chest radiology, ultrasonography or/and CT scan, hepatic and renal function tests and blood count. The patients were followed up in three month intervals; the check comprised a complete physical examination and blood chemistry, while repeated staging including gastroscopy was performed every six months in the first two postoperative years, and thereafter in 6 - month intervals.

The end point of the protocol was to determine the impact of adjuvant FAP on the survival and disease-free interval in patients treated by chemotherapy compared to those treated by surgery alone.

Survival and disease-free interval were calculated using Kaplan-Meier's method. The survival was assessed from the day of surgery until death or the most recent visit. The differences between groups were evaluated using log-rank test.

Results

The trial was conducted between January 1985 and January 1990. Fourty patients were entered into the trial; of these 33 were evaluable while 7 patients were lost to follow up. Patients' characteristics are shown in Table 1. There were 17 females and 16 males. Of 33 patients, 9 underwent total gastrectomy and 24 had subtotal gastrectomy. Seven patients underwent gastrectomy with incomplete removal of the primary (infiltrated tumor margins). For 11 patients surgery was the sole therapy, 21 cases received surgery plus FAP chemotherapy.

During 5-year observation period, 20 patients

Table 1. Characteristics of evaluable patients.

	Total	FAP	Control
Number of patients	33	22	11
Sex: male/female	16/17		
Age (years): median (range)	50 (37-62)		
Site of primary tumor			
Pylorus or antrum	20	10	10
Body	9	9	0
Cardia or fundus	4	3	1
Histological type			
Intestinal	12	9	3
Diffuse	21	13	8
Surgical procedure			
Subtotal gastrectomy	24	14	10
Total gastrectomy	9	8	1
Surgical margins status			
Negative	26	16	10
Positive	7	6	1
TNM stage			
T2	7	4	3
T3A	17	10	7
T3B	7	7	0
T4	2	1	1
N stage			
N0	7	4	3
N1	17	9	8
N2	8	8	0
N3	1	1	0
Stage			
II	11	7	4
IIIA	12	5	7
IIIB	8	8	0
IV	2	2	2

FAP = 5-FU, adriamicin, cisplatinum

Table 2. Causes of death.

Clinical cause of death	Total No.	FAP No.	Control No.
Metastatic disease	11	8	3
Local recurrence	9	7	2
Not recorded	3	3	0
Tumor unrelated	3	2	1
Total deaths	26	20	6

FAP = 5-FU, adriamycin, cisplatinum

in the treated arm and 6 in the control arm have relapsed and died. The causes of death are shown in Table 2.

At five years, 7 patients have been alive – 2 patients treated by chemotherapy and 5 controls. The overall survival for the whole group was 70% at two years, and 24% at 5 years (Figure 1), the corresponding numbers for NED being 52% and 24% respectively (Figure 2).

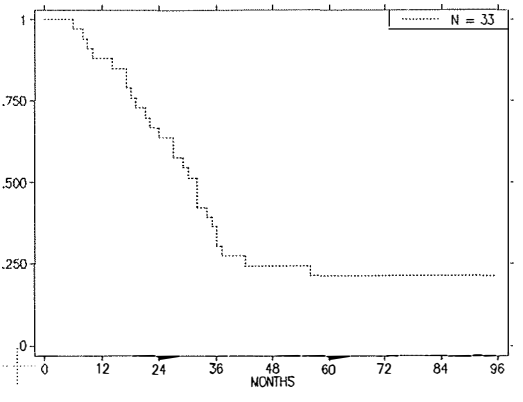

Figure 1. Overall survival of 33 patients with resectable gastric cancer.

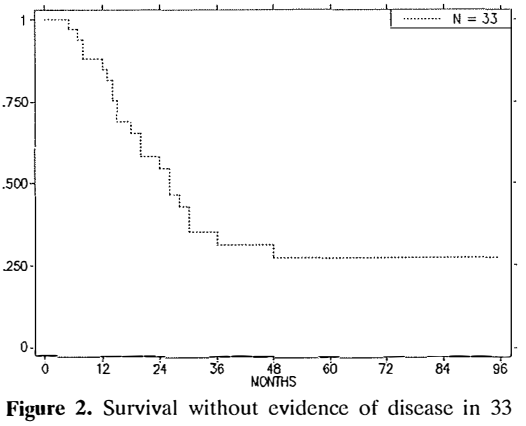

Figure 2. Survival without evidence of disease in 33 patients with resectable gastric cancer.

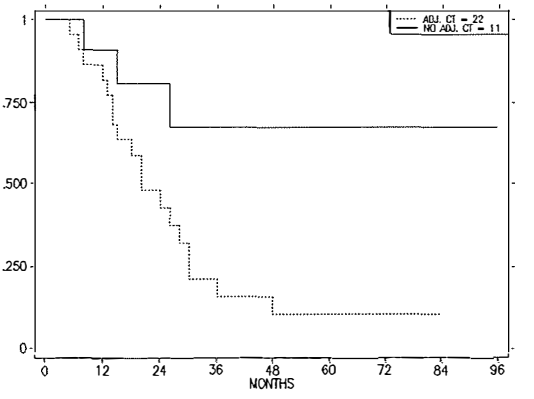

Figure 3. Survival without evidence of disease in 22 patients treated by adjuvant FAP (5-FU, adriamycin, cisplatinum) and 11 patients treated by surgery alone.

The comparison of the survival between both groups revealed statistically significant ($p < 0{,}0133$) difference in disease-free survival in favour of the untreated arm (Figure 3).

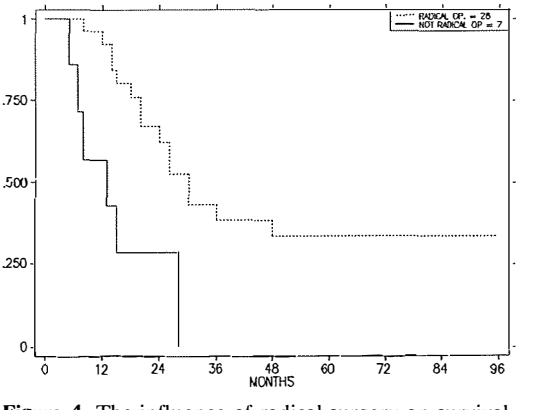

Figure 4. The influence of radical surgery on survival without evidence of disease.

A group analysis showed that patients who underwent radical surgery managed significantly better ($p < 0{,}0015$) than those who had incomplete resection (Figure 4). Adjuvant therapy worsened the survival in radically operated gastric cancer patients (Figure 5). The difference was however of borderline significance (p = NS). The histological type of the tumor has not exerted any influence on the survivals (P = NS) (Figure 6).

Side effects experienced by patients on chemotherapy are summarized in Table 3. Chemo-

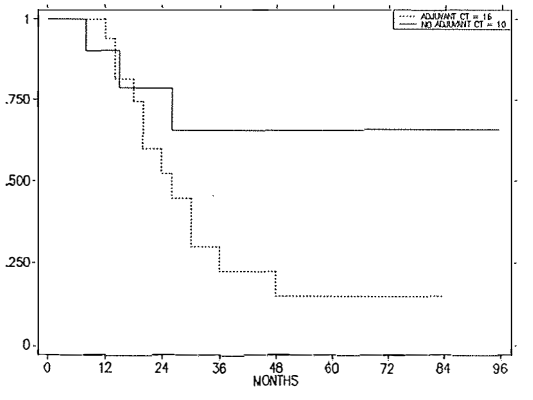

Figure 5. The influence of adjuvant chemotherapy on the survival without evidence of disease in 26 radically operated gastric cancer patients.

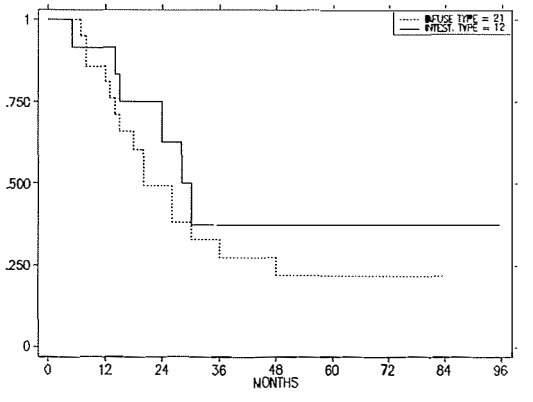

Figure 6. The influence of histology (Lauren classification) on the survival without evidence of disease in 33 resected gastric cancer patients.

therapy was discontinued after two or three courses in 9 (46%) patients because of poor gastrointestinal tolerance. Only 12 patients (54%) completed the planned therapy. There were no deaths related directly to chemotherapy in this study.

Table 3. Side effects of treatment with FAP (5-FU, adriamycin, cisplatinum).

Side effect (Grade 3–4)	No (%)
Nausea/vomiting	15 (68%)
Alopecia	16 (72%)
Nephrotoxicity	2 (9%)
Neurotoxicity	1 (4,5%)
Hemotoxicity	6 (27%)

Discussion

The role of systemic combination chemotherapy in the standard treatment for stomach cancer is limited to palliation. The most popular regimens used in gastric cancer treatment in Europe and the United States, such as FAB, FAM and FAP induce an objective response rate of 30–40%.[12,13,15,16] The FAP combination has been shown to be the most promising chemotherapy schedule at the beginning of the study, with a 50% response rate in advanced gastric cancer patients.[15] These results have suggested that FAP should be tested in patients with resectable gastric cancer.

The discussion of whether adjuvant chemotherapy is of any benefit in the treatment of gastric cancer is still open. Conflicting results have been obtained so far.[6,7,9–12,15] Therefore this kind of chemotherapy is used in resectable gastric cancer solely in randomized clinical trials. Several studies of adjuvant chemotherapy using different drug combinations have been conducted but have failed to demonstrate any benefit in improved survival.[3,6,7,9,12] There was however a suggestion that patients with T3 – T4 tumors do benefit from such treatment. Even though no statistically significant differences in the survival were established, a lower number of recurrences was found in the treated arms.[6]

The Japanese[5] have however reported a significant beneficial effect of combined chemo-immunotherapy in 1805 resected gastric cancer patients followed up for 5 years. Patients given immuno-chemotherapy survived longer than those treated by surgery alone. A curatively operated stage III subgroup seems to benefit the most from postoperative immuno-chemotherapy,[4,5,17] the beneficial effect was related to tumor infiltration by dendritic cells.[17] A combination of mitomycin, tegafur and PSK has become the most popular regimen for adjuvant treatment of gastric cancer in Japan.[5,16]

In adjuvant studies the stage of the disease (TNM), was shown to be the most important prognostic factor; this was followed by subtype

using Lauren classification, and site of the primary tumor.[1,17,18]

The results of this study have shown that the overall survival of all patients from both arms is not inferior to the survival data reported in patients with potentially curative resection for gastric cancer.[1,2] The finding of a significantly higher survival in nontreated arm compared to the treated arm, however, disagreed with other reports. By additional analysis of subgroups with different prognostic factors, it was shown that despite the random selection of operated patients, the unfavorable prognostic factors were all more prominent in the treated group. The treated group comprised six nonradically resected cases and all cases with N2 and N3 nodal involvement, vs. one nonradically resected and none N2 and N3 case in the control arm. In the German Gastric study, the survival was shown to be mainly dependent[19] on the absence of residual tumor. Non-radical resection shortened the survival. The results of the present study are in accordance with that finding. However the Gastrointestinal Tumor Study Group have found a 5 year survival rate of 17% obtained by chemotherapy plus radiotherapy in patients with microscopic locally recurrent or residual gastric cancer after surgery.[20] In our treated group none of the patients survived 5 years and all were dead within the first postoperative year.

Diffuse type carcinoma has been connected with worse prognosis in gastric cancer patients.[17,18] Statistically insignificant difference was shown also in the present study. Diffuse type was found to be the predominant histological type in the whole observed group with no difference between the two arms. The result shows that the worse outcome in the treated group was not related to the difference in tumor histology.

Adverse effects of the drug combination, especially gastrointestinal toxicity, posed a severe problem and required cessation of therapy in 46% of patients. Nausea and vomiting grade 3 and 4 were the reasons for patients' refusal of further therapy.

The results reported here indicate that as best this regimen can not be of benefit to patients with operable gastric cancer. In fact, there was a decreasing trend in the survival of the FAP treated patients. In view of the negative impact on survival, it would be reasonable not to conduct any further trials with this drug combination in adjuvant settings. However, the study included only 33 patients, and group evaluation revealed that despite randomisation, the differences between arms were very prominent. In future, studies of adjuvant therapy must comprise a sufficient number of cases to enable satisfactory evaluation.

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Survival of stage I lung cancer patients with previous or subsequent primary malignant neoplasms

Oleg A Vasiljev, Vladimir P Kartchenko, Igor V Kouzmine

Moscow Research Institute of Diagnosis and Surgery, Moscow, Russia

From 1965 to 1990 2161 patients underwent the complete resection for lung cancer. In 910 cases stage I was histologically proved. pT1 – 375 (41 %), pT2 – 532 (58,7 %). There were 90,9 % cases observed more then 5 years, 60,2 % – 10 years. Ninetysix (10,6 %) patients were found to have second primary neoplasms before or after the curative treatment of stage I lung cancer. 13 (13,5 %) patients died due to subsequent primary malignancy, 17 (17 %) – of other causes. Crude 5-year survival of stage I lung cancer patients was 65 %, 10-year survival was 53 %. In the group of 96 cases with multiple neoplasms accordingly 73 and 53 %. Our data confirm that the relative probability of the second primary malignancy increases in time of monitoring after the curative surgery or the combined treatment and depends on the spread of tumor (TNM factors) in connection with indirect influence on the survival. In early lung cancer second primary neoplasms after the curative treatment do not influence formal indices of survival. The paper discusses the results of adjuvant methods of treatment in connection with multiple primaries.

Key words: lung neoplasms – mortality; survival rate; neoplasms second primary

Introduction

Every item of multiple cancer with lung primaries (MCLP) has been intensively discussed for many decades but some of them haven't been studied properly. One of the inadequately studied problems is the survival of patients with early lung cancer. In the first place stage I patients have the curative treatment more frequently. Secondly, the survival is significantly longer. On the other hand, after organ-preserving surgery, a large volume of spare lung tissue with precancer changes rests the potential source of multiple growth. Moreover, there are many more possibilities for the realization of the curative surgery for the second and even third time. A repeated radical treatment is based on the certainty of pathologic determination of the new primary and the stage of its development.

The problem of MCLP plays the important role in the estimation of long-term results of

Correspondence to: Oleg A, Vasiljev, M.D., Moscow Research Institute of Diagnosis and Surgery, 117837, GSP7, Profsojuznaya str. 86, Moscow, Russia. Fax: +(095) 334-79-24, Email: DIRECTOR mniidih, MSK, SV.

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radical treatment. Generally, in order to leave out the influence of MCLP on survival, this kind of patients is not included in the analysis of clinical material. But this group of patients is the most important part of treatment program and constitutes up to 10–12 % of cases. At the same time, in most publications only mean duration of life in years and months was reported. According to general statistics, the crude 5-year survival of MCLP was near 30 % with the consideration of all stages of the disease.

Material and methods

During the years 1965–1990 2161 patients were operated in Moscow Research Institute of Diagnosis and Surgery. Stage I of the disease was stated histologically in 910 cases. TIS – 3, T1NO – 375, T2NO – 532 patients. Remote results were estimated to 05.05.92 (Kaplan-Meyer method). There are 827 (90,9 %) patients who have been observed for five years and 551 (60,3 %) patients for 10 years. In 96 (10,6 %) patients of 910 cases MCLP was detected. There are 48 patients who are still alive (Table 1). For the verification of multiple primaries generally accepted criteria were used.[1]

Results and discussion

Among 234 patients with central type of cancer the incidence of MCLP was 16,2 %, in peripheral (297) – 14,4 % ($p > .05$). It is important to underline the similar incidence of central and peripheral multiple lung cancer. It concerns extrathoracic primaries as well. The risk of second primary in T1NO patients is twice greater than in T2NO patients. The difference is significant ($p < .02$) without any connection with clinico-pathologic forms of lung cancer.

Table 1. Alive after curative treatment of stage I lung cancer.

Total	No recurrence	With progr.	MCLP
415	336	29	48
100 %	81,4 %	7 %	11,6 %

The mean diameter of the primary pulmonary tumor in MCLP patients was 34 mm, in solitary lung cancer – 30 mm ($p > .05$).

The incidence of MCLP has been studied for comparison in 90 operated T1N1 – 2 lung cancer patients. In this group 6,8 % of MCLP patients were found.

Age and sex

The mean age of MCLP patients (Stage I) was 57,9 years, of others – 55,6 ($p < ,005$). In patients of 60 years old and younger the incidence of MCLP was 8,3 %, in an elderly group of patients – 15,3 % ($p < .05$). The direct correlation of MCLP was not found but the annual relative risk of second malignant tumor was on average 2 %. During postoperative monitoring of patients two picks of increasing of multiple lesions of respiratory tract in 1–2 and 4–5 years after the radical treatment were observed. The same data have been already mentioned in the literature.[2]

Seventeen (18 %) MCLP patients were women. In the group of multiple cancer of respirtory tract patients women represent 7,1 % cases. In the entire group MCLP was observed in 12 % of women and in 10 % of men. The difference is not significant.

So the possibility of MCLP development is connected with the stage of the lung cancer and the period of monitoring: factors with direct influence on the survival of cancer patients. The risk of a new primary tumor seems to be equal for all stages, however, the incidence of MCLP is lower due to the shorter follow-up period. The majority of new cancers would appear only a few years after the primary treatment, i.e. only after the patients with advanced tumors already died.

Localization of MCLP

In 52 (55,8 %) patients the second cancer was found in lung, in 6 (6,3 %) – larynx, in 4 (4,3 %) – stomach, 3 (3,2 %) – esophagus, 2

both diseases, every new malignant tumor does not significantly impact the formal survival of stage I lung cancer patients.

3. The adjuvant irradiation of curatively treated patients does not produce the essential influence on the incidence of MCLP respiratory and extrathoracic localization and does not correlate with the long term results.

4. The influence of the modern chemotherapy (neoadjuvant including) could not be definitely proved. But according to our limited experience (without randomization) we could assume that chemotherapy decreases the risk of second primary cancer with stage I lung cancer patients.

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The air kerma-rate constant of high dose-rate Ir-192 sources

Matthew B. Podgorsak,[1] Larry A. DeWerd, and Bhudatt R. Paliwal

Departments of Medical Physics and Human Oncology, University of Wisconsin, Madison, Wisconsin, 53792. [1]Present address: Department of Radiation Medicine, Roswell Park Cancer Institute Buffalo, New York 14263

The current value of the air kerma rate constant used in dosimetry calculations for high dose-rate (HDR) Ir-192 sources is based on photon spectral information obtained with low activity Ir-192 sources different in size and encapsulation from the HDR Ir-192 sources used today. Since source configuration has been shown to affect the photon spectrum emitted by a radionuclide, the purpose of this work is to measure the photon spectrum emitted by an HDR Ir-192 source. To simplify the spectral measurements and increase the accuracy of the resulting spectrum, an Ir-192 source identical dimensionally to a clinical source but activated to as low an activity as technically possible was obtained from the manufacturer. Spectral measurements were made with a high purity germanium detector interfaced to a multichannel analyzer. It was found that the HDR source capsule attenuates photons with energies below 500 keV. In fact, no photons with energy below 60 keV can be identified in the HDR Ir-192 photon spectrum, even though the decay of Ir-192 results in several characteristic x-rays in this energy range. As a result, the fluence-weighted and energy-fluence-weighted average energies of the HDR Ir-192 spectrum were found to be 371 and 402 keV, respectively, higher than the average energies of a bare Ir-192 source. A calculation of the HDR Ir-192 air kerma-rate constant based on the measured photon spectrum gives a value of $(29.02 \pm 0.26) \times 10^{-18}$ *Gy* m^2 $Bq^{-1}s^{-1}$, *~5% lower than the value currently associated with HDR Ir-192 sources. The serious potential clinical implications resulting from this discrepancy in air kerma rate constant strongly support the abolishment of source activity in favor of reference air kerma rate for HDR Ir-192 source strength specification.*

Key words: brachytherapy; iridium radioisotopes; radiotherapy dosage; spectrum analysis; photons

Introduction

Presently, the most commonly used high dose-rate (HDR) remote afterloader in North America is the Microselectron (Nucletron Corporation, Leersum, Holland). This unit houses a single iridium (Ir-192) source with a nominal activity of 370 GBq (10 Ci) attached to a stainless steel cable. The source is driven by remote control between the storage safe located at the unit and user-programmed positions within the lumen of applicators implanted inside a patient. Treatment planning algorithms calculate the dose distribution in these implants using a formalism which includes several variables that describe the radiation properties of the HDR

Correspondence to: Matthew B. Podgorsak, Ph.D., Department of Radiation Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY, 14263.

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Ir-192 source.[1,2] Currently, it is predominately low dose-rate (LDR) Ir-192 decay data that is used in HDR Ir-192 dosimetry calculations. Recent characterizations of the HDR Ir-192 source, however, have shown that some radiation parameters are highly source-type specific,[3,4] suggesting that the use of LDR Ir-192 decay data in dosimetry calculations for HDR Ir-192 implants may be inappropriate.

One radiation parameter that has not yet been specifically determined for HDR Ir-192 sources in the air kerma-rate constant $(\Gamma_\delta)_K$. This quantity, in units of Gy m^2 s^{-1} Bq^{-1}, is defined by the photon spectrum emitted by a source and is related to the exposure rate constant $(\Gamma_\delta)_X$. Assuming a value 33.97 J/C for $(\overline{W}/e)_{air}$, it can be shown that the ratio of $(\Gamma_\delta)_K$ to $(\Gamma_\delta)_X$ is 6.58×10^{-17} Gy R^{-1} h s^{-1} Ci Bq^{-1}. There have been many publications that have reported values of $(\Gamma_\delta)_X$ for Ir-192 sources ranging from 0.400 to 0.496 R m^2 Ci^{-1} h^{-1} ($(\Gamma_\delta)_K$ = 26.3×10^{-18} to 32.6×10^{-18} Gy m^2 s^{-1} Bq^{-1}).[5-7] Recently, Ninkovic and Raicevic[8] reported a value of 30.0×10^{-18} Gy m^2 s^{-1} Bq^{-1} for the air kerma rate constant of an unfiltered low dose rate Ir-192 source. For an Ir-192 source encapsulated in 0.15 mm of platinum, they quoted a value of 27.8×10^{-18} Gy m^2 s^{-1} Bq^{-1}, approximately 7% lower than for the unfiltered source.

The large variation in the air kerma rate constant for Ir-192 sources in different configurations clearly demonstrates a strong dependence of this quality on source design, particularly the type and thickness of encapsulation surrounding the active source material. Because the design of an HDR Ir-192 source is different from any other Ir-192 source, it is not apparent which of the previously reported values of $(\Gamma_\delta)_K$ should be used in HDR Ir-192 dosimetry calculations. A value of 30.66×10^{-18} Gy m^2 s^{-1} Bq^{-1} (0.466 Rm^2 Ci^{-1} h^{-1}) has been adopted by manufacturers of the source and several brachytherapy treatment planning systems, while standardized calibration laboratories use a value of 30.24×10^{-18} Gy m^2 s^{-1} Bq^{-1} (0.4596 Rm^2 Ci^{-1} h^{-1}). This latter value is calculated from a theoretical modeling of the HDR Ir-192 spectrum based on attenuation in the source encapsulation of known photons emitted from Ir-192. Although both these values are well within the range of those previously reported, they are significantly different from each other and, furthermore, the methodology used in their determination is not in all cases entirely clear. It is the purpose of this paper to describe a measurement of the HDR Ir-192 photon spectrum and a subsequent evaluation of the air kerma-rate constant for these sources.

Materials and methods

HDR Ir-192 source driven by the Microselectron

The activation of an HDR Ir-192 source requires approximately 6 weeks of irradiation by the typical thermal neutron fluxes in most reactors used to produce these sources.[9] Prior to placement inside a reactor, the major component of the source material is expected to be Ir-191. The most likely activation therefore follows the Ir-191 (n,γ) Ir-192 reaction. Once activated to an activity of ~370 GBq, the source is removed from the reactor and carefully encapsulated in a stainless steel capsule. Even though technically more difficult, encapsulation of the source must be done only after activation. This is because some components of stainless steel (mostly iron-58, chromium-50, and cobalt-59) have non-negligible neutron activation cross-sections and could themselves be activated by thermal neutrons and contaminate the HDR source photon spectrum.[10,11] The source manufacturing process is completed by welding a stainless steel cable to the source capsule. The manufacturer (Mallinckrodt Diagnostica, Petten, Holland) then waits approximately one week before releasing the source for clinical use. This delay allows the Ir-194 contaminant, produced alongside Ir-192, to decay to the point where it will not contribute significantly to the energy spectrum of a clinical HDR Ir-192 source.

The most recent HDR Ir-192 source, shown

schematically in Figure 1,[12] was introduced in June 1991. In this design, the source capsule is 5.0 mm long with a diameter of 1.1 mm and a wall thickness of 0.25 mm. The active source material inside the capsule is 3.5 mm long and 0.6 mm in diameter. The center of source activity is 2 mm from the tip of the capsule.

Photon spectroscopy system: Description

Photon pulse-height spectra (PHS) were measured with a system consisting of a high-purity germanium (HPGe) detector (Canberra Industries, Inc., Meriden, CT) interfaced to a 4096 channel analyzer (MCA). The detector element was a coaxial germanium crystal (p-type) mounted in a cryostat consisting of a vacuum chamber thermally coupled to a liquid nitrogen heat sink. The impurity concentration in the germanium crystal was on the order of 10^{10} atoms/cm^3. The crystal was held in place inside the cryostat by an aluminum holder 0.5 to 1.0 mm thick. The outer vacuum jacket was also made of aluminum, 1.5 mm thick on the sides and 0.5 mm thick at the entrance window. The HPGe crystal face was located 5 mm from the inside wall of the entrance window. A bias of 1000 V was applied to the crystal during acquisition of pulse height spectra.

Photon spectroscopy system: Detector calibration

Calibration of the spectroscopy system was done using standard Cobalt-60 (Co-60) and Europium-152 (Eu-152) sources (set no. 1718, Amersham International, Arlington Heights, IL). For acquisition of pulse-height spectra, the Eu-152 and Co-60 sources were positioned 50 cm from the front surface of the detector element (49.5 cm from the detector faceplate). The acquisition times were 4200 and 900 seconds, respectively. Any scattering surface was at least 1 m from both the source and detector crystal. A background spectrum was collected over a period of 1628 seconds, and was prorated to either 4200 or 900 seconds. The number of counts N(c) in the vicinity of eack peak in the background-corrected Co-60 and Eu-152 pulse height spectra was then fitted with the following equation:

$$N(c) = a_1 + a_2 \exp\left[-\frac{(c - a_3)^2}{a_4^2}\right] + a_5(a_3 - c), \quad (1)$$

where c is channel number. Equation (1) includes terms for the following four components of the pulse-height spectrum in the vicinity of each peak: (1) a smoothly varying background signal produced by Compton interactions of higher energy photons in the detector crystal followed by escape of a scattered photon, (2) a Gaussian contribution from photoeffect interactions where the photon energy is entirely deposited in the detector with all resulting charge collected, (3) a low energy tail on the Gaussian distribution arising from imperfect charge collection in some regions of the detector or secondary electron or bremsstrahlung escape from the active volume, and (4) a step-like rise or fall in the Compton continuum due to Compton processes where the recoil electron receives almost all of the transferred energy.

Next, the parameters of Eq. (1) were used to derive two calibration models. The first was a second order polynomial in channel number relating the energy of a photon to the center of its Gaussian distribution. The correlation coefficient for the fit was 0.99999998, demonstrating an excellent fit. The second model, initially proposed by Singh,[13] related the efficiency for a full-energy event to the energy of the photon interacting in the detector. The maximum deviation of the model-predicted efficiency and the experimental values used in its determination was 3.4%, although most deviations were $<1\%$. The magnitude of these deviations is typical for a calibrated HPGe detector.[13]

Lower activity HDR Ir-192 source

To simplify the spectral measurements and increase the accuracy of the resulting spectrum, an Ir-192 source activated to as low an activity

as technically possible was obtained from the manufacturer (Mallinckrodt Diagnostica, Petten, Holland). The source was physically identical to the clinical HDR Ir-192 source shown in Figure 1, except its activity was much lower,

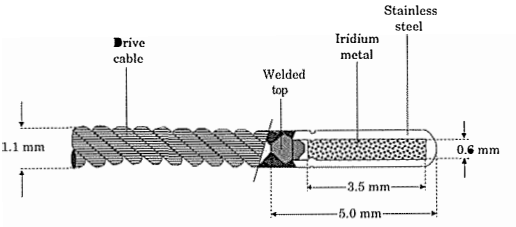

Figure 1. Schematic diagram showing a cross-section through the center of an HDR Ir-192 source remotely afterloaded by the Nucletron Microselectron. The diagram shows the most recent source design. The source is encapsulated in a 0.25 mm thick stainless steel capsule and a stainless steel cable connects the source capsule to the mechanical drivers inside the afterloader.

thus minimizing the effects of pulse pile-up and detector saturation on the measured pulse height spectrum. An initial calibration of the source was done with an HDR-1000 well ionization chamber (Standard Imaging, Middleton, WI), itself calibrated with a clinical HDR Ir-192 source whose air kerma strength had been determined using the inverse-square method.[14,15] The signal to noise ratio for ionization current readings with this source was >600. The air kerma strength of the source was found to be 1.929×10^{-6} Gy m^2 h^{-1}. According to the HDR-1000 calibration certificate, the uncertainty in this value is $\pm 2\%$. In practite, though, the error is most likely very much less than 1%, and will be neglected in the remainder of this paper. A second calibration done approximately two weeks later and just before acquisition of the pulse height spectrum gave an air kerma strength of 1.692×10^{-6} Gy m^2 h^{-1}. Over the 14 day period of time between calibrations, the source decayed with a half-life of 73.833 days, in excellent agreement with the recently reported half-life for decay of clinical HDR Ir-192 sources.[16]

A schematic diagram of the set-up used for the measurement of the HDR Ir-192 pulse height spectrum is shown in Figure 2. The source was suspended in air at a height of 120cm above the ground at a distance of 130 cm from the front end of the detector element (129.5 cm from the detector faceplate). This extended source-detector distance was necessary to reduce the effects of pulse-pileup and detector saturation. The detector was placed at the end of a table at a height that centered the source on the detector faceplate. Only air was between the source and the detector faceplate. The operating parameters of the spectroscopy system were identical to those used for system calibration.

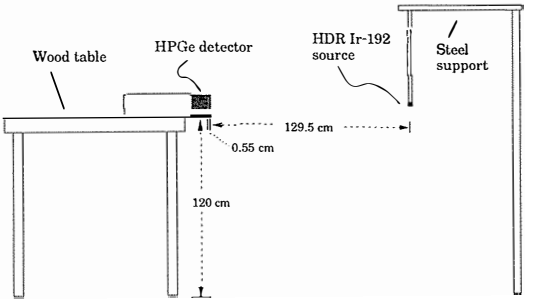

Figure 2. The experimental set-up for the measurement of the HDR Ir-192 pulse height spectrum. The walls in the room were all at least 100 cm either the detector or the source.

Results

HDR Ir-192 pulse height spectrum

The background corrected pulse-height spectrum for the lower activity HDR Ir-192 source is shown in Figure 3. The acquisition time was 1254 seconds. The spectrum is comprised of 16 peaks superimposed on a varying Compton background. Analysis of the spectrum consisted of fitting Eq. (1) to the number of counts in the vicinity of each peak (approximate peak center ± 38 channels). In the case of a doublet, where the events from one gamma ray could contribute to the distribution of a nearby peak created primarily by a different gamma ray, the sum of two such equations was fit to the pulse height spectrum in the vicinity of the two peaks comprising the doublet. In this work, the crite-

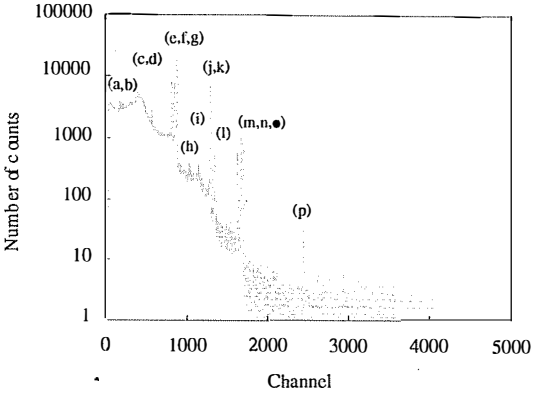

Figure 3. Backgound-corrected pulse height spectrum measured with an HDR Ir-192 source. The acquisition time was 1254 seconds.

rion for a doublet was the existence of two peaks within 30 channels of one another. Similarly, a triplet would be identified if there were three peaks within 60 channels. In the HDR Ir-192 pulse height spectrum shown in Figure 3, peaks (a) and (b), (c) and (d), (f) and (g), (k) and (l), and (n) and (o) were considered doublets; there were no triplets.

The position of each peak's center and the corresponding photon energy calculated from the calibration curve described above are listed in Table 1. The full-energy peak efficiency model derived with the calibration sources cannot be used directly with the Gaussian peak areas listed in Table 1. This is because the HDR Ir-192 pulse height spectrum was obtained with the source at a distance of 130 cm from the detector element, while the calibration curve was evaluated with pulse-height spectra measured at a source-detector distance of 50 cm. The measured peak area was corrected with a simple multiplicative correction factor based on geometrical considerations:

$$\text{area(E)} = \text{a(E)} \left[\frac{130}{50}\right]^2 \exp\{\mu(\text{E})[130-50]\}, \quad (2)$$

where μ(E) is the linear attenuation coefficient in air (in cm^{-1}) for a photon of energy E,[17] a(E) is the area of the Gaussian distribution corresponding to that photon in the measured pulse-height spectrum (source-detector distance = 130 cm), and area(E) is the area that would have been measured were the source-detector distance equal to that in the calibration geometry (50 cm). The equivalence of energy calibration curves measured at different distances with identical detector operating characteristics has been demonstrated by Kamboj et al.[18] They measured the full-energy peak efficiency for an HPGe detector with radium-226 (Ra-226) sources placed at distances of 53.5 and 164 cm from the detector, and they found identical calibration curves once inverse square fall-off photon fluence and photon attenuation in the air between the two measurement points were accounted for. Table 1 lists each identified photon in the HDR Ir-192 pulse-height spectrum along

Table 1. Fitting and efficiency data for the HPGe detector used in this work. The numbers in brackets are the uncertainty in the value above each bracket.

Peak	Position of maximum (channel)	Photon energy E (keV)	Efficiency $\eta(E)$ ($\times 10^{-4}$)	area(E) (count* channel)
(a)	179.83	64.72	2.8000	118836.11
	(0.12)	(0.05)		(3976.51)
(b)	206.33	74.29	2.8000	58822.17
	(0.21)	(0.08)		(3567.71)
(c)	558.69	201.55	2.0035	13941.29
	(1.73)	(0.62)		(4665.31)
(d)	570.37	205.77	1.9006	80685.99
	(0.23)	(0.08)		(4143.62)
(e)	820.12	295.96	0.9767	549015.61
	(0.02)	(0.01)		(3155.69)
(f)	854.75	308.46	0.9250	539980.08
	(0.02)	(0.01)		(2888.58)
(g)	877.03	316.50	0.8951	1455272.55
	(0.01)	(0.01)		(4305.75)
(h)	1037.25	374.35	0.7278	10258.73
	(0.27)	(0.10)		(834.69)
(i)	1154.60	416.72	0.6376	8997.67
	(0.42)	(0.15)		(1127.94)
(j)	1296.86	468.07	0.5502	531067.19
	(0.01)	(0.01)		(1974.23)
(k)	1342.63	484.59	0.5260	34556.46
	(0.06)	(0.02)		(669.86)
(l)	1355.55	489.25	0.5195	3662.26
	(0.44)	(0.16)		(579.75)
(m)	1630.74	588.58	0.4066	38703.94
	(0.04)	(0.01)		(466.05)
(n)	1674.67	604.43	0.3934	67144.46
	(0.04)	(0.02)		(860.98)
(o)	1696.91	612.45	0.3855	42126.47
	(0.06)	(0.02)		(813.53)
(p)	2450.51	884.30	0.2402	1723.80
	(0.24)	(0.09)		(121.64)

with its efficiency for a full-energy interaction with the detector and the corrected area under the peak evaluated using Eq.(2).

Air kerma rate constant

The air kerma strength K_{air} of the HDR Ir-192 source at the beginning of the acquisition of the pulse height spectrum was 1.689×10^{-6} Gy m^2 h^{-1} (4.692×10^{-10} Gy m^2 s^{-1}) $\pm 2\%$ It can be shown that over the acquisition time of the HDR Ir-192 pulse height spectrum (t = 1254 seconds) the total air kerma was 5.883×10^{-7} Gy m^2 $\pm 2\%$.

The emission frequency f(E) of each identified photon of energy E in the HDR Ir-192 pulse height spectrum, given in units of number of photons emitted per parent decay, is given by:

$$f(E) = \frac{\text{area}(E)}{\eta(E)N}, \quad (3)$$

where area(E) in the corrected area under each full energy peak, $\eta(E)$ is the full-energy peak efficiency, and N is the total number of decays of the parent atom. Calculating the number of HDR Ir-192 decays from the pulse height spectrum shown in Figure 3 is imprecise since the Compton continuum upon which the full-energy events are superimposed is not negligible, and the true detector crystal collecting volume is not known. It is, howewer, possible to relate N to the air kerma K_{air} as follows:

$$N = \frac{K_{air}}{(\Gamma_\delta)_K}, \quad (4)$$

Substituting Eq. (4) into Eq. (3) gives

$$f(E) = \frac{\text{area}(E)}{\eta(E)}\left[\frac{K_{air}}{(\Gamma_\delta)_K}\right]^{-1}. \quad (5)$$

Solving Eq. (5) for $(\Gamma_\delta)_K$ results in the following equation for the air kerma rate constant:

$$(\Gamma_\delta)_K = \frac{f(E)\,\eta(E)\,K_{air}}{\text{area}(E)}. \quad (6)$$

The necessary information to evaluate $(\Gamma_\delta)_K$ using Eq. (6) for the HDR Ir-192 source has either been determined in this work ($\eta(E)$, K_{air}, area (E)) or can be estimated from the literature (f(E)). The full energy peak efficiency $\eta(E)$ and the corrected area area(E) are listed in Table 1. The uncertainty in the corrected areas listed in Table 1 vary greatly depending on the peak. Not surprisingly, the four lowest fractional uncertainties occur with the four most prominent peaks in the pulse-height spectrum. These uncertainties range from 0.3 to 0.6 % for peaks representing the following energies: 295.96, 308.46, 316.50, and 468.07 keV. The uncertainties in the corrected area of the other peaks are all $>2\%$, too high to suggest use of data from these peaks in Eq. (6).

To approximate f(E) for a photon of energy E in the HDR Ir-192 photon spectrum, the emission frequencies for a bare Ir-192 source[19] can be corrected for photon attenuation in the stainless steel encapsulation surrounding the HDR Ir-192 source. Assuming stainless steel to be equivalent to iron in attenuation characteristics and using attenuation coefficients found in the literature,[17] the correction for attenuation in the encapsulation represents a 1.7 % decrease in f(E) for the 468.07 keV photon and a 2.1 % decrease in f(E) for the 295.96, 308.46, and 316.50 keV photons. The corrected emission frequencies to be used in Eq. (6) are therefore 0.277, 0.287, 0.813, and 0.469 for the following photons, respectively: 295.96, 308.46, 316.50, and 468.07 keV. Using Eq. (6) with pulse height spectrum data from each distribution corresponding to these four photons and the air kerma calculated above gives the following respective values of $(\Gamma_\delta)_K$: $(29.02 \pm 0.53) \times 10^{-18}$, $(28.95 \pm 0.46) \times 10^{-18}$, $(29.41 \pm 0.20) \times 10^{-18}$, and $(28.62 \pm 0.53) \times 10^{-18}$ Gy m^2 Bq^{-1} s^{-1}. These values are all equal within experimental error. The average value is $(29.02 \pm 0.26) \times 10^{-18}$ Gy m^2 Bq^{-1} s^{-1} (0.441 ± 0.004 R m^2 Ci^{-1} h^{-1}).

Discussion

Table 2 lists the energy and emission frequency of each photon component of the Ir-192 decay scheme described above alongside those of the

Table 2. HDR Ir-192 photon spectrum components compared to unencapsulated Ir-192 spectral

Peak	Photon energy (HDR Ir-192) (keV)	Photon energy (ref. [19]) (keV)	Emission frequency (HDR Ir-192) (γ's/decay)	Emission frequency (ref. [19]) (γ's/decay)
		7.822		0.00027
		8.266		0.00076
		8.904		0.0060
		9.337		0.000083
		9.435		0.0164
		9.975		0.000270
		10.469		0.0063
		11.174		0.0177
		12.213		0.00113
		13.025		0.00317
		61.485		0.0116
(a)	64.72 ± 0.05	63.000	0.021 ± 0.002	0.0200
		65.122		0.0266
		66.831		0.0456
		71.313		0.0069
(b)	74.29 ± 0.08	73.643	0.010 ± 0.001	0.00174
		75.634		0.0159
		78.123		0.00415
		136.34347		0.00181
		177.00		0.000073
(c)	201.55 ± 0.62	201.3805	0.003 ± 0.0005	0.00455
(d)	205.77 ± 0.08	205.79581	0.021 ± 0.001	0.0318
		219.221		0.000016
		283.2671		0.00252
(e)	295.96 ± 0.01	295.9582	0.277 ± 0.011	0.283
(f)	308.46 ± 0.01	308.45689	0.287 ± 0.012	0.293
(g)	316.50 ± 0.01	316.50789	0.801 ± 0.033	0.830
		329.348		0.00016
(h)	374.35 ± 0.10	374.5204	0.007 ± 0.001	0.00709
(i)	416.72 ± 0.15	416.4714	0.007 ± 0.001	0.00667
		420.601		0.00064
(j)	468.07 ± 0.01	468.07151	0.476 ± 0.021	0.477
(k)	484.59 ± 0.02	484.6473	0.032 ± 0.001	0.0313
		485.60		0.000022
(l)	489.25 ± 0.16	489.0626	0.003 ± 0.001	0.00432
(m)	588.58 ± 0.01	588.5845	0.047 ± 0.002	0.0447
		593.48		0.000438
(n)	604.43 ± 0.02	604.41463	0.084 ± 0.004	0.0823
(o)	612.45 ± 0.02	612.46561	0.054 ± 0.002	0.0534
		703.867		0.000058
(p)	884.30 ± 0.09	884.5418	0.004 ± 0.001	0.00284
		1061.55		0.000523
		1090.01		0.000011
		1378.05		0.000016

HDR Ir-192 spectrum determined in this work. The emission frequencies of the photons emitted by the HDR Ir-192 source were calculated using Eq. (5) with parameter values taken from Table 1. Figure 4 is a bar plot of the HDR Ir-192 photon spectrum compared with the photon spectra reported by several authors for unencapsulated Ir-192 sources.[8,19,20] All photons, including γ-rays and characteristic x-rays, with emission frequencies greater than 0.003 (0.3%) were identified in the HDR Ir-192 pulse-height spectrum, with the following ex-

ceptions. First, Table 2 shows that the decay of Ir-192 produces several characteristic x-rays with energies between 7.822 and 13.025 keV. The HDR Ir-192 pulse height spectrum, however, shows no peaks below channel 180 (corresponding to an energy of ~63 keV) where one would expect Gaussian distributions for each for these photons. Complete absorption of photons with energies below ~60 keV in encapsulated Ir-192 sources has been suggested by Ninkovic and Raicevic:[8] in evaluating the air kerma rate constant for an Ir-192 source encapsulated in 0.15 mm of platinum, they assumed a cutoff photon energy δ of 136.6 keV. Second, the four characteristic x-rays in the energy range of 61 to 67 keV emitted by Ir-192 could not be resolved in the HDR Ir-192 pulse-height spectrum with the current spectroscopy system. Instead, a single photon of energy roughly equal to the average of the four (64.72 keV) is suggested. Similarly, the two x-rays in the energy range of 71 to 76 keV are treated as one photon of energy equal to 74.29 keV.

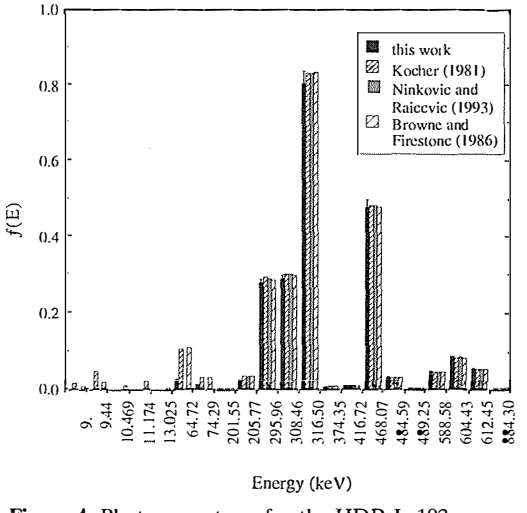

Figure 4. Photon spectrum for the HDR Ir-192 source evaluated in this work compared to the components of the photon spectra for bare Ir-192 sources with emission frequencies greater than 0.003. The energies listed are those determined in this work.

As shown in Table 2, the emission frequencies of high energy photons (E > 500 keV) emitted by the HDR Ir-192 source are essentially equal to those form a bare source. Lower energy photons, however, have emission frequencies which are consistently lower than those emitted by a bare source. The magnitude of the difference increases with decreasing photon energy. A direct result of attenuation of lower energy photons in the stainless steel encapsulation is an increase in the average energy of the HDR Ir-192 photon spectrum. For the spectrum shown in Figure 4, the fluence-weighted and energy-fluence-weighted average energies are 371 and 402 keV, respectively. These are higher than the respective average energies calculated for the unencapsulated Ir-192 source spectrum (~346 and 395 keV) (20). Furthermore, the air kerma-rate constant calculated above is ~5% lower than the value currently used by the HDR Ir-192 source manufacturer and several brachytherapy planning systems to relate apparent source activity and reference air kerma rate. The apparent source activity is calculated from the measured reference air kerma rate and the air kerma rate constant only to facilitate understanding of the amount of radioactivity present in the source. Based on the apparent activity, a planning algorithm calculates the corresponding air kerma strength using an air kerma rate constant and then continues with the evaluation of the dose distribution. The clinical implications of a discrepancy in the air kerma rate constant now become clear. If the values of $(\Gamma_\delta)_K$ used by a physicist (in calculating apparent activity from measured air kerma strength) and a planning system (doing the reverse calculation) are not the same, then the value of the source reference air kerma rate calculated by the treatment planning system will not equal the measured value. Inaccuracy in the calculated dose distribution with a subsequent dose delivery error will result directly from this discrepancy. The magnitude of the error will depend on the ratio of the two air kerma rate constants. The value of the air kerma rate constant has no effect on the dose distribution and subsequent dose delivery provided a consistent value is used throughout the source calibration and dose calculation procedures. As a result, the air kerma rate constant is a "dummy" constant in dose

calculation algorithms for sources calibrated in units of reference air kerma-rate.

The use of reference air kerma rate in place of activity for brachytherapy sources has been suggested several times in the recent literature.[21–23] Surprisingly, activity remains the dominant unit used for specification of HDR sources. In view of the potentially serious dose delivery errors resulting from the use of either air kerma rate or exposure rate constant in conjunction with source activity, we strongly encourage manufacturers of brachytherapy sources and treatment planning systems to eliminate activity as the measure of source strength and instead use reference air kerma rate. Since all HDR Ir-192 sources are calibrated in terms of reference air kerma rate, it makes little sense to use a quantity other than reference air kerma rate to describe the strength of these sources. While familiarity of the magnitude of the activity unit allows for a "feeling" of the amount of radioactivity present in a source, the radiation therapy community will eventually discover the same "feeling" from the magnitude of the reference air kerma-rate.

Conclusions

An estimate of the photon spectrum emitted by a clinical HDR Ir-192 source was made based on the pulse-height spectrum measured with a lower activity version of the source. The half-life for decay of this lower activity source was equal, within experimental error, to the value reported for clinical sources. This similar decay rate, coupled with the fact that the lower activity HDR Ir-192 source was manufactured to the same dimensional specifications as the clinical version, suggests that the low activity source had decay properties similar to a clinical source. Therefore, any radiation parameters evaluated from these properties will also pertain to clinical sources. Qualitatively, the photon spectrum showed that photons with an energy less than 60 keV do not escape the source capsule. Those most notably absent are the relatively abundant 9 and 9.44 keV photons that are a result of the decay of Ir-192. Overall, all photons with energies below 500 keV are attenuated. The emission frequencies of higher energy photons, though, were identical to those from a bare Ir-192 source, suggesting negligible attenuation of these high energy photons in the stainless steel encapsulation.

A direct result of the difference in photon spectra is an increase in the fluence-weighted and energy-fluence-weighted average energies of the HDR Ir-192 source relative to the respective average energies of a pure Ir-192 source. Consequently, the air kerma rate constant evaluated from the measured HDR Ir-192 photon spectrum was ~5 % lower than the value for a bare Ir-192 source. The air kerma rate constant was also lower than the value currently used by treatment planning systems. The serious potential clinical implications resulting from this discrepancy in air kerma rate (and exposure rate) constant strongly support the abolishment of source activity in favor of reference air kerma-rate for HDR Ir-192 source strength specification. This would make use of a modifying constant such as the air kerma rate or exposure rate constant unnecessary, and thus prevent dose delivery errors that could result from a misunderstanding of the value of either constant.

Acknowledgments

We are grateful to Dr. Edgar Loeffler of Nucletron Corporation for commissioning the lower activity version of the HDR Ir-192 source used in this work. Also appreciated are numerous helpful discussions with Drs. Loeffler, Paul DeLuca, Jr., Rock Mackie, and Wayne Newhauser.

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2. van der Laarse R. The Selectron treatment planning system. *Proceedings of the 7-th International Conference on the 7-th International Conference*

5. Joint Commission UEMS – EAR

Three main points were tabled:

The Charter on Training of Medical Specialists. UEMS published in 1992 a compendium on medical specialist training in the E.U. For the time being it intends to publish an updated compendium regarding all medical specialities recognized by the E.U. Authorities. To prepare this document, UEMS set up a charter that defines that specialists have to list their specific requirements. The matters under discussion by UEMS are the same as those discussed by the EAR Working Group EUCORE/Education Committee, such as: the *Core of Knowledge,* the *Guidelines for Training in Radiology (General)* and the *Requirements for Training Facilities.* They have been adopted by both the Joint Commission and the Executive Bureau.

Charter for Continuing Medical Education (CME) for specialists in E.U. countries. The charter was issued by UEMS and sets up guidelines and rules to be discussed by the respective UEMS sections.

A draft of EAR guidelines for CME reached the Executive Bureau. This document is to make circulating among the various EAR bodies involved in educational matters in order to harmonize the work of the European Board of Radiology.

European Society of Breast Imaging and Forensic Imaging

During the ECR'95 a group involved in Breast Imaging will meet with the aim of setting up for the future a European Society of Breast Imaging. A group involved in Forensic Imaging will also meet with the same objective.

7. Preparation of the EAR General Assembly (Vienna 9 March 1995)

The new articles to be voted at the General Assembly concern the Internal Regulations of the Committee for Computer Science Applications in Radiology and the Professional Organisation Committee. Furthermore research and cost effectiveness will be included in the *Aims* of the Association.

The Executive Bureau accepted Georgia and the Republic of Belarus as full members of the Association. This decision will be submitted for approval to the General Assembly.

Notices

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Breast cancer

The EORTC joint breast cancer meeting will be held in Nottingham, UK, *September 1, 1995.*

Contact Ms W. Bartlam, City Hospital, Proffesorial Unit Of Surgery, Nottingham NG5 1PG, UK; or call + 44 602 625 707. Fax: + 44 602 627 765.

Radiation physics

The ESTRO teaching course "Radiation Physics for Clinical Radiotherapy" will be offered in Leuven, Belgium, *September 3–7, 1995.*

Contact the ESTRO Secretariat, Radiotherapy Department, University Hospital St Rafael, Capucijnenvoer 35, B–3000 Leuven, Belgium; or call + 32 16 33 64 13; Fax: + 32 16 33 64 28.

Pathology

The 15th European Congress of Pathology will take place in Copenhagen, Denmark, *September 3–8, 1995.*

Contact Int Conf Services, PO Box 41, 2900 Hellerup, Denmark.

Haemathology

The "12th Meeting of International Society of Haemathology will be held in Istanbul, Turkey, *September 3–8, 1995.*

Contact VIP Tourism Inc, Cumhuriyet Conf 269/2, Harbiye 80230, Istanbul, Turkey.

Medical oncology

The advanced course on medical oncology will take place in Milan, Italy, *September 14–16, 1995.*

Contact European School of Oncology, Via Ripamonti 66, 20141 Milan, Italy; or call + 39 2 5730 5416; Fax: + 39 2 5730 7143; or contact ESO Vienna, c/o Arztekammer fuer Wien, Fortbildungsreferat, Weihburggasse 10–12, 1010 Vienna; or call + 43 1 51501293; Fax: + 43 1 51501240.

Psychiatry and psychology in cancer

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Supportive care in cancer

The "7th International Symposium" will be offered in Luxembourg, *September 20–23, 1995.*

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Radiology

The "Roentgen Centenary Congress" will take place in Wuerzburg, Germany, *September 20–23, 1995.*

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Radiobiology

The ESTRO teaching course "Basic Clinical Radiobiology" will be held in Tuebingen, Germany, *September 24–28, 1995.*

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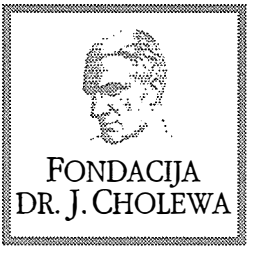

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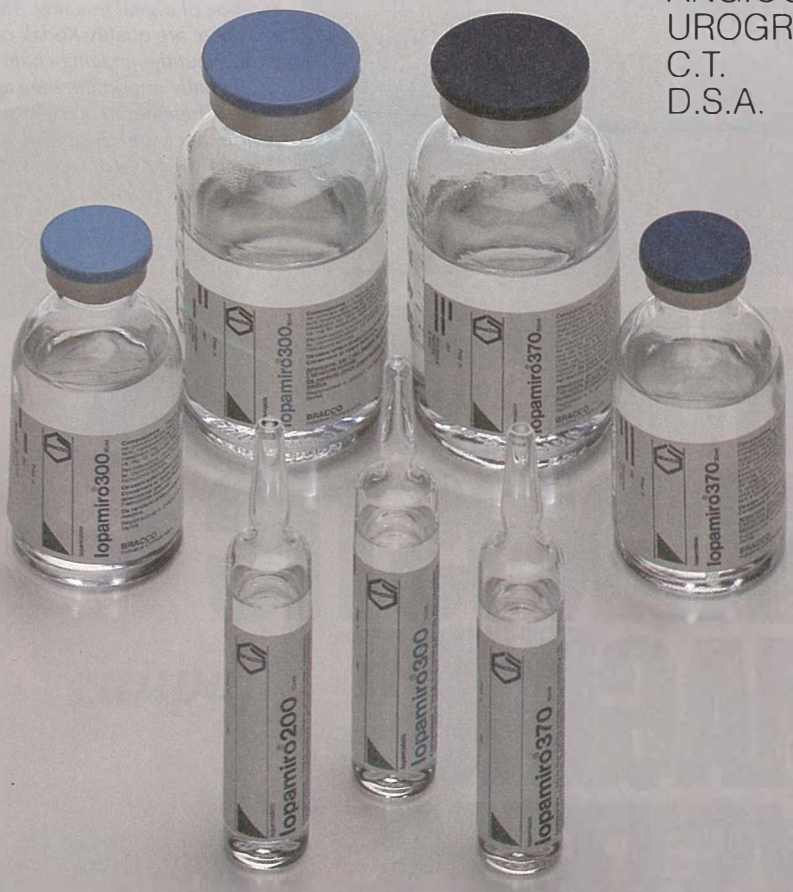

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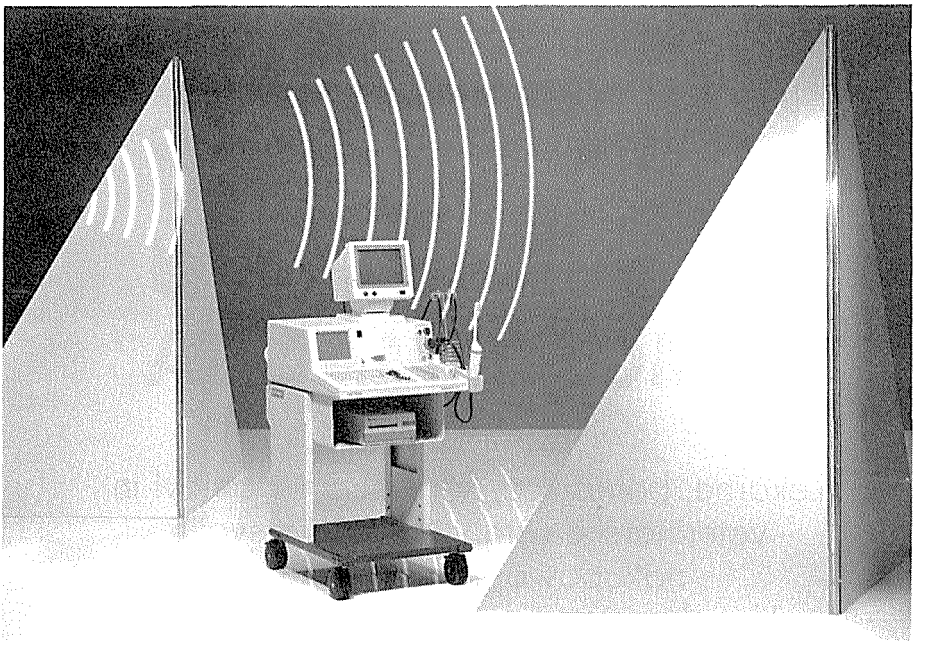

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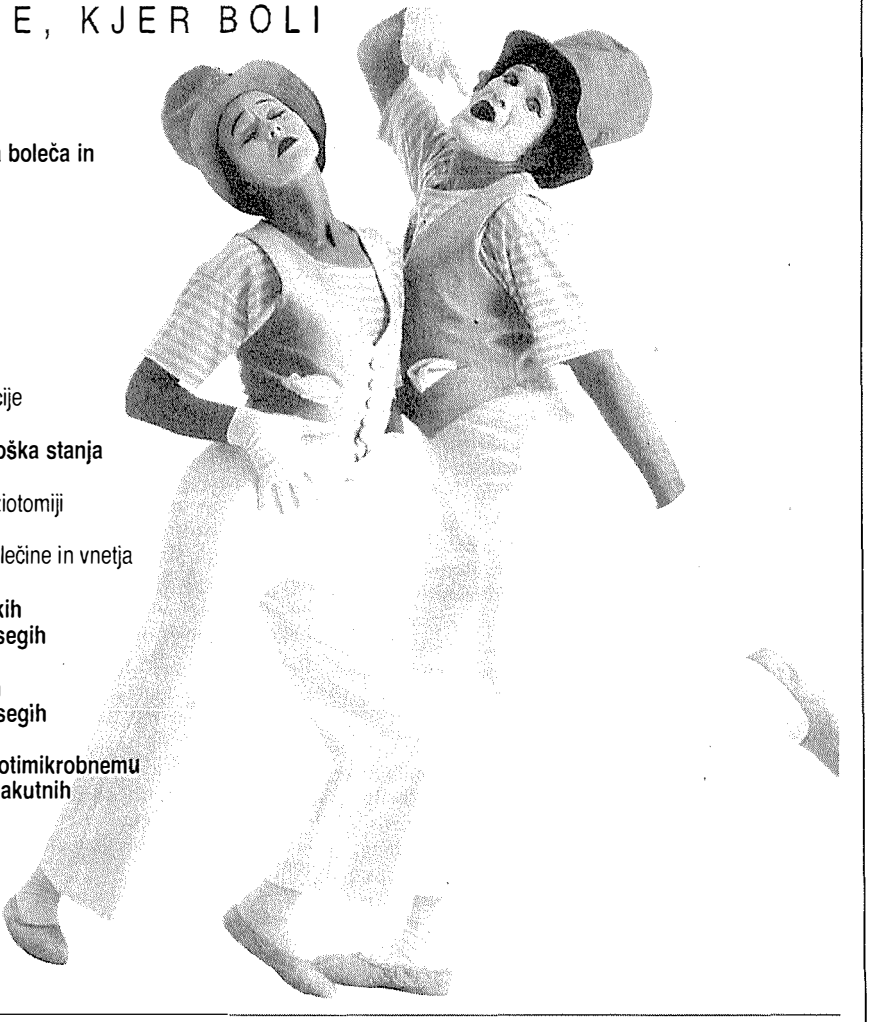

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