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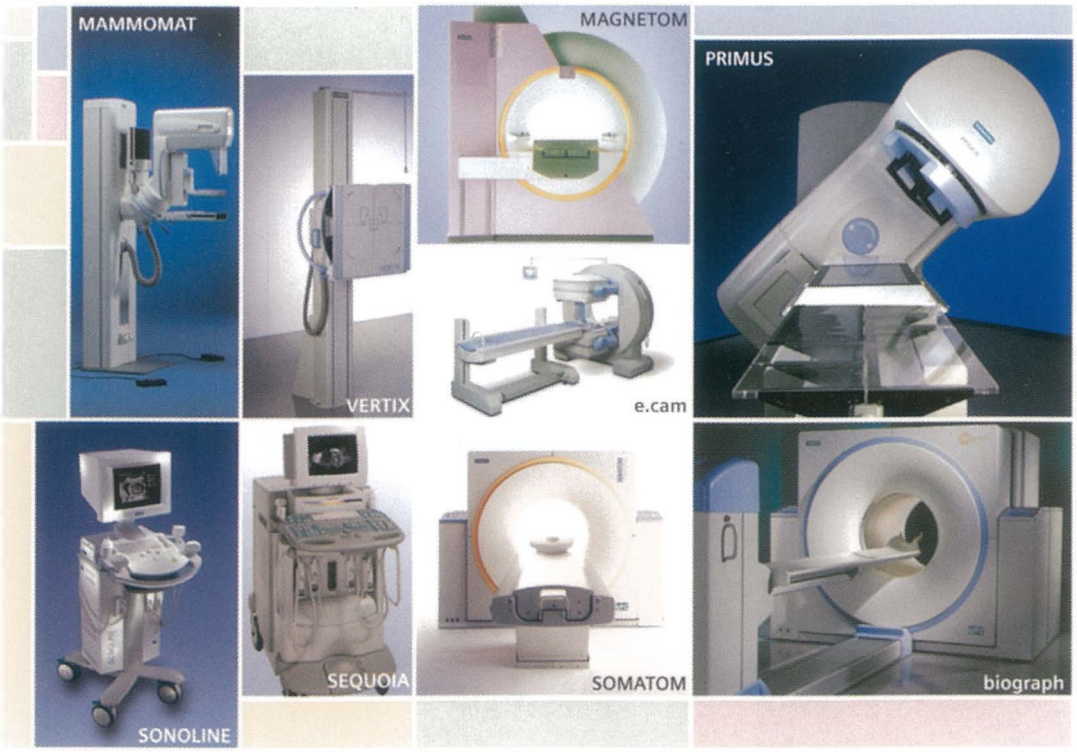




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# Boerhaave' s syndrome: a case with an atypical right-sided oesophageal perforation

**Ivica Sjekavica[1], Goran Pavliša[1], Marina Šeronja-Kuhar[1], Ines Moscatello[2], Ranka Štern-Padovan[1]**

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***Background.*** *Boerhaave's syndrome is a complete transmural perforation of the thoracic oesophagus, with the oesophageal tear occurring on the left posterolateral side in 90 % of the patients.*
***Case report.*** *We present a case of Boerhaave's syndrome with an atypical feature of right-sided oesophageal rupture. Chest CT has the advantage of imaging all thoracic structures and complications and excluding differentially diagnostic conditions in the case of a high clinical suspicion of oesophageal rupture.*
***Conclusions.*** *CT is especially important in patients whose severe clinical condition does not permit esophagography.*

*Key words: esophageal diseases, rupture, spontaneous; tomography, X-ray computed*

## Introduction

Boerhaave's syndrome is a spontaneous complete transmural perforation of the thoracic oesophagus secondary to food bolus impaction. Perforation in most cases results from violent retching or vomiting after excessive food and alcohol intake. The syndrome owes its' name to famous Dutch 17th century physician Hermann Boerhaave who described a case of Great Admiral of Dutch fleet who overate and after vomiting acquired this condition.

The syndrome is life threatening, with overall mortality of about 35%.[1-3] It is a consequence of neuromuscular incoordination, with a barogenic injury caused by a sudden increase in intraluminal pressure against a constricted cricopharyngeus muscle which fails to relax. Since the perforation is caused by vomiting and oesophageal barotrauma, it is, literally spoken, not spontaneous, but this term distinguishes it from much more often iatrogenic rupture. The oesophageal tear is usually linear, 1-5 cm in length, vertically ori-

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ented. It occurs in a majority of cases (90%) on the left posterolateral side, 2-3 cm above the gastroesophageal junction.[1,3] Gastric content extraluminates into mediastinum and pleural space, ensuing mediastinitis, sepsis and shock. No haematemesis occurs because blood escapes outside the oesophageal lumen after rupture. Haematemesis is a feature of more common Mallory-Weiss tear, which is a gastric (rarely oesophageal) mucosal and submucosal tear.

The clinical features of Boerhaave's syndrome are often misleading. The so-called Mackler triad is virtually pathognomonic, consisting of forceful vomiting, sudden onset of pain (substernal, neck, abdominal-epigastric, or radiating to the shoulder) and subcutaneous emphysema. Complete triad is seldom present. Other symptoms include dyspnea, tachypnea, abdominal rigidity and signs of haemodinamic shock. The mainstay of therapy is prompt surgical intervention with closure of the tear, intravenous volume resuscitation and mediastinal drainage, except for some cases of small-contained iatrogenic injuries and cervical perforations. Boerhaave's syndrome occurs 2-5 times more often in males than in females, typically in middle-aged men.[1,3]

We present a case of Boerhaave's syndrome with extensive bilateral intrathoracic pathology and an atypical feature of right-sided oesophageal rupture, reported in a minority of cases.[4,5]

## Case report

A 57-year old male patient was admitted to a county hospital after suffering a vomiting series. He presented with epigastric pain, forceful vomiting and signs of gastro-intestinal bleeding, without subcutaneous emphysema. His cardiac condition was stable. Plain abdominal film was normal. After insertion of nasogastric tube, about 700 ml of haematinic content was removed. Endoscopy revealed extensive blood coagula in the oesophageal and stomach lumen.

Thirty-six hours after the presentation the patient was transferred to Clinical Hospital Center in haemodynamically stable condition, with intermitent vomiting. Initial oesophagography and endoscopy both failed due to dyspnea and psychomotoric excitation of the patient. During ultrasound examination he developed cardiorespiratory arrest, and was transferred to the intensive care unit after cardio-pulmonary resuscitation. Ultrasound examination showed signs of intestinal paresis and extensive pleural effusion. Thoracocentesis acquired gastric-like content. Since the patient was not able to undergo oesophagography, urgent endoscopy was performed and demonstrated 1 cm long oesophagus tear, on the right lateral side, just above the gastro-oesophageal junction with irregular margins, covered with fibrin. The adjacent mucosa was normal and without varices. There were no signs of bleeding artery or fresh blood flow, while stomach was filled with blood clots.

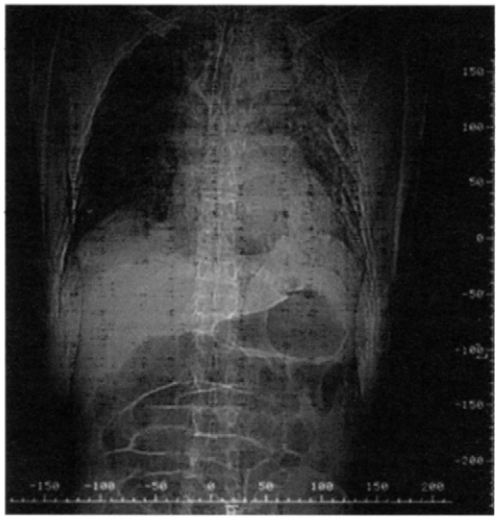

**Figure 1.** Chest CT scout view. Non-homogenous infiltration of the left lung, widened upper and middle mediastinum and signs of paralytic ileus.

CT was performed to demonstrate the extent of the disease. A scout view displayed a non-homogenous infiltration of the left lung, widened upper and middle mediastinum and signs of paralytic ileus (Figure 1).

Pleural effusions were bilateral, with right-sided major pneumothorax, infiltration of the left lung with atelectatic component and minor pneumothorax (Figure 2).

Pneumomediastinum was observed with tiny lucencies especially around distal oesophagus and air-fluid levels within mediastinum (Figures 3,4). Subcutaneous emphysema was also noted.

Shortly after CT examination the patient died. Pathology report confirmed right-sided oesophageal laceration and CT findings.

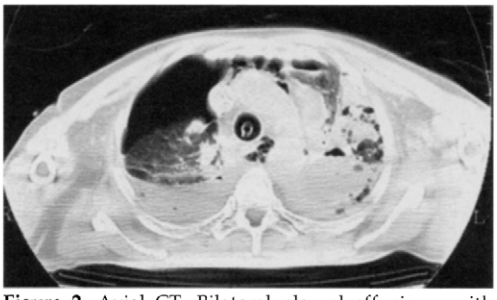

**Figure 2.** Axial CT. Bilateral pleural effusions, with right-sided major pneumothorax, non-homogenous infiltration of the left lung with atelectatic component and minor pneumothorax.

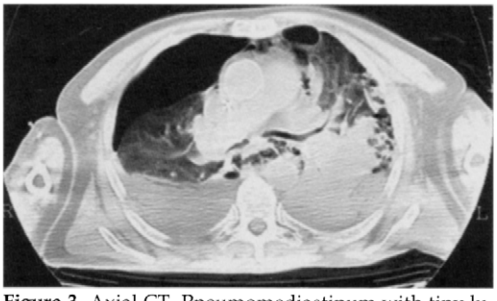

**Figure 3.** Axial CT. Pneumomediastinum with tiny lucencies especially around distal oesophagus.

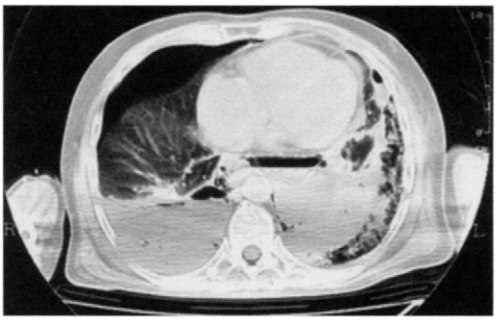

**Figure 4.** Axial CT. Air-fluid levels within mediastinum. Extensive pleural effusions.

## Discussion

Boerhaave's syndrome is a rare, but diagnostically demanding entity. Fast and accurate diagnostics is invaluable. Upright chest radiograph is initially abnormal in 90% of patients with pneumomediastinum as the most important finding.[3] The chest radiographs may be normal, because the findings may take an hour after the perforation to appear. The common feature is usually left-sided pleural effusion due to the site of perforation which mostly occurs in the left posterior aspect of the oesophagus; however if perforation occurs into right pleural cavity, it is usually in very young patients. Hydropneumothorax (in 51% of cases), subcutaneous emphysema or mediastinal widening may be present.[6] A specific, but insensitive radiographic sign is the »V-sign of Naclerio« - an air lucency between lower thoracic aorta, oesophagus and diaphragm in the shape of the letter V, presenting localized mediastinal emphysema.

All described signs were present in this case, seen at CT, with an atypical site of oesophageal tear on the right lateral side and major right-sided pneumothorax. Computerized tomography has the advantage of displaying all thoracic structures and excluding differentially diagnostic conditions, like such as: aortic dissection, myocardial infarction, acute pancreatitis, pneumothorax, oesophagitis, peptic ulcer disease, spontaneous intra-

mural haematoma of the oesophagus (SIHO, oesophageal apoplexy) and Mallory - Weiss tear.[7] CT scout view may replace chest radiograph in an urgent case. It is required especially in patients whose condition does not allow oesophagography,[8,9] demonstrating the extralumination of contrast material into mediastinum and displaying the presence, location and the length of the tear.

Presented case emphasises the severity of this syndrome and the importance of awareness of clinical manifestations. Survival rate is 70-75% if surgical repair of the rupture is performed in early injury, within 24 hours of the incident.[3] Significant number of patients are late in presentation for medical care.[10,11] With late intervention, the mortality rate (even with surgical intervention) rises to higher than 50% and to over 80% after 48 hours.[2,3,12] The delay in raising suspicion of oesophageal perforation results in postponing of appropriate and simple diagnostic method - oesophagography.

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# MR imaging of aortic coarctation

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***Purpose.*** *The purpose of this paper is to analyse the contribution of MRI as diagnostic procedure in the preoperative diagnosis of aortic coarctation (CoA), in patients with clinical and echocardiographic suspicion for this disease.*

***Patients and methods.*** *During the period of three years, eight patients were examined, 5 (62.5%) male and 3 (37.5%) female patients with clinical echocardiographic suspicion of CoA. The ratio between male and female patients was 1.7 : 1. The youngest patient was 3 and the oldest 46 years (median age was 15 years). Without administration of contrast media and using body coil the examinations were performed with MR machine Magnetom 1.0 Tesla (»Siemens«), with the slice thickness of 6 mm, Fast spin-echo (FSE) T1W sequences, Cine gradient echo (GRE) sequence with slab 7 mm and time of flight (TOF) sequence with MIP reconstructions were applied. During the examinations the patients underwent also ECG gating. Examinations were done in axial, coronal and oblique sagittal projections with measuring of the dimensions of cardiovascular structures.*

***Results.*** *CoA was found in 8 (100%) patients. In 7 (87.5%) cases, coarctation developed at isthmus and in one case, coarctation was detected at the horizontal part of aortic arch, between the truncus arteriosus of the left carotid communis artery. Aortal insufficiency was found in 7 (87.5%) patients; in four of them (50%), bicuspidia was confirmed (bicuspid aortic valve), 7 (87.5%) patients had slightly expressed hypertrophy of the left ventricle. Two (25%) patients had dilatation of the ascendant aorta, six (75%) wider outgoing vessels of the aortic arch, four (50%) had well developed arterial collaterals and 2 (25%) patients rib notching. In 2 (25%) patients as side finding thymus persistent was found. Average diameter of coarctation was 10 mm. In one patient, CoA was accompanied with stenosis of pulmonary artery, in one with ventricular septal defect, and one with tricuspid insufficiency. The results of MRI 100% were in correlation with clinical and echocardiographic findings.*

***Conclusions.*** *MRI is a non-invasive method of investigation of the heart and large blood vessels and it is more and more an alternative to the invasive angiographic investigations, especially in paediatrics, because there is no radiation at all. It is complementary to the echocardiographic, intra-arterial digital subtraction angiography (IA DSA) and helical CT (SCT).*

*Key words: aortic coarctation-diagnosis; magnetic resonance imaging*

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## Introduction

Coarctation of aorta (CoA) is acongenital anomaly of the aortic arch as anomaly of the caliber.[1] It occurs as the obstruction of aortic isthmus, very frequently localized distally to the left subclavian artery, opposite to insertion of the ductus arteriosus.[2-4] The level of the collateral blood circulation through the subclavial and intercostal arteries depends on the level of narrowing of the aortic coarctation.[3] A stenosed lumen can be narrowed into the size of the knitting needle, but it can be very rarely completely occluded.[5] Pathohistologicaly this is an obstruction membrane in location of aortic isthmus.[6]

Based on the statistics of M. Abbott, we meet this anomaly in 8% of overall congenital heart malformations; it is three times more frequently in males than in females patients.[5] This is the third most frequent anomaly of cardiovascular system.[3]

There are two types of CoA: juvenile - the diffuse type (preductal tubular hypoplasia) and the adult type - stenosis of short segment (postductal and periductal).[2-5]

This anomaly can be accompanied with the so-called coarctation syndrome, which is a coartctation triad of previous ductus arteriosus and ventricular septal defect. It can also be accompanied with hypoplasia of aortal arch (small arch) bicuspodia of the aortal valve (25-50%), aneurysm of sinus valsavle, aneurysm at the place of coartctation, aneurysms of subclavia artery, ductus arteriosus or circulus Willis, anomalies of aortal arch as in many other congenital heart diseases (until 70%).[2,3,6,7] We meet it also in Turner's syndrome.

Coarctation of abdominal aorta is seen in 2% of cases.[2]

Radiologically similar to coarctation is so called pseudocoarctation. It is unusual asymptomatic variant of coarctation, in which the descendent end of aortal arch retracted sharply in front, at the place of insertion of the arteriosum ligament. The aortal arch above the bended part is abnormally high and convex and it can look similar to the tumour of back upper part of the mediastinum. Stenosis, deficit of pulse and rib notches do not exist in pseudocoarctation.[2,6,8]

The idea of some authors is to declare all mediastinal masses as vascular etiology, until it is not proved the otherwise.[6]

Two changes are regarded as repercussion to coarctation: development of arterial collaterals and hypertrophy of left ventricle.[2]

Coarctation of the aorta is a disease which very frequently escapes on the early detection and treatment, too. This may causes cardiovascular accidents and early death as the consequence of the coartctation increase with delaying the treatment.[9]

It was diagnosed in about 20% of our patients at adolescence for the first time. In a big series of patients with coarctation of aorta the mean age at diagnosis was 10 years. In younger patients most frequent sign (mean age 6 years) was a murmur, and in older patients (mean age 18 years), was systemic hypertension.[9]

Average survival of patients with the adult type of this malformation is 33 year; only 25% survive 40 years.[5] Death occurs because of the rupture of aorta (around 25%), infective endocarditis or aortitis (around 20%), heart insufficiency (around 20%), intracranial haemorrhage (around 10%), and rupture of the heart (1%).[5]

Beside murmurs and hypertension, other accompanying signs are the delay of pulse between radial and femoral artery, difference in pressure between upper and lower extremities or rib notches in the lower margins of ribs on the thoracic plain film.[9] Rib notches were anatomically found by Meckel in 1827 and radiologically by Resler in year 1928. They are almost always present in adults, especially we meet them between the 3$^{th}$ and 6$^{th}$ rib, some authors found them between the 4$^{th}$ and 8$^{th}$ rib, bilaterally, but not symmetrically.

Although, usually they do not occur in children younger then 7-8 years of age, they can be met even at child nine months old. According to Pugh they are not present in 1/3 of cases.[2,5]

Beside rib notches, thoracic plain film shows hypertrophy of the left ventricle, aorta ascendant very frequently forms the right edge of the heart, and rarely aortal button is missing. The examination of the esophageous with barium contrast showed the number three sign. Lung vascularisation is normal.[2,5]

Most frequent clinical feature is hypertension of upper extremities, while femoral pulse is usually not palpable.[6]

The treatment of coarctation is surgery with resection of coarctation and end-to-end anastomosis, patch isthmio-plastics with synthetic material or subclavian patch, balloon angioplasty, for stenosis of short segment.[2,6]

Beside the above mentioned clinical findings and the thoracic plain film, in the diagnostics of the coarctation, the conventional angiography, intra arterial digital subtraction angiography (IA DSA), helical CT (SCT), trans-oesophageal echocardiography (TEE) and magnetic resonance imaging (MRI) are used.[4,6,9] The last three methods are non-invasive and more and more used in the diagnostics of the conditions of the heart and vascular anomalies. MRI is especially interesting in establishing the diagnosis of coarctation of aorta and planning the treatment in the early phase because of its multiplanarity, no radiation and information which it can give about the present haemodinamic disturbances.

The purpose of our study is to analyse the MRI contribution in diagnostics of CoA.

## Patients and methods

In the period of three years eight patients are examined and all of them were suspect clinically and echo-cardiographycally for CoA. Among those patients 5 (62.5%) were male and 3 (37.5%) female. The rate between male (5) and female (3) patients was 1.7 : 1. The youngest patient was three years old and the oldest 46 (average age was 15 years). Examinations were performed with MR machine Magnetom 1.0 Tesla (»Siemens«). We did not use the contrast media because of missing the proper connector required by the size of gantry. During the examination, fast spin-echo (FSE) T1W (black blood) sequences were used, especially in the oblique saggittal plane because of determining the location and level of the stenosis, the spread of the coarctation and presence of collateral vessels in regard to the morphology of vascular structures and accurate orientation Cine-gradient echo (GRE) sequence. From GRE (bright blood) sequence, Cine sequence is used aiming to evaluate the disturbance of signal void in the part of coarctation and valve apparatus (place of stenosis). In other words the evaluation of the functional state of the aortal coarctation and time of the flight (TOF) sequence was performed, with the use of maximum intensity projection (MIP) reconstructions, to show the place of coarctation, outgoing vessels of the aortic arch, collaterals and collateral flow. During the examination, ECG gating was also used.

Examinations were performed in axial, coronal and oblique positions, in the direction and extend of aortic arch, with the slice thickness of 6 mm. In cases of improper cross-section because of the thickness of the slices in the region of the coarctation e.g. in case of small children, stratified slices were made to acquire the best scan. During the investigation, measurements of the heart wall and heart cavity were performed, especially of the left ventricle, ascendant aorta, aortic arch, descendent aorta and the zone of coarctation. Examinations were done preoperatively in order to evaluate the severity of the disease and decide about the preoperative plan. Body coils are not used because they were not available.

## Results

Among the examined patients, coarctation of the aorta was found in 8 patients. In 7 (87.5%) cases, the coarctation developed at the isthmus, and in one case at the horizontal part of the aortic arch. Aortal insufficiency was confirmed in 7 (87.5%) patients, in 4 (50%) of them bicuspidia was observed, while in 7 (87.5%) patients hypertrophy of the left ventricle was slightly expressed. Wider outgoing vessels from the aortic arch were found in 6 (75%) patients. In 2 (25%) patients dilatation of the ascending aorta was observed. In 4 patients (50%), collateral flow was well developed, and in 2 (25%) patients, rib notching in the plain thoracic radiographs was revealed.

In one patient coarctation was accompanied by stenosis of pulmonary artery, in one by ventricular septal defect and in other one with tricuspid insufficiency. Those findings were in correlation with echo cardio graphic findings. The oldest patient (46 years) had in medical history the heart infarction and dilated cardiomyopathy. Patient was with coarctation in the horizontal part of the aortic arch between truncus brachyocephalicus and the left carotid communis artery, and with knocking of the same in its back part (variant of pseudocoarctation). As accompanying finding, in 2 (25%) younger patients, thymus persistent was found.

In all cases spin-echo (SE) sequence gave an excellent morphologic presentation of the location of coarctation of the ascendant aorta, aortic arch, with outgoing vessels from the arch, descendent thoracic aorta, discontinuity of the collateral flow and mammary artery. An average diameter of the coarctation place was 10 mm; in one young female patient 13 aged, the diameter was 5 mm.

Cine sequence in the slab of 7 mm, though providing satisfactory morphologic presentation in real time, appears to be extraordinary sensitive to the velocity, thus clearly showing the signal void in the region of the valve apparatus and at the site of coarctation.

The image of aortal coarctation was complete after using the time of flight (TOF) sequence that contributed enormously to morphology, in addition to providing an image of the collateral flow and the mammary artery.

Using this set of sequences - about the morphology of the coarctation and circulatory disorders - important information was obtained in a non-invasive way, and without using the contrast media.

MR results were in 100% of cases in correlation with the ones gained by echocardiography when it was about the heart's morphology and the valve apparatus.

## Discussion

As it was presented in the introductory part, CoA is the most frequent anomaly of the cardiovascular system. Its diagnostics is relatively easy and for a long time it has been made only clinically, based on the discovery of heart murmur, hypertension, differences in pressure between upper and lower limbs and rib notches in the thoracic plain films.

In this investigation the most frequent clinical sign in young patients was heart murmur and the difference in pressure between the upper and lower limbs, and in older patients hypertension. Rib notches were found in a 1/4 of patients, whereas in literature there were found in 1/3. Here we have to bear in mind that half of our patients were younger then 8 years.

In this series the oldest child was 13 year old, and the 2 grown patients were 30 and 46 years old, respectively. In the larger series the mean age of patients at diagnosis was 10 years, and in our series it was 15 years. The ratio between male and female patients was 1.7 : 1 in our study, while in literature it was 3 : 1.[5]

In adults over 40 years CoA is observed in

only 20 % of cases, and in our small series 1 (25%) patient was over 40 years. Aortal insufficiency was found in 7 patients; in 50% of them bicuspidia was discovered, which is in line with the percentage reported in literature, where it ranges between 25-50%.[2] Correlation with other congenital anomalies in CoA is high and reaches 70 %; in our series, it was 37.5%. The obtained results were in line with the one gained from echocardiography. MR proved to be very sensitive to flow disturbances.

CoA falls in the group of curable congenital anomalies of the vascular system. The treatment of choice is surgery; therefore, it is necessary to establish a precise diagnose and to identify all accompanying anomalies.

Today, several excellent methods for analysis of the big blood vessels and Coal, like SCT, MR and TEE, are used.[3]

Conventional angiography has been, until recently, the golden standard. It allows measuring the pressure, but it is invasive, risky because of radiation, haemorrhage, vascular lesions, thrombosis and allergic reactions to the contrast media.

Echocardiography is non-invasive alternative which is widely used today. However, at times, it is very hard to acquire good visualization of the site of coarctation because of small acoustic window, long distance between transducer and the isthmus region, and because of non-cooperation of patient.

In recent years the use of MR imaging have become more intensive and proved to be excellent tool for non-invasive investigation of cardiovascular system in older and younger patients.[10]

In our series clinical and echocardiographic suspicions on CoA were confirmed in 100% of cases by MRI with the use of fast spin echo (FSE), Cine and TOF (time of flight) sequences, that allow an extraordinary morphologic presentation of the heart and big vascular structures, as zones of disturbed flow (Figures 1,2,3,4).

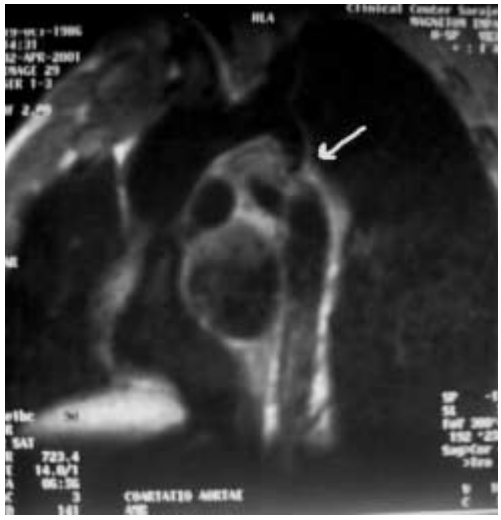

**Figure1.** Coarctation of aorta, spin-echo (SE) T1W (Black blood)

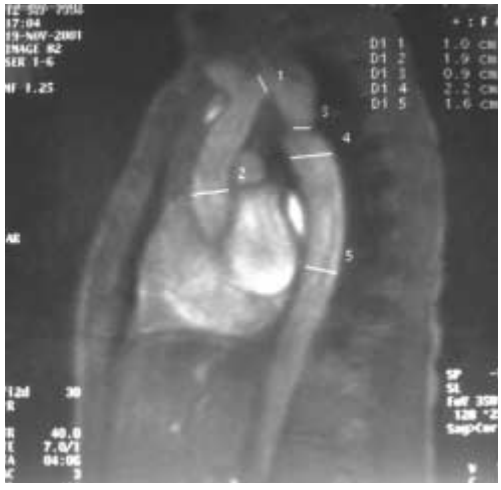

**Figure 2.** Coarctation of aorta on MRI with measurements

Drawbacks of this technique are its incapacity to measure the pressure in the zone of coarctation and the impossibility of applying of contrast media in the way as it is applied in contrast enhanced magnetic resonance angiography (CE MRA). Reasons for this were of technical nature. The shortage of the thoracic coil was, to a certain degree, substituted by proper sedation and preparation of patient before scanning.

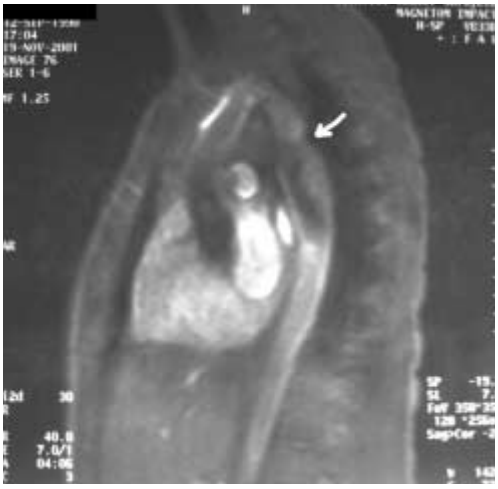

**Figure 3.** Coarctation of aorta, Cine - gradient echo (GRE) (Bright blood - signal void: arrow).

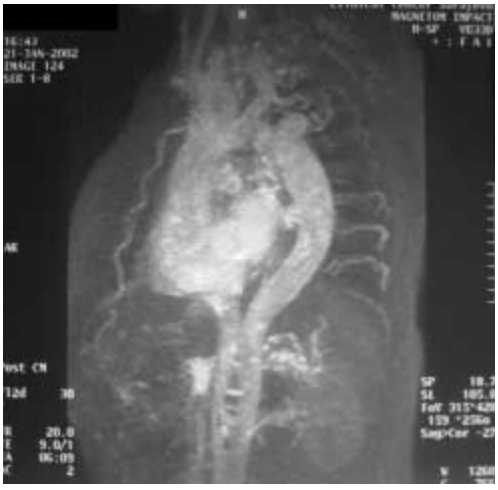

**Figure 4.** Coarctation of aorta, arterial collateral's time of flight (TOF).

According to literature MR, imaging is a powerful tool in the evaluation of full range of congenital and acquired diseases of the thoracic aorta. It is safe, accurate and can be repeated several times, giving extremely useful anatomic information and clearly detecting collateral vessels. It also provides information about the extraluminar relationship of aorta with the surrounding organs, no matter in which projections they are seen.[11]

In our investigation, this advantage was observed with the discovery of thymus in 2 younger patients with coarctation of aorta.

Today, in the diagnostics of aortal coarctation, FSE and angiographic gradient echo (Cine - GRE, TOF, PC and recently also CE 3D MR) sequence are used worldwide.

MRI SE sequences provide very useful anatomic details, while Cine MRI sequence can detect a turbulent jet of blood and the place of coarctation.

MR angiography (MRA) does not provide adequate information about the wall of the vessel; the intimal flap and parietal thrombus can be dizzy and hardly seen even with the help of MIP (maximum intensity projection) algorithm.

SE and GRE technique are complementary; the first takes a lot of time, especially when ECG triggering is used.

MRI is non-invasive and doesn't depend much on the experience of operator.

In children, sedation is needed, possibly general anaesthesia; echo navigator techniques have been developed to prevent image degradation.[12]

MRI can be used preoperatively to evaluate the severity of the disease and to decide about the operative plan.

Beside the analyses of morphologic abnormalities, it also allows to measure the size of vascular structures with the speed of the flow at the place of stenosis, in order to assess functional disturbances.[13]

It has also some limitations, as artefacts because of respiratory movements, saturation problems and long time of diagnostic orocedure.[14]

Basic (without contrast) MRA-GRE technique is time of flight (TOF) and phase-contrast (PC) sequences.15 Beside those the so-called contrast enhanced (CE) three-dimensional (3D) MRA sequence is also used today. CE 3D MRA and TSE sequence are used in the set for analyzing the morphology of aortal arch, vascular diameter, location and scope of

the abnormality of coarctation, its relationship to the outgoing vessels from aortic arch.[16] Measuring the dimensions of the aorta proved to be very useful before the surgical correction or balloon dilatation of the coarctation. A good correlation was observed between the measurement performed with MIP reconstruction and catheter angiography.[17]

3D reconstruction using the maximum intensity projection (MIP) technique is a reliable non-invasive technique which can replace the diagnostic catheter angiography, especially during postoperative controls of the coarctation. It provides the clinician with valuable information concerning further application of invasive procedures. In regard to decreasing the effect of altered flow dynamics, CE 3D MR angiography of thoracic aorta has several advantages over to spin-echo SE (black blood) and TOF (bright blood) MRI sequences. It is independent from ECG triggering, which is of special importance in patients with arrhythmias. This technique is proved to be reliable in the diagnosis of aortic coarctation.[15] ECG triggered breath-hold contrast material-enhanced magnetic resonance angiography sequence has been developed for imaging the thoracic aorta, aiming to decrease the respiratory motion artefacts and pulsation artefacts. 3D MRA is independent from that if the flow is laminar, turbulent or stagnating. Different congenital and acquired abnormalities are clearly identified with this technique.[18]

Breath hold contrast enhanced 3D MR angiography is faster and more accurate method in diagnostics of the diseases of thoracic aorta, but has limitations in the estimation of the aortal lumen. This is why black blood and bright blood MR sequences are necessary in the analysis of aortal wall, aortal valve and periaortic tissue.[19]

CE MRI is especially useful in small children who cannot keep their breath, which is required in 3D reconstructions.[10] Moreover; gadolinium has smaller nephrotoxicity and less allergic reactions as iodine based contrast medias.[12]

Aortal diameter, stenosis, aneurism, intimal calves or atherosclerotic plaques can be analyzed with 3D reconstruction using MIP technique.[17]

The role of MRI is also of special value for following the patient's with repaired cardiovascular anomalies and is also widely used for presenting the morphology of large blood vessels. MR flow mapping can be used for analyzing the flow in large vessels.[20]

3D CE MRA with 0.2 mmol/kg Gd. in IV bolus, more exactly 20 ml Gd was followed with 20 ml saline most frequently at a flow of 3ml/s with ECG gating and preceding bolus test may be necessary. With such proceeding it is obtains optimal quality of the image, made in the oblique saggittal plain with standard MIP/MPR reconstructions. It is important in case of artefacts from surgical clips which can disturb considerably the quality of the image.[21-23]

3D MRA (FISP) is used to measure the flow and elasticity of the vascular wall. With these techniques it is possible to have an adequate follow up of coarctation, meaning that, usually, IA DSA is not needed in defining the condition and size of the proximal and distal anastomosis and the morphology of the thoracic aorta.[23,24]

The so-called fluoroscopic triggering of centrically encoded 3D MR angiographic acquisitions have also been developed and have been reported as highly accurate methods of acquiring 3D MR angiograms with high spatial resolution.[25]

Because of the reasons mentioned earlier, the described 3D CE MRA sequences were not applied in this study.

## Conclusions

MRI is a non-invasive method of examination; it is becoming more and more an alter-

native to the invasive angiography, especially in paediatric patients, because it is radiation-free. It is complementary to the other methods, like US, DSA and SCT. MRI is an excellent technique for evaluating the morphologic anomalies of aortic isthmus before and after the operation or percutaneus treatment. It may be concluded that, by this method the coarctation of aorta can be followed up non-invasively.

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# Rituximab affects the prognosis of patients with nonHodgkin's lymphomas

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***Background.*** *Rituximab - the most widely used monoclonal antibody in the B cell lymphoid malignancies - has been applied successfully in the treatment of relapsed and refractory indolent CD20 positive B cell lymphomas and more recently, also in the treatment of aggressive lymphomas in combination with standard chemotherapy. Albeit the chemo-immunotherapy has a wide range of potential applications, there are still several issues that have to be resolved: (1) the optimal scheduling of antibody-chemotherapy combinations, (2) the most active of these combinations, as well as (3) the predictors of response to rituximab.*

***Patients and methods.*** *To facilitate addressing the first two questions, we performed an analysis in 25 patients with different histological types of CD20 positive nonHodgkin's lymphomas (10 aggressive and 15 indolent). Seventeen patients were treated with chemo-immunotherapy for a relapse, and just in 8 patients rituximab was added to first line chemotherapy. Most of the responders received the CHOP regimen, but also other regimens (FC, BVCPP) were effective in combination with rituximab.*

***Results.*** *The overall response rate was 76%, with 68% complete remissions. The median response duration has not been reached yet. The response was markedly better in the group of previously untreated patients, where the overall response rate reached 100%, with 7 patients in complete and 1 patient in partial remission. Most of the treatment failures occurred in heavily pretreated patients with aggressive lymphomas. No serious adverse effects were observed.*

***Conclusion*** *The chemo-immunotherapy improves the treatment outcomes in patients with untreated and relapsed CD20 positive nonHodgkin's lymphomas in comparison to chemotherapy alone. The combined treatment is the most effective when used as soon as possible (preferably as the first line treatment). To optimize the use of rituximab, not only the most active antibody-chemotherapy combination will have to be determined, but also the predictors of success of such treatment will have to be identified.*

*Key words: lymphoma, nonHodgkin's; rituximab*

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## Introduction

The CD20 antigen, a 35 kDa phosphoprotein, is restricted to the B cell lineage and is expressed by mature B cells and most malignant B cell lymphomas. While the exact functions of CD20 are unknown, it may play an integral role in the activation of cell cycle progression in B lymphocytes, possibly via calcium regulation. Its attributes, as its tetraspan binding in the cell membrane and the lack of internalization or downregulation upon antibody binding, make the CD20 suitable as a target for an effective antibody.[1]

Rituximab, a chimeric IgG κ monoclonal antibody that recognizes the CD20 antigen[2], is the most widely recognized and used monoclonal antibody in the B cell lymphoid malignancies. It has been applied successfully in the treatment of relapsed and refractory indolent CD20 positive B cell lymphomas and more recently, also in the treatment of aggressive lymphomas in combination with standard chemotherapy. The indications for its use are now expanding also to Hodgkin's disease and autoimmune diseases.[3]

Even though the results with rituximab as monotherapy as well as in combinations with chemotherapy have been encouraging, many questions still remain to be answered about optimizing its use in patients with malignant lymphomas. Actually, the optimal scheduling of antibody-chemotherapy combinations and the identification of the most active of these combinations have to be resolved, as have the details about its mechanisms of action and the predictors of response to this agent.

With the aim of seeking the optimal scheduling of antibody-chemotherapy combination and identifying an active combination, we performed a retrospective analysis of the results obtained from 25 patients with predominately relapsed CD20 positive nonHodgkin's lymphomas.

## Patients and methods

In the year 2001, 25 patients with CD20 positive nonHodgkin's lymphomas were treated with the combination of rituximab and chemotherapy at the Institute of Oncology in Ljubljana, Slovenia. The group consisted of 10 male and 15 female patients. According to the histological type, there were 1 patient with Burkitt's lymphoma, 5 patients with diffuse large B cell lymphoma, 2 patients with unclassified CD20 positive aggressive lymphoma, 13 patients with follicular lymphoma (5 patients grade I, 3 patients grade II, 2 patients grade II/III, 3 patients grade III, and 1 patient unspecified grade), 2 patients with mantle cell lymphoma, and 2 patients with small lymphocytic lymphoma/CLL. Most of the patients were treated for a relapse - in 12 patients the combined treatment with rituximab and chemotherapy was third (or more) line treatment, in 5 patients second line treatment, and just in 8 patients rituximab was added to inadequately successful first line chemotherapy.

The patients received at least 2 and not more than 6 cycles of chemo-immunotherapy. Rituximab was applied in standard doses (375 mg/m$^2$) on day 1 of the chemotherapy cycle, and was combined predominately with CHOP regimen (20 patients), but also with other chemotherapy schedules (1 patient COP, 2 patients FC, 1 patient VACPE, 1 patient BVCPP) according to their previous treatments. All patients received methylprednisolone, paracetamole and clemastine prior to the application of rituximab.

Treatment response was evaluated according to Cheson's criteria.[4]

## Results

In total, complete response was achieved in 17 patients, which represents 68%. The longest observed duration of complete re-

sponse until now is 19 months, and 11 patients are still in complete remission.

The partial response was observed in 2 patients (8%), with the median duration of 8 months. In 1 patient there was stable disease after rituximab and FC treatment, and the patient continued his treatment with a different chemotherapy regimen.

Five patients progressed during chemo-immunotherapy - they all received less than 6 cycles of therapy (at least 2 and at the most 4 cycles), and eventually died of lymphoma. In 3 of these patients, the chemo-immunotherapy was fifth line treatment, in 1 patient second line treatment, and in 1 patient third line treatment. Four of the 5 patients with progressive disease had aggressive histological types of lymphomas, and only 1 patient had indolent follicular lymphoma, but was heavily pretreated.

Surprisingly good results were observed in the small group of patients in whom rituximab wad added to the first line chemotherapy treatment. The overall response rate in this group was as high as 100% with 88% complete responders (7 out of 8 patients), and 1 partial responder. The patient with partial remission relapsed after 14 months, while 6 of 7 complete responders are still in remission.

The treatment outcomes according to histological subtypes are given in Table 1.

The chemo-immunotherapy was very well tolerated and no serious infusion related adverse effects were observed in more than 100 applications. The addition of rituximab to chemotherapy also had no significant influence on the hematological toxicity, and no WHO grade IV infections were observed.

**Table 1.** The treatment outcomes according to histological subtypes

| Histological subtype | No. of patients | Chemotherapy regimen | Line of treatment | Response | Duration of complete or partial response (months) |
|---|---|---|---|---|---|
| **Burkitt's lymphoma** | 1 | CHOP (1 pt.) | Second (1 pt.) | Progressive disease (1 pt.) | |
| **Diffuse large B cell lymphoma** | 5 | CHOP (2 pts.)<br>VACPE (1 pt.)<br>FC (1 pt.)<br>BVCPP (1 pt.) | First (1 pt.)<br>Second (1 pt.)<br>Third (3 pts.) | Complete response (4 pts.)<br>Progressive disease (1 pt.) | 12+ |
| **Unclassified aggressive lymphoma** | 2 | CHOP (1 pt.)<br>COP (1 pt.) | Third or more (2 pts.) | Progressive disease (2 pts.) | |
| **Follicular lymphoma** | 13 | CHOP (13 pts.) | First (5 pts.)<br>Second (3 pts.)<br>Third or more (5 pts.) | Complete response (11 pts.)<br>Partial response (1 pt.)<br>Progressive disease (1 pt.) | 8,8+<br>14 |
| **Mantle cell lymphoma** | 2 | CHOP (2 pts.) | First (2 pts.) | Complete response (2 pts.) | 4+ |
| **Small lymphocytic lymphoma/CLL** | 2 | CHOP (1 pt.)<br>FC (1 pt.) | Third or more (2 pts.) | Partial response (1 pt.)<br>Stable disease (1 pt.) | 2 |

## Discussion

Although various standard chemotherapeutic regimes are active in the treatment of patients with nonHodgkin's lymphomas, the results of such treatments are far from optimal. The addition of rituximab to chemotherapy seems to offer an advantage to these patients both in terms of the percentage of response as well as in terms of the response duration. As to the chemotherapy regimen choice it has been namely confirmed by *in vitro* observations that monoclonal antibody exposure may sensitize tumor cells to chemotherapy, and specifically to fludarabine, cisplatin, vinblastine, and doxorubicin.[5,6] Most of the applied regimens in our study included one of the above mentioned cytotoxic drugs, while for the others it has been expected that rituximab will enhance their effect through its interference with the apoptotic processes.[7]

Our outcomes are in accordance with the clinical results of various authors stating that the addition of rituximab to different chemotherapy regimens improves the treatment results.[8-12] However, more and more data confirm the fact that rituximab should be used as soon as possible (preferably in the first line treatment) in the treatment of lymphoma patients in order to achieve maximal efficacy.[13,14] Among our patients, in only 8 patients rituximab was added to inadequately successful first line chemotherapy, while all others received immunotherapy for relapses of nonHodgkin's lymphomas. All 8 patients actually achieved a remission after the addition of the rituximab to the chemotherapy regimen that they had been receiving before (in 7 patients a complete remission, and in 1 patient a partial remission). The results with relapsed lymphomas were convincingly worse. Out of 17 patients, 10 achieved a complete remission (59%), 1 a partial remission (6%), 1 a stable disease (6%), and 5 patients progressed (29%). Certainly, the significance of these results is inestimable due to a small number of patients. However, the results speak in favor of using rituximab as a first line treatment.

Since it is becoming obvious from the numerous clinical studies that rituximab improves the treatment outcomes when it is combined with various chemotherapy regimens, the next step in the research will have to be the identification of predictors for success with chemo-immunotherapy. Not only the IPI, but also new molecular, biologic, and immunologic factors will have to be recognized, before the use of rituximab can be stated as rational. Currently, the overexpression of certain genes involved in cellular immunity has already been confirmed in nonresponders to rituximab[15], as well as the meaning of pretreatment Mcl-1/Bax ratio.[16] Also the cytogenetic abnormality as del (17p13.1) was identified as the predictor of poor response to rituximab.[17] Another predictor, the bcl-2 overexpression, that according to Mournier *et al.*[18] foretells a better outcome of first line rituximab plus CHOP treatment (compared to bcl-2 negative patients) has not been confirmed in patients with relapsed diffuse large B cell lymphoma.[19] Thus to determine more accurately the patients that will benefit at most from the chemo-immunotherapy, further studies will have to be done on a larger number of patients.

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# Neuron specific enolase - selective marker for small-cell lung cancer

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***Background.*** *Neuron specific enolase (NSE) is an isomer of the glycolytic enzyme enolase, which was first found in extracts of brain tissue, and was later shown to be present in neuroendocrine cells and neuroendocrine tumours. The aim of the study was to confirm the importance of serum NSE as a tumour marker in patients with small-cell lung cancer.*

***Patients and methods.*** *Serum levels of NSE were measured by the radioimmunoassay in 71 patients with lung cancer (LC), in 24 patients with non malignant lung diseases and in 28 healthy adults.*

***Results.*** *According to the serum values in the group of healthy adults, 16.6 ng/ml was determined as a cut of level of NSE. By the specificity of 88.13 % in the group of non malignant lung diseases, the sensitivity of 47.82 % was obtained in patients with LC, which increased to 72.72 % in the patients with SCLC. In patients with non-small-cell lung cancer (NSCLC) the sensitivity of NSE test was 38.89 %. The patients with SCLC-extensive disease had a significantly higher mean NSE level (290.48 ng/ml) than patients with the limited stage disease (46.94 ng/ml). Serial measurements in 16 patients receiving combined chemotherapy and/or radiotherapy showed an excellent correlation between serum NSE level and clinical response.*

***Conclusions.*** *These results indicate that serum NSE may be a useful marker for diagnosis, staging and for monitoring response to the therapy in patients with SCLC.*

*Key words: lung neoplasms; carcinoma small cell; tumor markers; biological; neuron specific enolase*

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## Introduction

Enolase is a glycolytic cytoplasmic enzyme, present in all human cells, catalysing the conversion of 2-phosphoglycerate to 2-phosphoenolpyruvate.[1] The enzyme consists of thrree dimeric isoenzymes, called as α, β and γ. Neuron specific enolase (NSE) is γ-γ dimer and presents the neuronal form of the enolase.[2] Originally extracted from the bovine

brain tissue, it was first considered that the gene coding for NSE was restricted to neurons, and that it was only present in the central nervous system. In 1978 Schmechel *et al.* have shown that NSE is also present in all peripheral and central neuroendocrine cells, named APUD (amine precursor uptake and decarboxylation) cells.[3] Tapia *et al.* have extended this work with immunohistochemical and extraction techniques and showed that NSE is present in a wide variety of APUD neoplasms or APUDomas including: islet tumours of the pancreas, gastrinomas, VIPomas, medullary carcinoma of the thyroid, pheochromocytoma, and small-cell carcinoma of the lung (SCLC) among others.[4] In contrast, they could not find NSE presence in any non-neuroendocrine tumours.[4,5] High pre-treatment levels of NSE have been detected by the radioimmunoassay in the sera of the patients with neuroendocrine tumours, including SCLC.[6-8]

Therefore, this study was designed to re-evaluate the role of serum NSE in the diagnosis and differential diagnosis of the patients with lung carcinoma; to re-evaluate whether serum NSE levels are in the correlation with the extent of tumour dissemination or stages of the disease, and to re-evaluate the role of NSE as a marker for monitoring a therapeutic response in the patients with lung carcinoma.

## Patients and methods

### *Patients*

In this study 123 persons divided in three groups were included: first group - 71 newly diagnosed untreated patients with a different type of lung carcinoma; second group - 24 patients with non malignant lung diseases and third group - 28 healthy adults.

According to the histological types of lung carcinoma, the patients from the first group were further divided in two groups: 33 patients with SCLC and 38 patients with no-small-cell lung cancer (NSCLC).

### *Methods*

#### Clinical assessment

The routine pre-treatment staging procedures consisted of physical examination; biochemistry; chest X ray; lung functional tests; fiberoptic bronchoscopy (with bronchial biopsy and cytological examination of brushings and washings); ultrasound procedures; radionuclide scan of bone. Biopsy or fine needle aspiration specimens of enlarged lymph-nodes, subcutaneus nodules and pleural effusions were taken when clinically indicated. According to these findings, the patients with SCLC were staged as having limited disease (tumour confined to one hemithorax, including the ipsilateral lymph nodes) or extensive disease (outside these limits). The patients with NSCLC were divided in five stages of TNM classification. Only 16 patients were followed up and a response to chemotherapy and/or radiotherapy was evaluated. The response was judged to be: complete (CR) when both clinical and pathological evidence of tumour totally disappeared; partial (PR) when there was a reduction of 50% or more in the sum of all measurable and evaluable tumour masses. Lesser degrees of tumour reduction were judged as no response.

The diagnosis of all patients was confirmed at the Institute for Lung Diseases and Tuberculosis; the patients were treated at the Institute for Radiology and Oncology, Medical Faculty in Skopje.

#### Immunoassay

Blood specimens were collected from each of the 71 patients with lung carcinoma at diagnosis, as well as from the patients with non malignant lung diseases and healthy adults. Serial samples were obtained from 16 of 71 patients with lung carcinoma, usually at 6-week intervals, after each course of

chemotherapy or after the end of radiotherapy. The serum was separated immediately after the collection and was stored at - 20 °C before the assay. NSE levels were determined by a double-antibody solid phase radioimmunoassay technique (Pharmacia NSE-RIA test) at the Institute for Immunology, Medical Faculty, Skopje.

Student's t test, Newman- Keuls test and $x^2$ test were used to determine the statistical significance between the mean values and between raised frequencies separately.

## Results

Twenty eight healthy adults had NSE serum level ranging from 2.58 to 17.41 ng/ml (mean level 8.01 +/- 4.40 ng /ml). The upper limit of the normal interval for serum NSE 16.6 ng/ml is defined as the mean value for healthy controls plus 1.96 standard deviations. Only two patients from this group (7.14%) had a raised serum level above the normal value.

In the group of patients with non-malignant lung diseases NSE serum level was ranged from 2.61ng/ml to 41.87ng/ml, with the mean level of 11.79 +/- 9.53 ng/ml. Among them, five were serum NSE positive (20.83%). On the basis of these findings 88.13% was determined as a specificity of NSE test.

The mean level of NSE in the group of 71 patients with LC was 127.96 +/- 442.53 ng/ml. Thirty-four of them were found to have raised serum NSE concentrations that determined the sensitivity of NSE in LC of 47.82%. A statistical analysis between the positive NSE findings in the three groups showed a significant difference ($x^2 = 18.19$ $p< 0.001$). With Newman-Keuls test we obtained a statistical significant difference between the mean values in the three groups ($F=1.84$, $p<0.05$).

When the upper normal limit for serum NSE was taken to be 16.6 ng/ml, 73% of patients with SCLC were found to have raised NSE concentrations compared with 38% of patients with NSCLC ($x^2 = 12.78$, $p<0.001$).

Eighteen of 33 patients with SCLC had a limited stage disease and 56 had an extensive disease. NSE was raised in 10 of 18 (55.55%) limited-stage patients and in all 15 (100%) patients with an extensive-stage disease ($x^2 = 8.8$. $p<0.005$). The mean pre-treatment NSE in the limited-stage disease was 46.94 +/- 56.92 ng /ml, versus 290.48 +/- 325.24 ng/ml for the extensive-stage disease (Student's t test = 2.69, $p<0.001$; Table 1).

There was not a significant statistical difference between the number of patients with NSCLC in different TNM stages who had the raised serum NSE level above 16.6 ng/ml. The results are shown in the Table 2 ($x^2 = 7.27$, p non significant).

Serum NSE was measured again in 16 pa-

**Table 1.** Mean value and sensitivity of NSE in the patients with SCLC

| Group | Mean value | Frequency of raised value >16,6ng/ml | Sensitivity |
|---|---|---|---|
| SCLC limited diseases | 46.94 +/- 56.92 | 10/18 | 55.5 % |
| SCLC extensive diseases | 290.48 +/- 325.24 | 15/15 | 100 % |

**Table 2.** Sensitivity of NSE in patients with NSCLC in different TNM stages

| Group | Number | Freqensy of raised value> 16,6ng/ml | Sensitivity (%) |
|---|---|---|---|
| Stage I | 13 | 4 / 13 | 30.7 |
| Stage II | 12 | 1 / 8 | 12.5 |
| Stage IIIa | 10 | 2 / 6 | 33.3 |
| Stage IIIb | 9 | 2 / 5 | 40.0 |
| Stage IV | 11 | 5 / 6 | 83.3 |

tients after the end of each course of chemotherapy or at the end of radiotherapy when staging procedures were repeated. Eleven of these 16 patients were with SCLC, and 5 with NSCLC. In Figure 1a, there are the changes of serum NSE level in 13 patients who responded to therapy (responders); 9 were with SCLC and 2 with NSCLC. Eight patients had the elevated serum NSE level above 16.6 ng/ml and had a predominantly extensive disease.

According to the clinical signs, when a complete or a partial response was obtained, the serum NSE level in 6 patients decreases to a normal range; in one patient the serum NSE level decreased, but between 16 and 20 ng / ml, and in one patient the level remained stable. In other five patients who had the serum NSE level in a normal range at diagnosis, at the moment when CR or PR was clinically achieved, the serum NSE level decreased in 2 patients, versus slightly elevation in three patients, even in the normal range. However, when they had a relapse, the serum NSE rose again: in 11 patients above a normal range and in 2 patients to a normal value.

Figure 1b shows the changes in the serum level of NSE in three patients who did not response to chemotherapy. In one patient the pre-treatment level was in a normal range; in the other two patients NSE level was above 16.6 ng/ml. In all three patients there is a clear elevation in NSE during the chemotherapy that predicted the clinical recognition of relapse.

## Discussion and conclusions

A raised serum NSE was observed in 47.8% of the patients with LC; the sensibility of NSE was 72.72% in patients with SCLC *versus* 38.89% in NSCLC. Our results correspond to the findings of other authors: Carney et al.[6] - NSE sensibility of 69% in SCLC with the cut of level of 12 ng/ml, Cooper et al.[8] - NSE sensibility of 77% in SCLC with the cut of level of 13 ng/ml, Esscher et al.[1] - NSE sensibility of 85% in SCLC and 25% in NSCLC with the cut of level of 12 ng/ml, Lorenz et al.[9] - NSE sensibility of 98% in SCLC and 4% in NSCLC with the cut of level of 15 ng/ml.

NSE is a marker specific for the neuroendocrine system and for tumours that arise from it, the so-called ADUP neoplasms. The characteristics of these tumours are defined

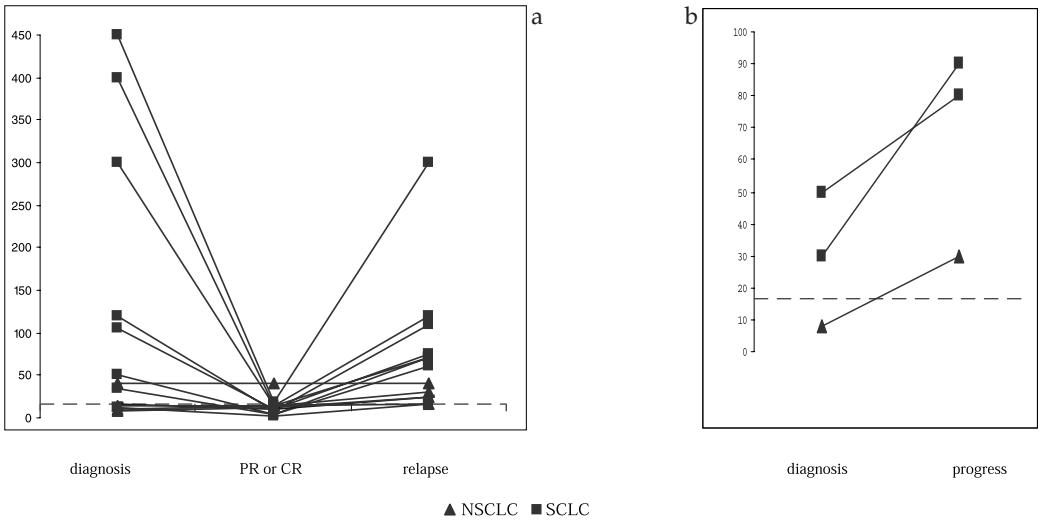


**Figure 1.** Serum NSE level changes (ng/ml) in patients with SCLC and NSCLC during treatment.

*in vivo* and *in vitro* studies: many neurosecretory granules, the ability for the production of different hormones and polypeptides, the high level of L-Dopa decarboxylasa and NSE.[10] When the characteristic features of SCLC were first described, this tumour was considered to be an anaplastic malignancy with which a variety of paraneoplastic syndromes were associated.[11] In the 1960, however, the presence of neurosecretory granules within the cells was described, which led to the inclusion of SCLC within the APUD system. It was thus presumed that the anaplastic cells were derived, in the normal bronchial mucosa, from the Kulchitsky cells which posses APUD properties. It is interesting why serum NSE is elevated in some of patients with NSCLC. The mechanisms by which NSCLC cells are capable of producing APUD-derived enzymes and hormones are not known. According to the findings of Gazard, there is a possibility of *in vitro* "conversion" of small-cell lung cacinoma to large cell cancer morphology. Although "transformed" cells had lost most or all of their "amine precusor uptake and decarboxylation characteristics" certain neuroendocrine features such as NSE were retained. Thus, it is possible that the large cell lung cancers were originally small cell tumours that "changed" histology, but "retained" NSE activity or were mixed tumours with the small cell component. The appearance of heterogeneous cell populations in the carcinomas is the reason why different parts of the tumour tissue show a different immunohistochemical expression for the same marker and why the tumour metastasises do not release some tumour marker which is released by the primary tumour.[12]

The results regarding the extension of the disease in patients with SCLC are comparable with the results reported by other authors (mean value of limited disease *versus* mean value of extensive disease): Fischbah and Berthold[13] - 8.4 +/- 0.8 / 47.7 +/- 8.8 ng/ml; Carney *et al.*[6] - 13.8 / 59.0 ng/ml; Johnson *et al.*[7] - 33.4 +/- 4.7 / 94.5 +/- 13.8 ng/ml; Cooper *et al.*[8] - 14 / 42 ng/ml; Splinter *et al.*[14] - 25 / 51 ng/ml. According to Carney *et al.*[6], Johnson *et al*[7] and others, the serum level of NSE, is more in correlation with the tumour burden and the number of metastatic site than with the individual ability of tumour to produce NSE.

Our follow-up studies in 16 patients showed the correlation between the tumour burden, the clinical response and serum NSE concentrations: the elevated, pre-treatment NSE levels decline to normal or nearly normal when CR or PR was achieved, while 1 responding patient maintained the essentially stable NSE level. When the relapse or progression in the disease occurred, the NSE level rose again; what is more important, raising was obtained before the clinical recognition of the relapse; a rising NSE level may predict relapse weeks to months in advance of other clinical evidence and signal the need to change a therapy sooner. A progressive rise in NSE levels during the treatment indicates the tumour resistance or relapse and also need to change the therapy. With serial NSE measurements we can follow up the disease course of the patients with SCLC, and give a different therapy at a time when it is likely to be most beneficial, i.e., when the tumour burden is low.[7,8,15] NSE is a useful tumour marker for the diagnosis and the differential diagnosis in patients with SCLC. This means that NSE measurements in patients with SCLC are at least a useful addition to standard investigational methods. Serial NSE measurements are useful for monitoring the course of the disease and therapeutical response; they provide information relevant to patient management which could not be obtained by the physical examination or routine staging procedures.

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# Breast cancer and breast health awareness as an evolving health promotion concept

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***Background.*** *Breast cancer is the most frequent malignant disease in the majority of developed countries. In the last few years the introduction of mammography screening programmes has resulted in an improved survival of breast cancer patients. However, the incidence of the disease in these countries is still on the increase. Present focus on secondary breast cancer prevention activities, consisting of early detection and treatment, cannot ensure a decrease of breast cancer incidence. Improved breast health awareness could therefore represent a part of specific health promotion activities aimed at decreasing the incidence of breast cancer.*

***Conclusions.*** *In developed countries breast cancer is a significant health care issue. Secondary breast cancer prevention activities should therefore be complemented by specific health promotion activities in order to reduce its incidence in the future. Primary breast cancer prevention would include health promotion activities aimed at enhancement of the individual as well as collective breast health awareness. Properly enlightened members of the influential population groups could attain appropriate changes in the fields of legislation, taxation, customs and commercial regulations that would enable women to control their own breast health.*

*Key words: breast neoplasms - prevention and control; health promotion*

## Introduction

Breast cancer is the most prevalent cancerous disease in women in the majority of developed countries. The incidence of breast cancer in most of these countries is still on the increase. However, the current increase of newly discovered cases is partly attributable to the introduction of efficient mammography screening tests. This also brought about an improvement in survival of the patients, measured with the length of survival after the discovery of breast cancer, and with an in-

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crease in the five-year survival rate.[1,2] Also in Slovenia breast cancer is major cancerous disease in women. According to the Cancer Registry of Slovenia the incidence of the disease is still on the increase; in the year 2000 there were 932 newly discovered cases in a two million population.[3]

Present health care activities with mammography screening tests are primarily focused on early breast cancer detection and treatment. These tests enable the discovery of the disease in the early stages of its clinical development, hence improving the chances for longer survival of breast cancer patients.[4] The truth is that the disease is usually relatively advanced when it is detected as a perceivable change in a mammography image or as a clinically ascertained, locally advanced or metastatically expanded tumorous formation.[2,4] In Slovenia, as in most developed countries, the greatest emphasis is put on the already mentioned secondary breast cancer prevention activities.

The methods of primary prevention are rarely or hardly ever mentioned, especially via health promotion activities. These activities could no doubt include initiatives for enactment of legislation that would create circumstances where choices for avoiding the risk factors leading to breast cancer were offered and made easily available to women. At least at the beginning we would try to get some of the influential population groups in the Republic of Slovenia better acquainted with breast cancer characteristics and with the role that the members of those groups could play in stopping the increase of the disease and later, hopefully, in its decrease.

## Present focus on secondary breast cancer prevention activities

For the last few years experts from different fields have been quite active in spreading information on breast changes that women should be attentive to. Above all, the importance of early detection and treatment of already existent breast cancer has been emphasised.[2,4] In doing this, professionals encounter women's fear of breast cancer, various myths and anxieties. They learn about different levels of their knowledge and understanding of cancerous alterations of the breast, as well as about their different opinions of benefits of being included in mammography screening test programmes.[2,4] In most women of all ages, breast cancer brings about fear, confusion and concern. When they visit a specialist those feelings are intensified by possible breast pain, asymmetry of the breasts, discharge, lumps or thickenings in the breasts, as well as positive family history.[1,5] Indirectly, breast health concern in women is quite well expressed, however, a deeper knowledge of healthy breast characteristics or breast health awareness can most often not be found. As a rule it is limited only to the absence of tumorous changes in the breasts.

In some countries certain measures have been adopted more than ten years ago in order to reduce the number of deaths caused by breast cancer. With methods of early detection the breast cancer mortality rate was supposed to drop to less than 25% by the year 2000. Therefore, numerous activities were aimed at increasing the number of women included in the mammography screening test programmes. In certain age groups with high risk for developing breast cancer the inclusion rate was expected to increase at least to 70%. In some places and regions of certain countries this inclusion rate was actually achieved, above all by dissemination of specific information about mammography screening tests.[2, 5-8]

In this context information about the benefits of being included in mammography screening tests was an integral part of specific health promotion activities. Traditional information methods aimed at an increase of

the inclusion rates comprised of information brochures and posters, newspaper, radio and sometimes television advertising, meetings with experts in local communities and periodical visits to the local centres for early breast cancer detection with the introduction of a mammography apparatus. Also, specific information and education programmes on this subject have been introduced for primary health care professionals. Women with first-hand breast cancer experience very often participated in those activities by writing newspaper articles and giving interviews in the media, and sometimes even their partners joined in with their support.[1,5,8] However, these activities are chiefly aimed at the increase of inclusion rates to mammography screening test programmes and as such their main aspect is emphasis on the secondary prevention that is focused on detecting and treating the already existing disease. Mostly they anticipate a change of attitude of a certain part of the health care system and also changes of women's attitude.[1,2,5-8] Despite an increase of the inclusion rate in mammography screening test programmes, the role of women in this process remains limited and passive.

New initiatives and activities would not be limited only to women in certain age groups, but would include women of all ages as well as everybody else. They would be aimed at overreaching the existing cultural and social differences among women.[5] Such initiatives and activities would encompass a wider, more holistic and, maybe some time in the future, more successful approach to the breast cancer problem. Apart from disseminating and adapting information on breast cancer in healthy women, we would like to put special emphasis on breast health awareness.[2,5,9-12] Lower average clinical stages in patients with subsequently citologically confirmed breast cancer and longer survival can be achieved with high inclusion rates into the mammography programmes.[1,2] However, the incidence of breast cancer itself can not be reduced solely in this way.

## Health promotion, individual and collective breast health awareness and breast cancer incidence reduction

Long-term changes in the community in response to the decreased incidence of breast cancer (as well as some other cancers) could possibly be achieved by applying intersectional and multidisciplinary approaches.[4,5,13] Primary prevention activities, first of all health promotion activities with quite specific aims (e.g. the already mentioned breast cancer incidence reduction) would have to be implemented on the individual as well as on the community or collective level with the participation of the interested public and the adequately educated experts. The sole involvement of doctors and other health care professionals would most probably not suffice.[4,5] On the individual level, breast health awareness means accepting health responsibilities to greater extent by being able to recognize normal appearance and structure of breasts during different cycle periods and with regard to age, and by being able to recognize undue changes and inform the physician immediately.[14] It could therefore probably also be enhanced by learning how to choose healthy nutrition, a healthy lifestyle and by realisation of biological potentials, as well as by getting to know the structure and composition of healthy breasts with regular self-examination. On the community level (local, regional and state institutions), breast health awareness could also be explained as arising from the underlying collective breast health awareness; initiatives would have to be instigated that would stimulate groups of influential individuals to actively participate in the implementation of adequate changes of legislation, taxation, customs and commercial regulations, enabling every woman to have at

least partial control over her own health.[13] Breast health awareness would therefore not be limited only to individual women but would become a collective and community prospect, thus gaining a wider social dimension.

Planning of the integral initiatives in the field of health promotion, including the achievement of greater collective breast health awareness, can be taken up only on the basis of reliable data. Although data on women's views and perceptions of breast health are not available in Slovenia, regular yearly reports of the Cancer Registry of Slovenia render possible a notion the influence of life-style changes have on the incidence of breast cancer and other cancers in the second half of the 20th century in Slovenia.[3-5] The overall strategy for achieving the goal (breast cancer incidence reduction) could therefore include smaller, and temporarily, only hypothetical projects with a common basic outline (Figure 1). In the case of breast cancer, a decreased exposure to some of the risk factors connected to the development of this cancerous disease, would be attained with time (Table 1).[1,2] Some of these factors could be influenced only indirectly with the hope that after a longer period of time breast cancer incidence would finally decrease. A more direct influence could be exerted by banning cancerous agents in food, at the work place and in the living environment. The specific importance of adequate health education could also be defined.

**1. Project design**
▼
**2. Project development and goal specification**
▼
**3. Acquiring funds and active project participants**
▼
**4. Identification of individual and group goals (e.g. within the National Assembly)**
▼
**5. Evaluation**
▼
**6. Data presentation (symposium, workshop,...)**
▼
**7. Evaluation**
▼
**8. Project evaluation**
▼
**9. Presentation of project results**

**Figure 1.** Outline of a hypothetical health promotion project (possible reduction of exposure to breast cancer risk factors).

In the beginning, planning of integral initiatives aimed at achieving greater collective breast health awareness would be focused on different influential and other population groups: perhaps even the members of the National Assembly of the Republic of Slovenia. Specific health promotion activities would include projects that would introduce breast cancer risk factors, breast cancer epidemiology in Slovenia and basic information on carcinogenesis at least to some members of these groups. The beginning of any such hypothetical projects for improvement of collective breast health awareness with the help of influential population groups would definitely be marked by endeavours to identify the interested individuals in those groups. Later they could be joined by the other members of these groups. However, in the beginning, they could represent important parts of alliances or coalitions for achieving the strategic goals. Different professionals from different educational areas, members of government, as well as non-government organisations and volunteers could work together.[5]

## Execution of a hypothetical project for improvement of collective breast health awareness within an influential group

The elected members of the legislative bodies are definitely one of the most powerful groups in society. They should serve as an example for illustrating the form and anticipat-

ed development of health promotion projects, with a long-term goal of reducing the incidence of breast cancer. In the Republic of Slovenia there are 90 members of the National Assembly; many of them are also members of various committees, councils and other bodies.[15] The powers of the National Assembly enable their members to pass laws and executive regulations that could help women to make healthy choices towards an active breast cancer prevention role. Assistance for the realisation of such projects should be sought from women members of the Assembly, deputies that are doctors and other medical professionals, and probably amongst those members of the Assembly with women relatives who have developed breast cancer. These people alone could represent a particularly influential group within the National Assembly and the project could be carried through. In favourable conditions it could be later repeated with the participation of all the members of the National Assembly (or of any other influential group). Interested groups and individuals could probably also be found among volunteers and other participants of such a pilot project, and participation of women who recovered from breast cancer would also be invaluable.

In the initial part of health promotion strategic activities, focused on decreasing the exposure to breast cancer risk factors, a smaller multiphase project would be used to gather information about the views of specific groups (or all members) of the National Assembly of the Republic of Slovenia (Figure 1). According to the results, we would later try to introduce significant characteristics of this type of cancer and to discuss with Assembly members to what extent they would be willing to participate in specific health promotion activities with the final goal of decreasing the breast cancer incidence.

Already in the conceptional phase of the project pertinent references to the subject of »breast cancer and health promotion« would be found in professional publications. Alliance and/or coalition of the interested participants would be identified (Table 2), and at the end of this phase, the leadership of the project would be determined. During the designing phase of the project, attainable and

**Table 1.** Breast cancer risk factors

| |
|---|
| Early menarche, late menopause |
| Nulliparity, age at first birth, number of born children |
| Excessive body weight |
| Treatment with estrogens |
| Excessive alcohol consumption and high energy nutrients intake |
| Benign epithelial proliferative lesions |
| Family history of breast cancer |
| Genetic mutations (BRCA1, BRCA2, TP53) |

**Table 2.** The expected participants of a hypothetical health promotion project for the reduction of exposure to breast cancer risk factors

| |
|---|
| Interested members of influential groups (e.g. members of the National Assembly, ...) |
| Ministries |
| Epidemiology, carcinogenesis and breast cancer experts |
| Clinical specialists (doctors, nurses, ...) |
| Non-government organisations (Cancer Society of Slovenia, »Europa Donna« Society, ...) |
| Volunteers |

realistic goals would be set and suitable sponsors found. The contents, the structure and the methodology of the project would be discussed with the project participants, and, if possible, the interested individuals and specifically interested groups among the National Assembly members would be identified. Qualitative and quantitative data on how well the National Assembly members are acquainted with this particular health promotion project and how willing they are to participate in it would be gathered via specially prepared questionnaires. The relevant information about this topic would be presented in a form of a symposium, a workshop (brainstorming) or in another manner of conveying information, and it would be followed by handing out evaluation questionnaires. Processing of the gathered information and the following discussion would reveal whether the continuation of the project is viable. This discussion would also cover the participants' perception of breast health and an exchange of possible experiences with breast cancer within their families. Experts would help clarify any dilemmas that might occur, and concrete health promotion activities with the goal of reducing the incidence of breast cancer in the future would also be discussed. Reports on the evaluation of the project results would be presented to the participants, sponsors and to the National Assembly members, and in various other forms possibly also to the professional and lay public.

One can only guess at the expected results of the project. Nevertheless, it could be put to good use as a means of spreading information about breast cancer among the members of the group that crucially influences the life of the population. Data on the attitude of this group towards an important health issue and at least some reflections about the chosen method of presenting information on breast cancer would also be gathered.

## Discussion

In developed countries worldwide and also in Slovenia, breast cancer represents an important public health problem together with other cancerous diseases.[2,4,5,16-18] In the last decades, introduction of and constant perfecting of different treatment methods with surgical procedures, radiotherapy, chemotherapy and supportive treatment have markedly improved survival rate and quality of life of breast cancer patients in these countries.[2,19,20] However, in the majority of developed countries, including Slovenia, the incidence of breast cancer is still on the increase.[2,3,13,18,21,22] Improved breast health awareness for the individual and for the collective level could therefore represent a part of specific health promotion activities with the goal of decreasing the incidence of this disease.

Health promotion activities aimed at greater individual and collective breast health awareness can only be a supplement and by no means a substitute for the secondary breast cancer prevention activities. Early detection and timely treatment have contributed to longer survival of breast cancer patients.[2,23-32] The use of these secondary prevention methods instigated deliberations about breast health and breast health awareness.[5,10,13] Certain activities, that could be conditionally viewed as health promotion activities, are aimed at increasing the inclusion of women from specifically defined groups (certain age groups with some specific exceptions at younger age) into mammography screening test programmes.[2,5,23-32] One should bear in mind that the carcinogenesis of breast cancer is a phasic and continuous process at all ages, that it takes several years for breast cancer to develop, and that it takes quite some time for a tumorous formation inside the breast to become clinically observable.[2,33,34] New attitude towards breast health that would focus not only on the absence of

tumorous formations in the breasts could in time probably result in the decreased exposure to breast cancer risk factors that directly or indirectly intensify the processes of carcinogenesis in the breast tissue. It would be an attempt at introducing subtle and hardly measurable changes in women's and the general population's way of daily living that could in longer time frame bring about the decrease of breast cancer incidence.

Individual and collective breast health awareness levels are co-dependent up to a point, and improvement of one could probably trigger a positive change in the other. Goal oriented activities of influential groups of population could probably represent also an incentive for the improvement of breast health awareness on the collective level. The most influential of all groups in every democratic country is undoubtedly the highest legislative body. In the Republic of Slovenia this is the National Assembly with its 90 members. On different levels health promotion activities usually include also politics, therefore the idea of a project that would inform the members of the influential groups (the most influential group being the National Assembly) about the meaning and the burden of breast cancer in Slovenia and also about breast health awareness, should not come as a surprise.[13,35]

Since in Slovenia breast cancer is an important public health issue, the inclusion of influential population groups into health promotion activities would be reasonable and acceptable. Just like the whole community and its every individual, the members of these groups should be adequately educated and informed about this problem. Specific health promotion activities in connection with breast cancer within the framework of well considered public health policy would thus come near to the sphere of activities, recommended in the Ottawa Charter.[4,13,35] The reduction of breast cancer incidence as a possible outcome of these activities would significantly influence the health of a large part of women in the community and consequently the health of the entire community.

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*review*

# Psychosocial coping strategies in cancer patients

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***Background.*** *The aim of this review is to present common psychosocial problems in cancer patients and their possible coping strategies. Cancer patients are occupied with many psychosocial problems, which are only partially related to their health state and medical treatments. They are faced with a high social pressure, based on prejudices and stereotypes of this illness. The review presents the process of confrontation with the cancer diagnosis and of managing the psychological consequences of cancer. The effects of specific coping styles, psychosocial interventions and a social support on initiation, progression and recurrence of cancer are also described.*

***Conclusions.*** *Although some recent meta-analysis could not provide scientific evidence for the association between coping strategies and the cancer initiation, the progression or the recurrence (neither have studies rejected the thesis of association), the therapeutic window for the psychosocial intervention is still wide and shows an important effect on the quality of lives of many cancer patients.*

*Key words: neoplasms-psychology; social support; cancer patients, coping strategies psychosocial problems, psychosocial support*

## Introduction

Coping is a complex mental process by which a person deals with stress, solves problems, and makes decisions. It is an emotional, cognitive and behavioural response of a patient to an illness. Coping process involves at least two stages: confronting (»*Is this something to bother about?*«) and managing (»*What can I do about it?*«) with different aspects of illness or disability. Since every patient is a unique person, an emotional, cognitive and behavioural response can vary a lot and can occasionally be quite unpredictable in the same patient.

Despite striking differences in the progress of different cancers and the increasing effectiveness of medical treatments, cancer continues to be the most widely feared group of diseases. Undoubtedly, cancer causes considerable psychological distress in patents, families, and often those health professionals who care for them. Some socially determined problems often augment distress in patients as well. Besides unpleasant symptoms such as pain, nausea, fatigue and the distress, financial problems and problems concerning employment, housing, childcare, family worries and existential doubts also oc-

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cur. Only a well-planned care that fully involves patients and their families can minimize these problems.

How do patients adapt to cancer? The number of studies aimed at answering this question has grown rapidly over the past twenty years. Consequently, much more is known today about the patient's psychological functioning during the course of cancer and about the strategies they use in order to deal with this disease.[1]

It is commonly believed that a person's mental attitude in response to the cancer diagnosis affects his or her chances of the survival. Although different coping strategies in cancer patients are predominantly designed in order to diminish the distress and to improve their quality of life, all studies did not prove convincing evidence that some psychological coping styles like acceptance, fatalism, denial, helplessness, hopelessness can play a clinically important part in the survival or recurrence of cancer.[2,3] At the same time, many studies lay great stress on psychological and social factors that could be involved in the aetiology and response to cancer and its treatment.[4-6]

## Confrontation with cancer diagnosis

The topic of cancer is associated with many social and clinical taboos. In popular language and in medical settings, euphemisms such as »growth«, »tumour«, »lump«, »shadow« are used to avoid the word »cancer«.[7] Communications and reticence from communicating about cancer reflect numerous negative attitudes widespread among patients, their families, health professionals (including doctors and nurses), other hospital personnel and the wider lay community as well.[8,9] These kinds of communications may arise from the fears and misconceptions surrounding cancer and using them and may give rise to their rootedness. Doctors may refrain from using the word »cancer«, because they believe patients prefer not to be given a potentially terminal diagnosis. However, research studies show that members of the general public were more likely to say that they wish to be informed of a terminal diagnosis than doctors estimated they would be, nevertheless they may not take these opportunities when offered.[10,11]

Some researchers pointed out that every patient searches for the information about the identity, consequences and causes of an illness, time line and the cure. These components of common sense representations tend to be reasonably stable over time and across different illness episodes.[12] Illness cognitions also tend to affect changes in health-locus-of-control-belief, different propensities to visit a doctor, changing attributions of getting sick and taking personal responsibilities over the treatment. Since the effectiveness of therapy not always depends on the medical treatment but also on patient's representations of the illness, the medical staffs have to recognize them and re-establish an effective communication.[13] Cancer specialists are beginning to acknowledge the value of improving communication skills via training models, residential workshops and educational programs and thus reducing the risk of patient's maladaptations to an improperly delivered diagnosis.[14]

Although most of the patients have already constructed their own representations of their illnesses while waiting for the diagnosis, the final diagnosis is mainly a stressful event. Patients have varied ways of copings with a cancer diagnosis. The response to a poor prognosis is ranging from shock and denial through anger, depression and finally acceptance.[15] While there is considerable doubt about the actual sequence of stages, this range of responses is commonly observed in patients with cancer. Researchers tempt to reveal whether the application of some of the coping strategies may result in a better adjustment prognosis. In general, coping strate-

gies that focus on emotional aspects of the response are associated with a poorer emotional adjustment. By contrast, patients whose strategies also focus on thinking about the issue in a different way, e.g. by acceptance of the condition, or on seeking solutions to problems, show a better subsequent adjustment.[16,17] Some coping strategies may also influence the prognosis. Patients that predominantly show »denial«, »fighting spirit« or »stoic acceptance« were found to have better survival chances than patients whose coping responses reflected »helplessness / hopelessness«.[18-20]

## Managing the psychological consequences of cancer

The acknowledged psychological model of coping processes with the illness in general, is derived from the presumption that managing with the illness is usually a long graduate process, accompanied with many ego-defence patterns (e.g. denial, repression, projection, compensation, fatalism, dissimulation, etc.) and consecutively with a cognitive, emotional and behavioural consilidation.[21,22] Heim[21] described the coping process in a four step integrative model with alternating coping phases. The start point of the patient's perception phase is the moment, when the patient identifies some changes in his/her physiological condition and well-being and begins to analyze them. During the cognitive phase the patient is preoccupied with the disease and tries to find the right definitions and estimations about his/her illness. Adjusted by numerous defence mechanisms (repression, withdrawal, escapism, focusing, projection, dissimulation, aggravation, isolation, rationalization, reactive formation, regression, sublimation, symbolization), the patient's coping process finally ends with a cognitive, emotional and behavioural consolidation. It should be pointed out that coping is a very delicate process, primary orientated on patient's needs and therefore often aggravating for the medical staff, patient's family and other patients as well. Conformed patients are socially more accepted than aggravating ones but in many occasions this condition can be a disadvantage that obstructs the coping process.

After facing with the cancer diagnosis and the first abrupt reaction of a shock, which is a normal response to a stressful event, patients often show signs of negation, disbelief and despair. This first step of the personal crisis usually lasts about a week. During the following step patients slowly recognize the reality and become anxious, frightened, panic, depressed, having problems with cognitive functioning, sexual life, appetite, and sleeping and with managing daily routine.[22-24] Some of the mentioned psychological adjustment problems may occur only in a smaller number of patients, while a range of psychological responses (denial, anxiety and depression) that accompany the cancer diagnosis, have been seen in the majority of cancer patients.[25]

*Denial* is a mechanism of denying the presence of illness and medical diagnosis. It is normally activated after the first stages of a shock, and usually disappears after a short time.[26,27] The denial may have a favourable effect when it appears in the first phase of coping, after the diagnosis has been established because it reduces anxiety. However, some negative effects of the denial have been observed, for example: it may interfere with the getting treatment (e.g., a delay in going to the doctor, not showing up for follow-ups, non-compliance) or it may disrupt the process of assimilating the stressful event. Furthermore, it may, adversely, affect interpersonal relations and constitute a cumulative stress depression - even immunocompetence.[26] Some researches revealed that a tendency toward denial could be one of the important risk factors for cancer.[28]

*Anxiety* is the response to a perceived threat. It is manifested as apprehension, uncontrollable worry, restlessness, panic attacks, and avoidance of people and of reminders of cancer, together with the signs of the autonomic arousal.[29] In certain circumstances anxious patients may overestimate the risks associated with the treatment and the likelihood of a poor outcome. The anxiety may also exacerbate perceptions of physical symptoms (such as breathlessness in lung cancer), and post-traumatic stress symptoms (with intrusive thoughts and the avoidance of reminders of cancer). Certain cancers and treatments are associated with specific fears. Thus, patients with head and neck cancers may worry about being able to breathe and swallow. Some patients may also develop phobias and conditioned vomiting in relation to unpleasant treatments such as chemotherapy.[30,31]

Insecurity, the outer locus of control over the situation, learned helplessness and perceived loss often result in *depression*. In contrast to anxiety, which arises immediately after the offspring of the disease and accompanies the clinical screenings, the *depression* is progressing more slowly. A diagnosis of cancer and the awareness of associated losses may precipitate feelings similar to the bereavement. The loss may be linked with lost parts of the body (such as a breast or hair), the role in family or society, or the impending loss of life. A severe and persistent depressive disorder is up to four times more common in cancer patients than in the general population, occurring in 10-20 % during the disease.[31] There is evidence that the depression predicts the cancer progression and the mortality, although disentangling the deleterious effects of disease progression on the mood complicates this research, as does the fact that some symptoms of cancer and its treatment mimic the depression. Obviously clinical signs of depression are often difficult to distinguish from the signs, which develop due to the chronic illness and side-effects of chemotherapeutic and radiological treatment (e.g. vomiting, weight loss, insomnia, tiredness, etc).[32,33] The depression in chronic patients frequently leads to the high morbidity and suicide, especially in old patients, patients with the psychiatric diagnosis and patients without partners.[34,35]

## Managing the psychosocial problems of cancer

Cancer patients are occupied with many psychosocial problems, which are only partially related to their state of health and medical treatments. They are faced with a high social pressure, based on prejudices and stereotypes of this illness (e.g. suffering, dying, loneliness, dependence, no cure, loss of hair, mastectomy, etc).[22] Only a few diseases are associated with as many negative connotations as cancer. Nonverbal signs, absence of spontaneous speech and reactions, embarrassment, avoidance of interpersonal contacts or eye-contacts, poor communication and deficient concealing information are only a few signs of the prejudiced behaviour of medical staff, family members, friends and colleagues towards the cancer patient. Without doubt, these are representative behavioural patterns that reflect social perceptions of patients with cancer.[36] Although psycho-oncology literature concerned with coping strategies indicates that the coping style »thinking positive« is correlated with the cancer patient's overall level of mental health and mortality rates, the mentioned coping style could also represent a stress factor for cancer patients. In this case, »thinking positive« does not represent an accurate report of internal cognitive state, but rather a conversational idiom, summarizing a socially normative moral requirement.[37]

A social environment has an important impact on the patient's crises; together with the

disease it can affect different aspects of the patient's life quality and discomfort. In such a manner some patients can transform from dominant to passive persons during hospitalisations, suffer from the social isolation and existential fears, concern about family relationships and childcare and are anxious about their working career and financial situation and have lower self-esteem and poor interpersonal relationships.[38]

Since the social support was found to be a preventive factor against stress and diseases and a curative factor by chronic diseases, it might serve as a significant cue in cancer patients. The social support involves a social net, an important system of social relationships within the family, relatives, friends and colleagues. In most cases it is found to be useful but on some occasions it might have a distressed effect. For instance, when the patient prefers to be alone because he/she feels that other people feel pity for him/her or in case when someone has taken control over the patient and has broken the balance between support and control. It was also found that a continuous verbal communication about problems often leads to the depression in cancer patients.[39,40]

An effective social support increases self-esteem and decreases depression, but not all forms of support are necessary appropriate for cancer patients. For example, a marriage was found to have mixed effects. It was discovered that some spouses who had been very concerned about the partner's health provoked depression and suffering in them.[41]

## Psychosocial coping styles and their relevance to survival / recurrence of cancer

Until recently there has been a common belief that psychosocial factors have a great influence on the initiation and the survival from cancer. An association between psychosocial factors and the initiation or the survival from cancer are biologically plausible through some immunological and neuroendocrine mechanisms.[42-45] Surprisingly, some meta-analysis studies discovered a little evidence that psychological coping styles and psychosocial interventions are important in the survival or the recurrence of cancer. In addition, there is no evident association between stressful life events, amount of social support, personality, locus of control, coping styles, negative emotional states / psychiatric symptoms, psychiatric diagnoses on repression, initiation and progression of cancer.[2,3,6]

Although some studies indicated specific coping styles and psychosocial adjustments that influence the survival and the recurrence of cancer, the evidence of these discoveries is inconsistent, probably due to publication bias and methodological flaws (small samples, uncontrolled and confounding variables, lack of studies of interactive effects). Some authors emphasized that people with cancer should not feel pressured into adopting particular coping styles (e.g. »fighting spirit«, problem focused coping, emotion focused coping, etc.) to improve the survival or reduce the risk of the recurrence because there is no good proof that a particular psychological coping style prolongs the survival or is more effective than some other.[2]

These findings suggest that psychological interventions should not be focused only on enhancing a certain coping style in regard to prolong survival. Therapists should be rather orientated to widening of a therapeutic window and to helping cancer patients to achieve a better quality of life.[46,47] A group therapy should be used first of all for the psychological benefit of cancer patients, not in order to prolong their life. Establishing a new social support network, expressing emotions, confronting existential issues, improving relationships, enhancing communication, learning coping skills, reducing of distress and pain, confronting with the possibility of dying and destigmatising of cancer and cancer

patients are many of benefits that the psychotherapy offers to their users. A well-trained and supervised staff should be encouraged to achieve a notable and positive effect on the quality of life in cancer patients.[14,47]

## Conclusions

In spite of the lack of convincing evidence that psychological coping styles and psychosocial interventions are important in the survival or the recurrence of cancer, there is no doubt that during the confrontation and managing with cancer some psychosocial intervention should be employed in cancer patients in order to diminish their distress. Some subgroups of cancer patients are especially vulnerable and need to be recognized in order to prevent serious psychological complications.[6,34,46,48,49] Particularly attention is advised in groups of patients with the history of chronic depression, patients undergoing chemotherapy and radiotherapy, patients with breast and genitalia cancer, patients experiencing uncontrollable pain, patients with terminal illness, patients who practice unhealthy behaviours, patients without social support, children patients and elderly patients. These patients are found to drive particular benefit from psychosocial interventions. Their quality of life was improved by reducing psychological symptoms and distress, by enhancing psychological and functional adjustment and by improving rehabilitation. Furthermore subtle benefits are predicted to correlate with psychosocial programs.

People with cancer benefit from care if psychological and medical cares are coordinated. Apart from the obvious benefits to quality of life, there is some evidence that encouraging an active approach to living with cancer can improve the survival. As for all chronic illnesses, a multidisciplinary approach and management protocols that include psychological as well as medical assessment and intervention are required also for cancer. These protocols need not be specific for cancer as the issues are common to many medical conditions. The danger is that psychological care can be neglected by the medical focus on the cancer treatment. A case manager, whether nurse or doctor, who can coordinate the often diverse agencies involved in cancer patient's care can ensure that the treatment is delivered efficiently.[31]

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# Comet assay in the assessment of the human genome damage induced by γ-radiation *in vitro*

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***Background.*** *The aim of the present study was to estimate a possible application of comet assay in the evaluation of DNA damage caused by different gamma radiation doses in peripheral human lymphocytes in vitro.*

***Materials and methods.*** *Whole blood samples of young healthy, non-smoking donors were taken. The samples were divided in 4 specimens. The first specimen was used as the control. Other three specimens were irradiated using constant gamma irradiation source ($^{60}Co$) giving the dose rate of 0.907 cGy/s. Different specimens were irradiated for 51 s, 437 s and 1099 s, giving the doses of 0.5 Gy, 4 Gy and 10 Gy. In order to estimate dose-response curve on the control and all 3 irradiated whole blood samples, the comet assay under alkali conditions was performed.*

***Results and conclusions.*** *The comet assay endpoints showed statistically significantly higher values for all irradiated blood samples compared to the control. For both, tail length and tail moment, dose-effect relationship was found to be linear in a dose range of 0.5Gy and 10 Gy. By this work we also pointed out possible usage of the comet assay in the detection of DNA lesions caused by extremely high radiation dose, which is not possible by using standard cytogenetic methods.*

*Key words: lymphocytes-radiation effects; DNA damage; comet assay*

## Introduction

In radiobiology there is always a need for the development of new rapid and more sensitive methods for DNA damage evaluation. So far, an analysis of structural chromosomal aberrations and micronucleus test have had great value in radiation biomonitoring.[1,2] Recently, the comet assay, also called the single-cell gel electrophoresis (SCGE) assay appeared as new method of choice because it is a rapid and sensitive method for the detection of various DNA damages (strand breaks and alkalilabile sites) in individual cells, induced by a variety of genotoxic agents. Since radiation may cause SSB, DSB, DNA-DNA as well as DNA-protein crosslinkings and damage to bases, all detectable by comet assay, this method could provide information on the to-

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tal DNA damage caused by ionizing radiation. This is not the case for standard cytogenetic methods that, due to heterogeneity in genome damage caused by ionizing radiation, provide only average DNA damage information.[3]

Comet assay was first introduced by Östling and Johanson[4], and later modified independently by Singh *et al.*[5] and Olive *et al.*[6]. The assay is based on the embedding of cells in agarose, their lysis in alkaline buffer and finally subjection to an electric current. The electric current pulls the charged DNA from the nucleus so that relaxed and broken DNA fragments migrate further from the nucleus than intact DNA. The resulting images, named for their appearance as comets, are measured to determine the extent of DNA lesion. Image analysis provides three important parameters for each comet: tail length, tail fluorescence intensity (percent of DNA in tail) and tail moment (roughly, the product of tail length and tail intensity).[3]

Although there were many papers considering dose-DNA damage relations for structural chromosome aberration analysis, until recently only few authors investigated those effects applying the comet assay[2,6-9], which is essential for better understanding and interpretation of the results in the field of radiation biomonitoring obtained by this method.

In the present paper, possible application of comet assay in the evaluation of DNA damage caused by different gamma radiation doses in peripheral human lymphocytes *in vitro* was studied. We also wanted to point out possible usage of the comet assay in the detection of DNA lesions caused by extremely high radiation dose, which is not possible by using standard cytogenetic methods. On the basis of these results using polynomial regression dose, a response curve for tail length and tail moment as comet assay endpoints was plotted.

## Materials and methods

### *In vitro whole blood sample irradiation*

Two whole blood samples of young healthy, non-smoking donors from the cubital vein by using heparinized syringes were taken. Twelve months before blood sampling donors were not exposed to any physical or chemical agent that might interfere with the results obtained by radiation. Immediately after the sampling, the blood from each donor was divided in 4 specimens. The first specimen was used as the control. Other three specimens were irradiated using Gammacel irradiator, Model 220, with constant gamma irradiation source ($^{60}$Co) giving the dose of 0.907 cGy/s.[10] Different specimens were irradiated for 51 s, 437 s and 1099 s, giving the doses of 0.5 Gy, 4 Gy and 10 Gy.

### *Description of gamma irradiation source*

The 60Co source consists of 48 linear source elements equidistantly spaced in a stainless steel rack to form a cylindrical shell or annulus, with a diameter of 20,9 cm, measured between the centers of opposing elements. Each linear element consists of a welded stainless steel pencil filled with $^{60}$Co in the form of metallic cobalt. Internal dimensions of each pencil are 1 cm in diameter and 20.3 cm in length.[10]

The drawer is centrally located in the radiation shield and is power driven vertically through the center of the source. The material to be irradiated is placed in the sample chamber, then lowered to the irradiation position, *i.e.* the sample chamber is then in the center of the source.[10]

### *Comet assay*

After the irradiation the blood was put in ice and transferred to the laboratory. In order to estimate dose-response curve on the control and all 3 irradiated whole blood samples, the comet assay was immediately performed. The comet assay was conducted under alkali con-

ditions according to Singh *et al.*[5] All chemicals used to perform the comet assay were obtained by Sigma. Two μl of whole blood were suspended in 0.5% low melting agarose and sandwiched between a layer of 0.6% normal melting agarose and a top layer of 0.5% low melting agarose on fully frosted slides. During the polymerization of each gel-layer, the slides were kept on ice. After the solidification of 0.6% agarose layer, the slides were immersed in lysis solution (1% sodium sarcosinate, 2.5 M NaCl, 100 mM $Na_2EDTA$, 10 mM Tris-HCl, 1% Triton X-100 and DMSO 10%) at 4°C. After 1 hour, the slides were placed in electrophoresis buffer (0.3 M NaOH, 1 mM $Na_2EDTA$, pH 10) for 20 minutes at room temperature to allow for DNA unwinding. Electrophoresis was conducted in a horizontal electrophoresis platform in fresh, chilled electrophoresis buffer for 20 minutes at 300 mA and 19 V. The slides were neutralized with Tris-HCl buffer (pH 7.5) three times for 5 minutes and stained with 10% ethidium-bromide for 10 minutes. Each slide was analyzed by using Leitz Orthoplan epifluorescence microscope equipped with an excitation filter of 515 - 560 nm. For each irradiation dose, 100 cells were analyzed by automatic digital analysis system Comet assay II (Perceptive Instruments Ltd., Suffolk, Halstead, UK), determining tail length and tail moment (tail length x tail % DNA/100).

*Statistical analysis*

Possible comet assay endpoints between control and exposed group were evaluated by using the Mann-Whitney *U*-test. The dose-response curve was obtained using the method of linear regression.[11]

## Results

As shown in Figure 1, tail length values for the control blood specimen varied between 10.37 μm and 17.50 μm (mean value 14.19 ± 1.49 μm). After the irradiation of the whole blood with the dose of 0.5, Gy the tail length ranged from 12.97 μm to 27.88 μm (mean value 17.81 ± 2.40 μm). At the dose of 4 Gy, it ranged from 14.26 μm to 44.73 μm (mean value 21.12 ± 5.06 μm) and at 10 Gy, from 21.39 μm to 55.75 μm (mean value 33.80 ± 7.80 μm). Tail moment values (Figure 2) ranged for the control from 6.43 μm to 14.62 μm (mean value 11.04 ± 1.92 μm), at 0.5 Gy, from 10.54 μm to 23.84 μm (mean value 14.81 ± 2.20 μm), at 4 Gy, from 9.33 μm to 34.10 μm (mean value 16.91 ± 4.52 μm), and at 10 Gy, from 15.04 μm to 81.96 μm (mean value 28.64 ± 8.74 μm).

For both, tail length and tail moment, dose-effect relationship was found to be linear in a dose range of 0.5Gy and 10 Gy (Figures 3,4).

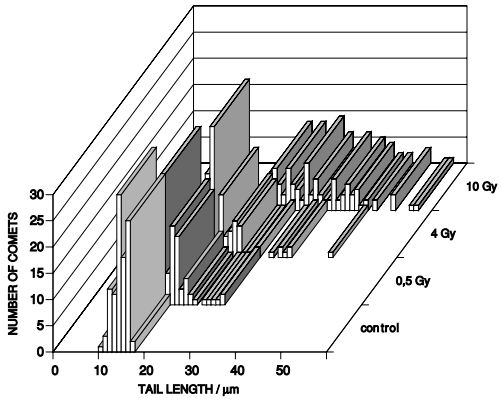


**Figure 1.** Distribution of the comets regarding their tail length.

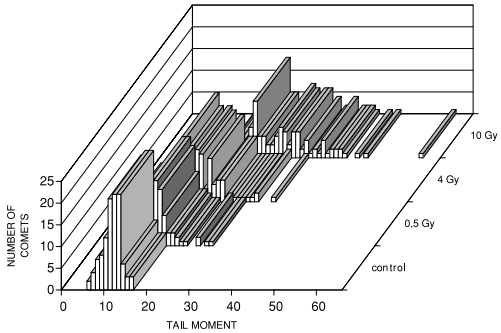


**Figure 2.** Distribution of the comets regarding their tail moment.

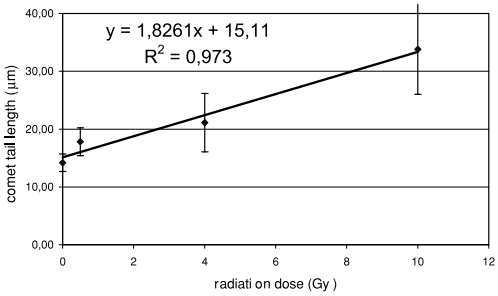


**Figure 3.** Tail length dose-response curve

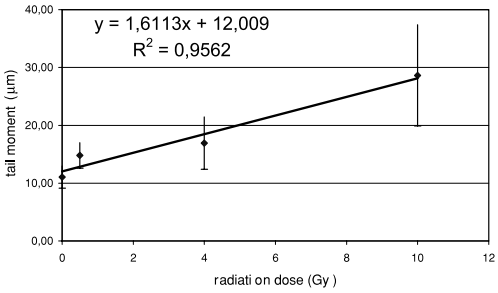


**Figure 4.** Tail moment dose-response curve.

## Discussion

Our goal was to determine the extent of DNA breakage measured with the comet assay induced by ionizing gamma radiation as DNA damaging agent. Under the alkaline conditions used here, the comet assay detects double- and single strand breaks and alkali-labile sites that could occur as the result of physiochemical interaction of ionizing radiation with cellular DNA.[12] The comet values that increased with the applied irradiation dose indicate a dependence of the extent of radiation-induced primary DNA damage on the dose value.

Similar results, but only for the low-dose radiation, were obtained by Kormos *et al.*[7], Olive *et al.*[6], Vijayalaxmi *et al.*[13], Plappert *et al.*[8], Singh *et. al.*[5], He *et al.*[2]. He *et al.* found the dose-response curve for tail length to be linear between doses of 1 Gy and 2 Gy.[2] They also assumed that the curve could remain linear at the higher radiation doses. Also for the low dose irradiation, some other authors showed a good relationship between comet assay endpoints and results obtained by micronucleus assay.[2,9] But due to the mitotic activity requirements by standard cytogenetic methods (micronucleus assay, chromosomal aberration assay) which is significantly reduced after the high dose irradiation, it is impossible to apply these techniques at dose levels higher than 5 Gy.[8,14] As shown in the present paper, the comet assay does note require prior cell cultivation; it could therefore be used in the evaluation of the DNA damage even at the dose as high as 10 Gy which is essential in case of accidents involving ionizing radiation.

As shown in the Figures 1 and 2, the application of higher irradiation dose caused a shift of tail length and tail moment toward higher values. Regardless to the dose in all irradiated blood samples lymphocytes with comet endpoint, values were significantly higher than the sample mean value. According to Plappert *et al.* these cells were considered to express a deficiency in DNA repair efficiency.[8]

Beside the already mentioned absence of need for cell cultivation, there are many other advantages of the comet assay application in the ionizing radiation induced DNA damage risk assessment. The method is simple, rapid and it detects primary DNA lesions, whereas the other cytogenetic techniques are based on the detection of lesions left unrepaired and/or structural aberrations that could possibly occur as the result of the repair mechanisms.[14]

Comet assay also provides information on intercellular differences in the irradiation susceptibility. Because it does not involve cell cultivation, there is no need for the cell treatment with the chemicals as colchicine and cytochalasine B that are found to be mutagenic themselves and could possibly lead to false positive results.[15] Therefore the comet assay could be widely applied in radiation biology and ionizing radiation risk assessment, espe-

cially in the studies of high dose effects on the DNA level.

**Acknowledgments**

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# A web-application that extends functionality of medical device for tumor treatment by means of electrochemotherapy

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*Electrochemotherapy (ECT) is a novel method for efficient tumor treatment in clinical environment. It combines local drug delivery and application of short high voltage pulses, which permeabilize the plasma membrane by electroporation. Drug can enter only the cells with permeabilzed membrane. Recently, medical device Cliniporator™ for controlled electroporation was developed. Here, we present a web-application that extends the functionality of this medical device. The aim of the application is to collect, store and to allow the analysis of every ECT application using this medical device. The application helps transferring data collected by device during the electroporation process to the central database, and enables filling of medical records through the web-forms. The application is based on technologies ASP, HTML, Flash, JavaScript, XML and others. The application main advantages are easy and rapid data access, scalability and independence of client computer operating system as well as easy application debugging and upgrading.*

*Key words: neoplasms-drug therapy; drug delivery systems; electroporation-instrumentation; internet*

## Introduction

In the cooperation with the European partners, the medical device called Cliniporator™ (IGEA s.r.l., Carpi, Italy) was developed, in the frame of the *Cliniporator* project (2000-03) funded by European Community. This device was designed for controlled *in vivo* cell permeabilization by electroporation. Electroporation is used to provide access to molecules distributed freely in the vascular and extracellular compartments that normally do not enter the intracellular compartments.[1,2,3] This technique is already used clinically to deliver cytotoxic molecules like bleomycin and cisplatin to solid tumors by *electrochemotherapy* (ECT).[4,5]

For a successful cell electroporation a voltage applied for a given electrode tissue geometry, pulse duration and number of pulses should always be in the range between reversible and irreversible threshold value. If the voltage applied exceeds the irreversible threshold value, a change in a cell membrane becomes permanent and destroys the cell. The most commonly very short (100 μs) high-voltage pulse or a sequence of such pulses are delivered. Pulses are generated in the high-voltage generator of Cliniporator™ and deliv-

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ered through the needle or plate electrodes to the tissue. By measuring both current and voltage simultaneously the device is monitoring electrical property changes of tissue in real time.

Cliniporator™ is also the first medical device designed for *in vivo* DNA electrotransfer in clinical applications. The two key steps of DNA electrotransfer are the electroporation of the target cells and the electrophoresis of the DNA within the tissue. Therefore, the device delivers to the target cells a combination of short high-voltage pulse(s) that permeabilize the cells without substantial DNA transfer/transport, and a long low-voltage pulse(s) that do not cause permeabilization but facilitate DNA transfer into the cells. This non viral gene therapy method is called *electrogenetherapy* (EGT) and has many advantages with respect to viral methods.[6]

Indeed, the medical device Cliniporator™ is already used in clinical trials. They are performed in four approved medical centers in Europe, funded by European Community in a frame of ESOPE project (2003-2004). The aim of the project is to define Standard Operating Procedures (SOP) for electrochemotherapy and electrogenetherapy. Definition of the SOP can only be based on the wide study of ECT and EGT efficiency. Therefore, it is necessary to carefully follow and collect outcomes of ECT and EGT clinical trials.

For collection of data acquired in ECT clinical trials a standard paper forms (Clinical Report Forms - CRF) were prepared. The CRF consists of a number of subforms, of which extent depends on the number of treated tumors and number of sessions required to treat the tumor. The CRF include patient's general data, his/her medical history, tumor treatment data and response data. A tumor treatment can be repeated if necessary. The melanoma nodules can efficiently be treated by ECT, therefore patients with this type of tumors were included in the study. For every patient, medical personnel has to fill in 40 pages of forms on average. Since all forms are predefined and same for all patients, we decided to set up a unified database (*central database*) for collection of data from all four medical centers involved in the study. For submission of relatively high number of data into the central database we developed a web-application, which enables access to the central database and filling of forms from any computer connected to the World Wide Web.

## Cliniporator™

Cliniporator™ is a medical device for electrochemotherapy and electrogenetherapy. It consists of two parts: a console (industrial PC compatible computer) for local collection of treatment data and user friendly interface; and an electroporator. Electroporator consists of a control unit, high voltage amplifier and low voltage amplifier. Control unit consists of a processor board, a measurement card for current and voltage measurement, a control card for driving voltage amplifiers and a control-relay card for switching between the electrodes.

A user controls the electroporator through graphical display and a keyboard of the console unit. He/she can enter relevant patient data, choose appropriate electrodes, and define pulse parameters such as number (e.g. 8 pulses), amplitude (up to 1000 V), duration (e.g. 100 μs), and repetition frequency (e.g. 1 Hz) of pulses. All users' presets are stored in a local database, which is integrated into the console. By pressing a foot switch, the user triggers pulse generation. Square-shaped pulses are delivered. During the pulse delivery, the control unit measures voltage and current through the load (a cell suspension or a tissue). After the pulse application voltage and current measurements are stored into the local database. User can use the local database for later analysis of performed treatments. Based on collected data we intend to

develop an algorithm, which will allow device to adjust pulse voltage according to the current and voltage measurements in the real time and thus prevent irreversible changes in the cell membranes.

## Central database

The central database (Microsoft SQL Server) stores following data collected from all the medical centers involved in study:

- patient data (demography, medical history, physical examination,...etc.),
- treatment data (sessions, evaluation visits, follow-ups,...etc.),
- data submitted from local databases of Cliniporator™ medical devices,
- images of tumor nodules in a different phases of treatment.

A backup copy of central database is automatically generated once per week.

Each medical center has limited data access. Users from one medical center cannot read or modify data entered by other centers. Entered data are protected by username and password. Every medical center can have more authorized users, who all have access to the same data. Users can lock selected data, so they cannot be accidentally modified (it is like signing medical forms).

## Web-application

Since medical centers that share data in the central database are spread all over Europe, we had to develop an application for user interaction with the database, which is easy to install, debug and upgrade. It also had to be very intuitive for using, so the users (a medical personnel) should not require any computer knowledge background or excessive training. It had to involve functionalities like: filling the clinical report forms (CRF), interactive human map for marking location of nodules, uploading images to the central database, image gallery, uploading local databases to the central database, and review of already submitted data. In order to follow the progress of individual centers the application also involves statistical representation of the submitted data. An important prerequisite, common in research studies, was that the system has to be upgradeable.

A client-server application would be costly to maintain and upgrade, therefore such solution was not acceptable. Therefore, we developed a web-application (*called Cliniporator Web-Recorder*), which is in our opinion an optimal solution. Such solution does not need any installations on a client computer. Clients can access the central database through the web-application from any computer connected to the World Wide Web and installed internet browser (Internet Explorer, Netscape, Mozzila,...). The web-application is executing on a web-server. The application speed depends only on the web-server capabilities and the internet communication bandwidth while the client computer does not affect the application speed. By submitting username and password users can access all the application functionalities according to their level of authorization.

Cliniporator Web-Recorder maintenance and upgrade is performed exclusively on the web-server. This is the quickest and the most effective and inexpensive way for debugging and upgrading the system. During the application development users have a possibility to participate in testing, which is very important for timely detection of irregularities in the system.

Cliniporator Web-Recorder functionalities are:

- web-forms (digital clinical report file (CRF));
- interactive human map for marking location of tumor nodules;
- image upload;
- local database upload;

- basic statistics (statistical processing of the submitted data).

**Web-forms (digital CRF)** are form-like web pages (Figure 1). Through digital CRF users submit patient and treatment data to the central database. Digital CRF have the same form as the paper-based CRF. They are organized in the following sections: pre-study visit, sessions, adverse events, concomitant medications, follow-up and end of study. The particular section is divided into several pages. *Pre-study visit* consists of few pages where users enter patient's demography data, medical history (history of cancer, previous treatments and history of chronic non malignant diseases), vital signs, physical examinations, tumor lesions, laboratory results, inclusion criteria and exclusion criteria. Users can add any number of *sessions* (most usually two sessions). For every session users have to mark treated nodules and fill several pages with the following data: the time of the begin and the end of the session, vital signs, physical examination, post procedure data (memory from the procedure and pain assessment), and, later, day 15 and day 30 evaluation visit data (response to the treatment and memory from the procedure). Users can create one or more *follow-up* sections and enter data like date of the visit and lesion measurements. In the *end of study* section users should enter the reason for study termination. According to the already submitted data, some form-like web pages are dynamically generated, (e.g. if a patient has more tumor nodules, each nodule requires few form-like web pages for its description).

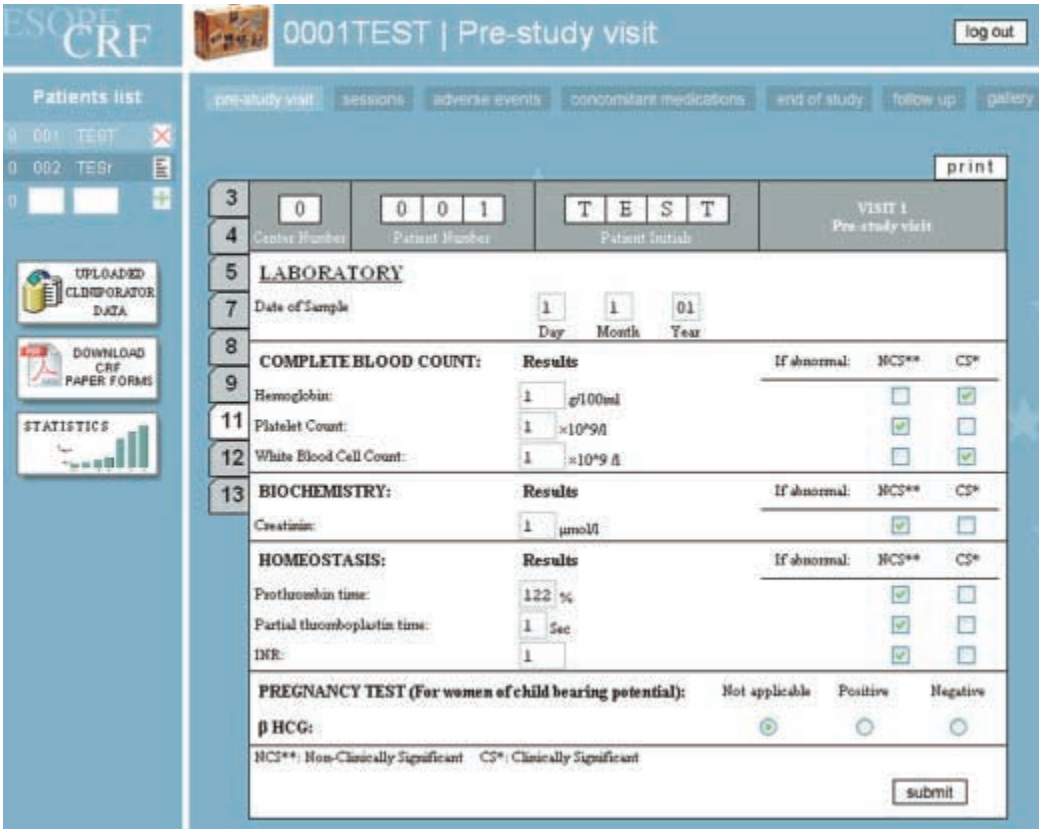


**Figure 1.** A digital CRF page.

An important advantage of the digital CRF is an automatic data checking. The web-application warns a user if he/she mistypes or enters erroneous data. The other advantage is a simple navigation through numbered forms.

At the end of every section users have an opportunity to »digitally sign« the completed section. By signing a section the corresponding forms are »locked« and all further modifications are disabled.

The purpose of the **interactive human map** is a visual representation of the tumor locations. According to the patient's sex, appropriate body map is displayed. Users can switch between four views: front, rear, left and right. By simply clicking on the map, user can »add« a tumor, and then submit some principal data about the tumor (location, measurement lesion, date and method of examination) and corresponding images. During the sessions, users can select on the map which of the pre-registered tumors are treated. The interactive human map is shown on the Figure 2.

**Image upload** enables storing of tumor images into the central database. Images, captured by a digital camera, can be uploaded in the original size. A smaller image, suitable for displaying, as well as a thumbnail of the image, are dynamically generated and also stored in the database. Users can add a caption and a description to every image. Images can be added in every phase of the treatment (pre-study, sessions, follow-up,...). In the *image gallery* (Figure 3) users can review all the uploaded images of one patient, or only the pictures of a particular phase of the treatment. This is very useful for the visual observation of tumor changes.

**Local database upload** is also performed trough the internet browser. The user simply selects the local database file and fills in comments. The rest of the process is automatic: application saves uploaded file on the server, records some upload information (date and time, user id, name of the file,...), and then copy data from the uploaded file to the central database. Application takes care of a duplicate data and their overwriting - the newer data will overwrite the older ones. At the end of the upload process user is informed about the upload success. In the list of the uploaded data user can check all the data uploaded from his/her center.

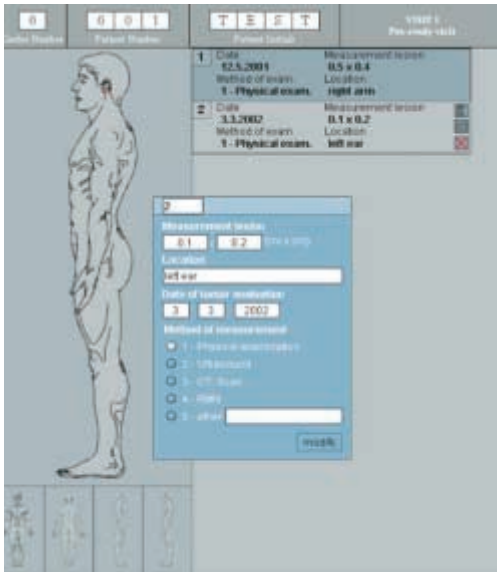

**Figure 2.** Interactive human map.


**Figure 3.** Image gallery: images are grouped by nodule and sorted by time.

**Basic statistics**, which allow the follow-up of the project progress, are dynamically generated from the data in the central database. Therefore, it offers information about the number of treated patients per center as well as number of ended therapies, number of tumor sessions and uploaded corresponding local databases, distributions of applications of different electrode types and different drugs. Every center has access to these statistics and can compare its activities with others. Some statistics (usually local statistics) can be dedicated to a particular center and therefore hidden from other users.

## Conclusion

We have developed a web-application, *Cliniporator Web-Recorder*, for user interaction with the database of medical records collected during the testing period of medical device Cliniporator™. It also supports central collection of data stored in local databases of Cliniporator™ medical devices. This is important for fast detecting of possible device malfunctions and for following the single-use electrode stocks. The amount of data collected in the central database gives us an opportunity to perform a wide analysis of clinical trial results. The results of analysis will contribute to establish standard operating procedures (SOP) for electrochemotherapy and later for electrogenetherapy. These results will also help us in improving the Cliniporator™ medical device and determining algorithms for intelligent pulse delivery. A large collection of medical records can also be helpful to clinicians in choosing optimal treatment protocol for a particular tumor lesion. Our aim is to build a decision making system that will be able to suggest an optimal therapy for a particular tumor.

The advantage of the *Cliniporator Web-Recorder* is that the system can easily be upgraded without any users' disturbance. Due to the web-application and database centralization all system modifications are implemented locally on the server, while users are just informed about the improvements.

## Acknowledgement

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# Evaluation of water equivalency of Plastic Water™ for high-energy electron beams using IAEA TRS-398 Code of Practice

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***Introduction.*** *In the International Code of Practice for dosimetry TRS-398 published by International Atomic Energy Agency (IAEA), water is recommended as the reference medium for the determination of absorbed dose for high-energy electron beams. Plastic phantoms may be used under certain circumstances for electron beam dosimetry for beam qualities R50 < 4g/cm$^2$ ($E_0$ below 10 MeV). In our study, water equivalency of Plastic Water™ was evaluated in order to determine fluence scaling factors $h_{pl}$ for Plastic Water. Extended set of measurements in water and in Plastic Water were performed.*

***Material and methods.*** *The absorbed dose was determined according to IAEA TRS-398 dosimetry protocol following recommendations for all relevant parameters involved. Water equivalency of Plastic Water was evaluated for five electron beams with nominal energies from 6 MeV to 18 MeV generated by linear accelerator Varian Clinac 2100 C/D. Adequate dosimetry equipment was used throughout the measurements and reference conditions, set by IAEA TRS-398, were followed carefully.*

***Results.*** *The results are presented as ratios $D_{pl}/D_w$ of absorbed dose in Plastic Water and water. Upon the selection of electron energy, the ratios vary from 0.9990 - 1.0058 with combined uncertainties (1SD) of 0.46% - 0.68%. From the measured data, the fluence scaling factors $h_{pl}$ were determined and found to be in the range from 0.9942 to 1.0010. Measurements were taken over a period of 18 months, within the frame of a Coordinated Research Project of the International Atomic Energy Agency.*

***Conclusions.*** *Our results are compatible with previously published data.*

*Key words: dosimetry; electron bcams; Plastic Water; IAEA TRS-398*

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## Introduction

In the International Code of Practice for dosimetry TRS-398 published in the year 2000 by International Atomic Energy Agency (IAEA),[1] water is recommended as the reference medium for the determination of absorbed dose for high energy photon and electron beams. Plastic phantoms should not be

used for reference dosimetry in photon beams, however, they can be used for routine quality assurance measurements (daily or weekly output checks), provided a transfer factor between plastic and water has been established. According to IAEA TRS-398 dosimetry protocol, plastic phantoms in the form of slabs may be used under certain circumstances for electron beam dosimetry for the beam qualities $R_{50} < 4$ g/cm$^2$ ($E_0$ below 10 MeV); their use is permitted when no waterproof chamber is available or when accurate positioning in water is not possible.

Presently, many different plastic materials are used for dosimetry purposes in radiotherapy and radiophysics departments: white and clear polystyrene, PMMA, Solid water WT1, Solid water RMI-457, Virtual water, Plastic water and possibly a few others. Several articles comparing the equivalency of various plastics as phantom material to water for electron beam dosimetry have been published.[2-8] Ideally, the phantom material should be water equivalent; that is, it should have the same absorption and scatter properties as water for selected range of photon or electron energies used clinically.

In our study we evaluated the water equivalency of Plastic Water™ developed by Computerized Imaging Reference Systems Inc. Norfolk, VA, USA, also marketed by Nuclear Associates, Inc. Carle Place, NY, USA. We limited our evaluation only to five electron beams within a range of energies from 6 MeV to 18 MeV. The aim of the study was to determine the energy fluence scaling factor $h_{pl}$ for Plastic Water at the selected five electron energies and to compare this factor to the recommended one in the IAEA TRS-398 dosimetry protocol.

## Material and methods

### *A. Theoretical background*

According to IAEA TRS-398 Code of Practice, the calculation of absorbed dose by water $D_{w,Q}(z_{ref,w})$ for high-energy electron beams at the reference depth $z_{ref,w}$ in water, for the reference beam quality Q, and in the absence of the chamber, is given by the equation

$$D_{w,Q}(z_{ref,w}) = M_Q \, N_{D,w,Qo} \, k_{Q,Qo} \qquad [1]$$

where $M_Q$ is electrometer reading $M_1$ corrected for temperature and pressure $k_{T,p}$, as well as for other influencing quantities - polarity $k_{pol}$ and recombination effects $k_s$. $N_{D,W,Qo}$ is the calibration factor of the selected ionisation chamber in terms of absorbed dose by water in $^{60}$Co beam (reference quality $Qo$), and $k_{Q,Qo}$ is chamber specific factor correcting for the difference between the beam of reference quality $Q_o$ and user quality $Q$. In TRS-398, electron beam quality is characterized in terms of half-value depth in water $R_{50}$, which is a depth in water where the absorbed dose in water is 50 % of the maximum absorbed dose. The reference depth $z_{ref,w}$ is also specified by $R_{50}$ and is given by the equation

$$z_{ref,w}(cm) = 0.6 \, R_{50} - 0.1 \qquad [2]$$

To determine the absorbed dose in water at $z_{ref,w}$ using a plastic phantom, the reference point of the chamber must be positioned at a scaled reference depth $z_{ref,pl}$ in plastic. For particular beam quality, the measurement depth in plastic expressed in g/cm$^2$ is obtained from the equation

$$z_{ref,pl} = \frac{z_{ref,w}}{c_{pl}} \qquad [3]$$

where $c_{pl}$ is a depth-scaling factor. The $c_{pl}$ is the ratio of the average depth of electron penetration in water $z_{av,w}$ and in plastic $z_{av,pl}$, where these depths are expressed in g/cm$^2$

$$c_{pl} = \frac{z_{av,w}\rho_w}{z_{av,pl}\rho_{pl}} \qquad [4]$$

Additonally to depth scaling, the electrometer reading $M_{Q,pl}$ at the reference depth in

plastic $z_{ref,pl}$ must be converted to the equivalent reading $M_{Q,w}$ at the reference depth in water $z_{ref,w}$ using the relation

$$M_{Q,w}(z_{ref,w}) = M_{Q,pl}(z_{ref,pl})h_{pl} \quad [5]$$

where $h_{pl}$ is the fluence scaling factor and is generally energy dependant. The uncertainty associated with this scaling factor is the main reason for avoiding the use of plastic phantoms.

*B. Experimental conditions and setup*

Experimental equipment

In the study, well guarded waterproof plane parallel ionisation chamber PPC 40 was used together with DOSE 1 electrometer (both produced by IBA Scanditronix - Wellhöfer). The ionisation chamber was calibrated at the IAEA Standard Dosimetry Laboratory in Seibersdorf. The comparison was done for five high-energy electron beams with the energies of 6 MeV, 9 MeV, 12 MeV, 15 MeV and 18 MeV generated by linear accelerator Varian Clinac 2100 C/D. The temperature was monitored with a digital thermometer of the resolution of 0.1 °C and the pressure with a digital barometer of resolution of 0.1 mbar.

1D water phantom (produced by MEDTEC) with PMMA walls was used for the measurements in water. The phantom was equipped with a fine mechanical depth adjustment mechanism with the resolution of 0.1 mm. Distilled water was used throughout the measurements.

For the measurements in plastic phantom, Plastic Water (cream coloured) in the form of slabs of the size of 30 x 30 cm$^2$ was used. The thickness of the slabs varied from 1 mm up to 60 mm. Chemical composition (fraction by weight), nominal density, mean atomic number and depth scaling factor for Plastic Water are given in Table 1. For comparison, the data for liquid water are included.

**Table 1.** Chemical composition in terms of fractional weight, nominal density ρ[g/cm$^3$], mean atomic number $\bar{Z}$ and depth scaling factor $c_{pl}$ for Plastic Water. Liquid water data are included for comparison

| | Liquid water | Plastic Water |
|---|---|---|
| H | 0.1119 | 0.0925 |
| C | | 0.6282 |
| N | | 0.0100 |
| O | 0.8881 | 0.1794 |
| Cl | | 0.0096 |
| Ca | | 0.0795 |
| Br | | 0.0003 |
| $\rho$[g/cm$^3$] | 1.000 | 1.013 |
| $\bar{Z}$ | 6.6 | 6.62 |
| $c_{pl}$ | 1.000 | 0.982 |

Reference conditions and set-up

Measurements were done in four sessions on four different days. In each session five measurements were done in water as well as in plastic for five high-energy electron beams. Chamber, water and plastic were left in a bunker for several hours before measurements in order to reach as thermal equilibrium. Before we started with measurements in water, the chamber was dipped into water for at least 15 minutes. Reference conditions were always the same: SSD = 100 cm, 10 x 10 cm$^2$ electron applicator was used and the irradiation time was 200 MU at a constant dose-rate of 300 MU/min. Gantry and collimator were set to 0° and all the measurements were made along the central axis of the beam. Polarising voltage of the chamber was +300 V - the same as during the chamber calibration.

The reference depths were set according to the expressions [2] and [3] for water and plastic, respectively. $R_{50}$ was determined in separate relative dosimetry measurements using a computer controlled water phantom (Blue Phantom made by IBA Scanditronix - Wellhöfer), where the data were collected in 0.4 mm increments. As the thinnest available slab was 1 mm thick, the actual depth of the

chamber reference point in plastic was at the depth that was nearest to the calculated one and not exactly at the calculated one. However, the differences were small. As defined in TRS-398 dosimetry protocol, the reference point of the chamber (effective point of measurement) is at the inner surface of the entrance window. Reference depths and some other chamber parameters for selected set of energies are presented in Table 2.

When dipping the chamber into water we were careful not to trap any air bubble at the chamber bottom because it could lower the absorbed dose. For setting up the chamber in plastic, a special cylindrical disc made of white polystyrene was fitted in the chamber hole at its bottom. This was to ensure that no scattered radiation would be lacking due to the absence of scattered material at the chambers bottom. One of the blocks was machined to fit exactly to ionisation chamber PPC40 so that the entrance window of the chamber was at the level of one surface of the block. Under the point of measurement, 6 cm of Plastic Water was always kept to provide an adequate backscatter conditions.

## Results and discussion

The results are presented in Table 3 and Figure 1, as the dose ratios Plastic Water/water as a function of nominal beam energy

$$R = \frac{D_{pl,Q}(z_{ref,pl})}{D_{w,Q}(z_{ref,w})} \quad [6]$$

Depending upon the beam energy, the ratios varied from 0.9990 to 1.0058. From the calculated ratios, the fluence scaling factors $h_{pl}$ can be determined.

The measured doses in Plastic Water are within 1% of those measured in water for all electron beam energies, and all the ratios are higher than 1.0 (apart from the ratios for 18 MeV electron beam, where ratios are lower than 1.0). Combined measurement uncertainties (1SD) of type A and type B (detailed explanation about uncertainties is given in reference1), joining the uncertainties from re-

**Table 3.** Ratios $D_{pl}/D_w$ of absorbed doses measured in Plastic Water and in water for five high energy electron beams produced by Varian Clinac 2100 C/D linear accelerator. Combined measurement uncertainties (1SD) of type A and type B (detailed explanation about uncertainties is given in reference1), joining the uncertainties from repeated measurements from four sessions and estimated uncertainties due to setup and other influencing quantities (pressure, temperature.) Corresponding fluence scaling factors $h_{pl}$ for each electron energy are presented without standard deviations.

| | $D_{pl}/D_w$ | $h_{pl}$ |
|---|---|---|
| 6 MeV | 1.0020 ± 0.0068 | 0.9980 |
| 9 MeV | 1.0035 ± 0.0050 | 0.9965 |
| 12 MeV | 1.0058 ± 0.0046 | 0.9942 |
| 15 MeV | 1.0022 ± 0.0061 | 0.9978 |
| 18 MeV | 0.9990 ± 0.0053 | 1.0010 |

**Table 2.** Various beam and ionisation chamber (PPC40) parameters used for calculation and measurements of the absorbed dose in water for high energy electron beams generated by linear accelerator Varian Clinac 2100 C/D

| | 6 MeV | 9 MeV | 12 MeV | 15 MeV | 18 MeV |
|---|---|---|---|---|---|
| R50 [cm] | 2.31 | 3.54 | 4.97 | 6.28 | 7.58 |
| Rp [cm] | 2.91 | 4.37 | 6.02 | 7.54 | 9.18 |
| $z_{ref,w}$[a] [cm] | 1.29 | 2.02 | 2.88 | 3.67 | 4.45 |
| $z_{ref,pl}$[b] [cm] | 1.31 | 2.06 | 2.93 | 3.74 | 4.53 |
| $z_{ref,pl}$[c] [cm] | 1.30 | 2.10 | 2.90 | 3.70 | 3.50 |

[a] Reference depth in water of the effective measurement point of the chamber according to TRS-398
[b] Reference depth in Plastic Water of the effective measurement point of the chamber according to TRS-398 obtained from formula expression [3]
[c] Actual depth in PW of the effective measurement point of the chamber due to limitation of minimal slab thickness of 1 mm

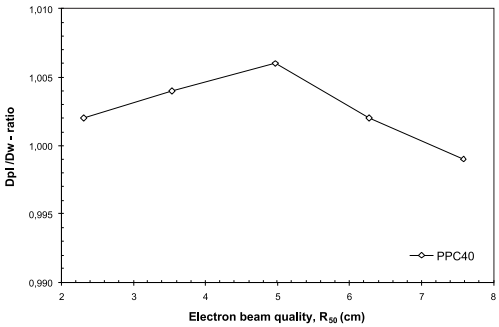


**Figure 1.** Ratios $D_{pl}/D_w$ of absorbed doses determined with measurements in Plastic Water and in water for five high-energy electron beams - electron beam qualities. Measurements were performed with plane parallel ionisation chamber PPC40. Beam data are in Table 2.

peated measurements from four sessions and the estimated uncertainties due to setup and other influencing quantities (pressure, temperature) are presented in Table 3 and are in the range from 0.46% to 0.68%.

In our study, the average value for $h_{pl}$ for energies below 10 MeV is 0.9973, which is in line with the value published in TRS-398, where $h_{pl}$ is 0.998. Average value of $h_{pl}$ for all electron energies in our study is 0.9975. A slight disagreement with results obtained by Tello *et al.*[5] was observed, but well within the reported uncertainties. We can conclude that our results confirm previously published data for $h_{pl}$ for Plastic Water.

However, we must emphasize, that the temperature of the air in the chamber cavity was probably not the same as the temperature of water when the measurements in water phantom were performed. Due to specific temperature conditions in the accelerators bunker, we could assume that the temperature of the air in the chamber cavity was always at least a little bit higher than the measured water temperature; this, sometimes large difference (up to 3°C) between the temperature measured in water and the room temperature was due to a slow but permanent rising of room temperature (air condition didn't work optimally). The measured and reported ratios $D_{pl}/D_w$ could thus be too high by up to 0.3%, which corresponds to the temperature difference of 1°C. As it was not possible to measure actual temperature of the air in the chamber cavity, we included 0.3% of possible temperature variation in the uncertainties of our measurements, rather that in the systematic errors.

We can conclude, that when no water phantom is available in the clinic, or when the use of plastic phantom would be less time consuming or, from any other reason, more appropriate for physicists, the Plastic Water phantom can be used for routine constancy checks of high energy electron beams within the energy range checked in this study and also taking into account the fluence scaling factors as suggested in this study. Even if we take an average fluence scaling factor for all beams in the energy range from 6 MeV - 18 MeV, which is in our case 0.9975, the estimated difference of the absorbed dose determination in Plastic Water should be below 1% comparing to the absorbed dose in water. However, before Plastic Water is to be used as water substitute for reference dosimetry, a careful comparison with measurement in water should be performed.

## Acknowledgements

Present study was done in the framework of Co-ordinated Research Project (CRP E2.40.09) of the International Atomic Energy Agency. The main goal of the extended project was testing of the procedures recommended in TRS-398 dosimetry protocol for different types of radiation beams and ionisation chambers as well as comparison of the results obtained with the existing protocols. Authors would like to thank colleagues in the project group: Mariella Affonseca, Ivaldo Ferreira, Günther Hartmann, Saiful Huq, Govinda Rajan and specially to Scientific Officer of the project Stanislav Vatnitsky.

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# Boerhaavejev sindrom: primer neznačilnega predrtja požiralnikove desne stene

**Sjekavica I, Pavliša G, Šeronja-Kuhar M, Moscatello I, Štern-Padovan R**

**Izhodišča.** Boerhaavejev sindrom imenujemo popolno predrtje požiralnikove stene v predelu prsnega koša. V 90 % se pojavi raztrganina na levi posterolateralni strani požiravnika.
**Prikaz primera.** Prikazujemo primer Boerhaavejevega sindroma z neznačilno raztrganino desnega dela požiravnikove stene.
**Zaključki.** CT prsnega koša je prednostna preiskava, saj ob prikazu struktur v prsnem košu lahko vidimo tudi morebitne komplikacije obolenja in CT pomaga pri diferencialni diagnozi, kadar sumimo, da ima bolnik predrt požiralnik. Posebno pomembna pa je CT preiskava, kadar je bolnikovo stanje tako resno, da ne dovoljuje esofagografije.

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# Ugotavljanje zožitve aorte z magnetno resonanco

**Bešlić Š**

**Izhodišča.** Namen pričujočega članka je analizirati pomen magnetne resonance pri ugotavljanju zožitve aorte pri bolnikih, ki so imeli klinično in ultrazvočno sumljive znake bolezni.
**Bolniki in metode.** V treh letih smo pregledali 8 bolnikov, 5 (62,5%) moških in 3 (37,5%) ženske, pri katerih smo sumili, da imajo zožitev aorte. Razmerje med moškimi in ženskami je bilo 1,7 : 1. Najmlajši bolnik je bil star 3 leta, najstarejši pa 46 (srednja starost 15 let). Preiskave smo naredili z napravo Magnetom 1.0 Tesla, Siemensove proizvodnje, s 6 mm rezi, brez kontrasta in ob uporabi telesne tuljave. Uporabili smo T1 obtežene frekvence s hitrim spinskim odmevom (*fast spin-echo T1W*) in z rezi debeline 6 mm brez uporabe kontrastnega sredstva ter gradient echo sekvence z rezi debeline 7mm. Naredili smo magnetno resonančno angiografijo vrste *time of flight (TOF)* z rekonstrukcijami projekcije največje intenzitete *(MIP)*. Med preiskavami smo uporabljali EKG usklajevalnik, preiskave pa naredili v transverzalnih, koronarnih in poševnih sagitalnih ravninah in ob tem merili obsežnost srčno žilnih struktur.
**Rezultati.** Zožitev aorte smo odkrili pri vseh osmih bolnikih (100%). Pri sedmih bolnikih (87,5%) je bila aorta zožena na mestu isthmus aorte in pri enem primeru bolniku na mestu horizontalnega dela loka aore, med truncus arteriosus in levo carotidno arterijo. Aortno insuficienco smo našli pri sedmih bolnikih (87,5%), od katerih so štirje (50%) imeli bicuspidijo (bicuspidija aortne zaklopke), sedem bolnikov (87,5%) pa je imelo rahlo izraženo hipertrofijo levega prekata. Pri dveh bolnikih (25%) smo odkrili dilatacijo ascendentnega dela aorte, pri šestih (75%) pa razširitev iztočnih žil aortnega loka. Štirje bolniki (50%) so imeli dobro razvite kolateralne arterije, ki so pri dveh bolnikih povzročile spremembe na rebrih. Pri dveh bolnikih (25%) smo naključno odkrili, da imata ohranjen thymus. Povprečen premer aortne zožitve je bil 10 mm. Pri enem bolniku je zožitev aorte spremljala stenoza pulmonarne arterije, pri enem ventricularni septalni defekt in pri enem trikuspidalna insuficienca. Izsledki, ki smo jih dobili z magnetno resonanco, so bili v celoti (100 %) enaki izsledkom kliničnih in ultrazvočnih preiskav.
**Zaključki.** Magnetna resonance je neinvazivna preiskovalna metoda srca in velikih žil in lahko v vedno večji meri predstavlja nadomestilo invazivnim angiograskim preiskavam, zlasti v pediatriji, ker se na ta način izognemo sevanju. Uporabljamo jo kot komplementarno preiskavo ultrazvočni priskavi, intraarterialni digitalni subtrakcijski angiografiji (IA DSA) in špiralnemu CT-ju (SCT).

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# Rituximab spreminja prognozo bolnikov z neHodgkinovimi limfomi

**Jezeršek Novaković B, Vovk M, Borštnar S, Tomšič R**

**Izhodišča.** Rituximab - najpogosteje uporabljeno monoklonalno protitelo s področja B celičnih limfoproliferativnih obolenj - se je izkazal kot uspešno zdravilo pri zdravljenju ponovitev ali refraktarnih oblik indolentnih CD20 pozitivnih B celičnih limfomov, v novejšem času pa tudi pri zdravljenju agresivnih limfomov v kombinaciji s standardno citostatsko terapijo. Čeprav ima takšna kemo-imunoterapija širok razpon indikacij, ostajajo v zvezi z njo številna vprašanja, ki jih je potrebno razjasniti: (1) kakšno je optimalno časovno zaporedje aplikacij protiteles in citostatikov in kateri odmerki omenjenih substanc so najbolj učinkoviti, (2) kateri citostatiki so najbolj učinkoviti v kombinaciji z rituximabom, ter nenazadnje, (3) kateri so napovedni dejavniki, ki napovedujejo ugoden odziv na rituximab.

**Bolniki in metode.** Z namenom delno razjasniti prvi dve vprašanji, smo opravili analizo rezultatov zdravljenja s kemo-imunoterapijo pri 25 bolnikih z različnimi histološkimi podtipi CD20 pozitivnih B celičnih limfomov (10 agresivnih in 15 indolentnih). Sedemnajst bolnikov je prejemalo kemo-imunoterapijo za zdravljenje ponovitev limfoma in le pri 8 bolnikih smo rituximab dodali k citostatski terapiji prvega reda. Večina bolnikov, ki se je ugodno odzvala na zdravljenje, je v kombinaciji z rituximabom prejemala shemo CHOP, kot uspešne pa so se izkazale tudi druge kombinacije citostatikov (FC, BVCPP).

**Rezultati.** V celoti smo odgovor na kemo-imunoterapijo dosegli pri 76% bolnikov, pri 68% smo ugotovili popolni odgovor. Srednjega trajanja odgovora še nismo dosegli. Odgovor na terapijo je bil precej boljši v skupini bolnikov, ki pred tem še ni bila zdravljena, saj smo v tej skupini odgovor na terapijo dosegli pri vseh (100%) bolnikih in sicer popolni odgovor pri 7 in delni odgovor pri 1 bolniku. Kemo-imunoterapija pa je bila neuspešna prvenstveno pri bolnikih z agresivnimi limfomi, ki so bili pred tem že večkrat zdravljeni. V teku raziskave nismo opazili resnejših stranskih učinkov.

**Zaključki.** Kemo-imunoterapija izboljša rezultate zdravljenja v primerjavi s samim citostatskim zdravljenjem tako pri prej nezdravljenih bolnikih kot tudi pri bolnikih, ki so bili že prej zdravljeni. Kombinirano zdravljenje je najbolj uspešno, kadar ga uporabimo čimbolj zgodaj v poteku bolezni (najbolje kot terapijo prvega reda). Da pa bi optimizirali (oz. racionalizirali) uporabo rituximaba, bo potrebno določiti najbolj učinkovite kombinacije citostatikov s protitelesi, predvsem pa tudi ugotoviti napovedne dejavnike za uspeh terapije z rituximabom.

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# Neuronsko specifična enolaza - selektivni tumorski označevalec za drobnocelični pljučni rak

**Ilievska Poposka B, Spirovski M, Trajkov D, Stefanovski T, Atanasova S, Metodieva M**

**Izhodišča.** Nevronsko specifična enolaza (NSE) je izomer glicolitičnega encima enolaza, ki je bil prvič odkrit v ekstraktu možganskega tkiva, kasneje pa so dokazali njegovo prisotnost v normalnih neuroendokrinih celicah in neuroendokrinih tumorjih. Namen raziskave je bil potrditi pomen serumske NSE kot tumorskega označevalca pri bolnikih z drobnoceličnim pljučnim rakom.

**Bolniki in metode.** Serumski nivo NSE smo merili z radioimunološko metodo pri 71 bolnikih s pljučnim rakom, pri 24 bolnikih z nemaligno pljučno boleznijo in pri 28 zdravih odraslih osebah.

**Rezultati.** Glede na serumsko vrednost NSE pri skupini zdravih odraslih osebah smo določili zgornjo mejo normalne vrednosti NSE v srumu, ki je bila 16,6 ng/ml. Glede na vrednosti serumske NSE pri bolnikih z nemaligno pljučno boleznijo pa smo določili specifičnost preiskave, ki je bila 88,13 %. Pri bolnikih s pljučnim rakom je bila senzitivnost preiskave 47,82%, pri bolnikih z drobnocelišnim pljučnim rakom je narastla na 72,72%, pri bolnikih z nedrobnoceličnim pljučnim rakom pa je bila le 38,89%. Bolniki z razširjeno obliko drobnoceličnega pljučnega raka so imeli statistično značilno višjo srednjo vrednost serumske NSE (290,48 ng/ml), kot bolniki z omejeno obliko bolezni (46,94 ng/ml). Vrednosti serumske NSE smo spremljali tudi pri 16 bolnikih, ki so dobivali kombinirano kemoterapijo in/ali bili obsevani in ugotovili zelo visoko soodvisnost s kliničnim odgovorom na zdravljenje.

**Zaključki.** Tudi pričujoči rezultati potrjujejo, da je lahko serumska NSE koristen tumorski označevalec pri bolnikih z drobnoceličnim pljučnim rakom. Koristi nam lahko pri diagnosticiranju, ugotavljanju razširjenosti bolezni, predvsem pa pri ugotavljanju odgovora na zdravljenja in ponovitve bolezni.

Radiol Oncol 2004; 38(1): 27-34.

# Rak dojke in ozaveščenost o zdravju dojk kot razvijajoči načrt promocije zdravja

**Plesničar A, Kovač V, Kralj B**

**Izhodišča.** Rak dojke je najpogostejša maligna bolezen žensk v večini razvitih držav. V zadnjih nekaj letih se je po uvedbi presejalnih programov z mamografijo preživetje bolnic z rakom dojke izboljšalo, vendar incidenca te bolezni v omenjenih državah še vedno narašča. Ob osredotočenosti na sekundarno prevencijo raka dojk z zgodnjo detekcijo in zgodnjim zdravljenjem zmanjšanja incidence raka dojk ni mogoče doseči. Pomembna je primarna prevencija, ki lahko zmanjša incidence raka dojk.. Tako lahko ozaveščenost o zdravju dojk predstavlja del specifičnih aktivnosti promocije zdravja.
**Zaključki.** Rak dojke je v razvitih državah velik problem javnega zdravja. Aktivnosti na področju sekundarne prevencije raka dojke bi zato morali dopolniti s specifičnimi aktivnostmi promocije zdravja in v prihodnosti zmanjšati njegovo incidenco. Promocija zdravja bi kot del primarne prevencije raka dojke vključevala aktivnosti pri izboljšanju individualne in skupne ozaveščenosti o zdravju dojk. Člani vplivnih skupin prebivalstva bi s primerno kolektivno ozaveščenostjo lahko dosegli ustrezne spremembe zakonodaje, davčnih ukrepov, carinskih in trgovinskih predpisov, ki bi ženskam omogočale nadzor nad lastnim zdravjem dojk. Z zmanjšanjem incidence raka dojke bi lahko pomembno vplivali na zdravje celotne skupnosti.

Radiol Oncol 2004; 38(1): 35-42.

# Soočanje, spoprijemanje in obvladovanje psihosocialne obremenjenosti pri bolnikih z rakom

**Šprah L, Šoštarič M**

**Izhodišča.** Namen preglednega članka je predstaviti najpogostejše psihosocialne obremenitve pri bolnikih z rakom in njihove psihosocialne strategije spoprijemanja s to boleznijo. Bolniki z rakom se srečujejo s številnimi psihosocialnimi težavami, ki niso samo posledica razvoja bolezni in njenega zdravljenja. Soočajo se tudi s socialnim pritiskom, ki izhaja iz predsodkov in stereotipov do te bolezni. V članku so predstavljeni nekateri procesi soočanja z diagnozo in spoprijemanja s psihološkimi posledicami raka. Prav tako so opisani vplivi učinkovitosti posameznih načinov spoprijemanja z rakom in vplivi psihosocialnih intervencij ter socialne podpore na razvoj, potek in ponavljanje bolezni.
**Zaključki.** V zadnjem času je bilo opravljenih nekaj metaanaliz, ki niso povsem potrdile povezanosti med psihosocialnimi strategijami spoprijemanja z rakom in razvojem, potekom bolezni ter ozdravitvijo. Terapevtsko okno v primerih psihosocialnih intervencij je široko in lahko v precejšnji meri izboljša kvaliteto življenja mnogih bolnikov z rakom.

Radiol Oncol 2004; 38(1):43-7.

# Test komet *in vitro* pri ocenjevanju poškodbe človeškega genoma po obsevanju z žarki γ

**Garaj Vrhovac V, Zeljezic D**

**Namen.** Z raziskavo smo želeli preveriti možnost uporabe testa komet pri ocenjevanju poškodb DNK, ki jih povzročijo različne doze žarkov x na perifernih človeških limfocitih in vitro.
**Materiali in metode.** Čiste krvne vzorce smo odvzeli mladim, zdravim prostovoljcem - nekadilcem. Vzorce smo razdelili v 4 skupine. Prvo smo uporabili kot kontrolo, ostale tri pa smo obsevali z napravo s konstantnim obsevalnim virom žarkov γ ($^{60}$Co) s hitrostjo doze 0,907 cGy/s. Skupine krvnih vzorcev smo obsevali 51 sekund, 437 sekund in 1099 sekund z ustretajočimi dozami 0,5 Gy, 4 Gy in 10 Gy. Za oceno krivulj, ki so ponazarjale odgovor kontrolne skupine vzorcev in treh obsevanih skupin vzorcev na obsevanje, smo opravili kometni test v alkalnih pogojih.
**Rezultati in zaključki.** Izid kometnega testa je pokazal statistično pomembno višje vrednosti pri obsevanih skupinah vzorcev v primerjavi s kontrolno skupino. Učinek doze v razponu od 0,5 Gy do 10 Gy je bil premosorazmeren tako z dolžino kometovega repa kot z momentom. Z raziskavo smo tudi potrdili, da je kometni test mogoče uporabiti za odkrivanje poškodb DNK, ki jih povzročijo visoke obsevalne doze. Takšnih poškodb s citogenetskimi metodami ni mogoče odkriti.

Radiol Oncol 2004; 38(1):49-54.

# Spletna aplikacija kot nadgradnja funkcionalnosti medicinske naprave za zdravljenje tumorjev s pomočjo elektrokemoterapije

**Pavlović I, Kramar P, Čorović S, Cukjati D, Miklavčič D**

Elektrokemoterapija (ECT) je sodobna metoda za učinkovito zdravljenje tumorjev v kliničnem okolju. Metoda temelji na elektroporaciji, s katero omogočimo lokalno vbrizganemu kemoterapevtiku vstop v celice tumorja. Kemoterapevtik lahko vstopi le v celice, katerih membrano smo predhodno uspešno permeabilizirali z elektroporacijo, kar dosežemo z uporabo kratkih visokonapetostnih pulzov. V ta namen je bila nedavno razvita medicinska naprava imenovana Cliniporator™. Tako vam predstavljamo spletno aplikacijo, ki smo jo razvili z namenom povečanja njene funkcionalnosti. Osnovni namen aplikacije je zbiranje, shranjevanje in analiza elektrokemoterapij izvedenih s pomočjo te medicinske naprave. Že med samim potekom elektroporacije naprava zbira in lokalno shranjuje vse podatke povezane s tem procesom, razvita spletna aplikacija pa omogoča enostavno zbiranje teh podatkov na enem mestu, t.j. v centralni bazi podatkov. Prav tako pa preko spletnih obrazcev omogoča izpolnjevanje medicinskih obrazcev, ki opisujejo zdravstveno stanje bolnika, tumorje in potek zdravljenja, ter izdelavo poročil statističnih obdelav. Spletna aplikacija temelji na sodobnih tehnologijah kot so ASP, HTML, Flash, JavaScript in XML. Glavne prednosti takšne rešitve centraliziranega zbiranja in obdelave podatkov so lahek in hiter dostop do podatkov, neodvisnost od operacijskega sistema in spletnega brskalnika, ki ga uporablja uporabnik, ter enostavno odpravljanje napak in nadgradljivost sistema.

Radiol Oncol 2004; 38(1): 55-60.

# Ocenitev ekvivalentnosti plastičnega materiala (Plastic Water™) in vode za visokoenergijske elektronske žarke ob upoštevanju dozimetričnega protokola IAEA TRS-398

**Casar B, Zdešar U, Robar V**

**Izhodišča.** V mednarodnem protokolu za dozimetrijo TRS-398, ki ga je izdala Mednarodna agencija za atomsko energijo (IAEA), je za določitev absorbirane doze za visokoenergijske elektronske žarke kot referenčni medij priporočena voda. Plastične fantome lahko uporabljamo le pod določenimi pogoji za kvalitete žarkov $R_{50}$ < 4 g/cm$^2$ ($E_0$ pod 10 MeV). V naši študiji smo ocenjevali ekvivalentnost plastičnega materiala Plastic Water™ in vode, z namenom da bi za to plastiko določili faktor hpl. Opravili smo obsežne meritve v vodi in v plastičnem fantomu.

**Material in metode.** Absorbirano dozo smo določili v skladu z dozimetričnim protokolom IAEA TRS-398 ter upoštevali priporočila za vse pomembne parametre. Ekvivalentnost izbranega plastičnega materiala smo ocenili za 5 elektronskih žarkov z energijami od 6 MeV do 18 MeV. Pri meritvah smo uporabili primerno dozimetrično opremo ter natančno sledili referenčnim pogojem iz TRS-398.

**Rezultati.** Rezultate smo predstavili kot razmerje $D_{pl}/D_w$ med absorbirano dozo v plastiki in absorbirano dozo v vodi. Dobljena razmerja so bila od 0.9990 - 1.0058, odvisno od izbrane energije z negotovostjo rezultatov (1SD) od 0,46% - 0,68 %.

**Zaključki.** Naši rezultati so primerljivi z do sedaj objavljenimi izsledki drugih raziskav.

# Notices

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

**Radiation oncology**

*May 2-6, 2004*

The ESTRO course »Radiation Oncology: a Molecular Approach« will take place in Giardini Naxos, Italy.

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

**Radiotherapy**

*May 2-6, 2004*

The ESTRO course »Dose Determination in Radiotherapy: Beam Characterisation, Dose Calculation and Dose Verification« will take place in Nice, France.

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**Brachytherapy**

*May 13-15, 2004*

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

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**Radiology**

*June 6-8, 2004*

The UK Radiological Congress will be held in Manchester, U.K.

**Contact** Ms. Rebecca Gladdish, UKRC 2003 Secretariat, PO Box 2895, London W1A 5RS, U.K., or call +44(0) 20 7307 1410/20, or fax +44(0) 20 7307 1414; or e-mail conference@ukrc.org.uk / exhibition@ukrc.org.uk; or see www.ukrc.org.uk

**Radiation oncology**

*June 13-18, 2004*

The ESTRO course »Evidence-Bases Radiation Oncology: Methodological Basis and Clinical Application« will take place in Moscow, Russia.

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**Radiotherapy**

*June 20-24, 2004*

The ESTRO course »IMRT and Other Conformal Techniques in Practice« will take place in Amsterdam, The Netherlands.

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**Prostate cancer**

*June 27-29, 2004*

The ESTRO course »Brachytherapy for Prostate Cancer« will take place in Leeds, U.K..

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**Oncology**

*July 3-6, 2004*

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

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

### Gynaecological cancer

*August 26-28, 2004*

The ESTRO advanced teaching course on »Brachyherapy for Gynaecological Cancer« will take place in Vienna, Austria.

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### Medical physics

*August 29 - September 2, 2004*

The ESTRO course »Physics for Clinical Radiotherapy« will take place in Leuven, Belgium.

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

### Paediatric oncology

*September, 2004*

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

**See** http://www.siop.nl

### Radiobiology

*September 19-23, 2004*

The ESTRO course »Basic Clinical Radiobiology« will take place in Lausanne, Switzerland.

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

### Lung cancer

*September 23-25, 2004*

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

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

### Radiation therapy

*October 3-7, 2004*

ASTRO Annual meeting will be held in Atlanta, USA.

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

### Therapeutic radiology and oncology

*October 24-28, 2004*

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

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

### Medical oncology

*October 29 - November 2, 2004*

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

**See** http://www.esmo.org

### Radiation oncology

*November 7-12, 2004*

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

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

### Radiation oncology

*November 25-28, 2004*

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

**See** http://www.isro.be

**Radiation oncology**

*March, 2005*

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

**See** http://www.isro.be

**Lung cancer**

*July 3-6, 2005*

The »11th World Conference on Lung Cancer« will be offered in Barcelona, Spain.

**Contact** Heather Drew, Imedex, Inc., 70 Technology Drive, Alpharetta, GA 30005 USA; or call +1 770 751 7332, or fax +1 770 751 7334; or e-mail h.drew@imedex.com, or see www.imedex.com/calenders/oncology/htm

**Radiation oncology**

*September - October, 2005*

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

**See** http://www.isro.be

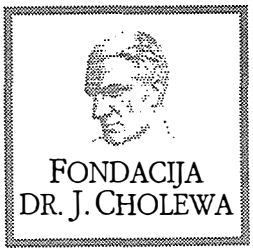
**Oncology**

*October 30 - November 3, 2005*

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

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

*As a service to our readers, notices of meetings or courses will be inserted free of charge.*
*Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.*

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## Activity of »Dr. J. Cholewa« Foundation for Cancer Research and Education - A Report for the First Quarter Of 2004

In the start of the year 2004 the Administrative and Supervising Boards of the Dr. J. Cholewa Foundation for Cancer Research and Education Foundation and the Health experts Commission of the Foundation reflected upon some aspects of the previous year. Although several new members joined the Foundation and the acquirement of the generous and important donation to the Foundation by Dr Ana Hinterlechner Ravnik, it remains the fact that various public and privately owned enterprises find it more and more difficult to contribute financially to help running day to day operations of the Foundation and its many scopes of activity. Other topics were also discussed and were presented at the last meeting of the Administrative and Supervising Boards of the Dr. J. Cholewa Foundation for Cancer Research and Education Foundation at their last joint meeting in the year 2003. Despite aforementioned financial constraints the detailed review of the Foundation's activity for the year 2003 shows that it achieved all the anticipated and stated goals for that year. In short, the main goal still remains to support and sustain research in cancer in Slovenia, and various pathways are to be undertaken to achieve this goal.

The Foundation will continue to support the regular publication of »Radiology and Oncology« international scientific journal, which is edited, published and printed in Ljubljana, Slovenia. The Dr. J. Cholewa Foundation for Cancer Research and Education also remains optimistic about the prospects in the year 2004. Republic of Slovenia will join the European Union in 2004, and this important fact may help the Foundation to gain more information, to expand its existing framework of activities and to find and deal with new challenges in the new economic and political surroundings. This may help the Foundation to find the ways to collaborate with similar institutions all over Europe and elsewhere, and the Foundation may in this way further expand its scope and goals.

Borut Štabuc, MD, PhD
Andrej Plesničar, MD
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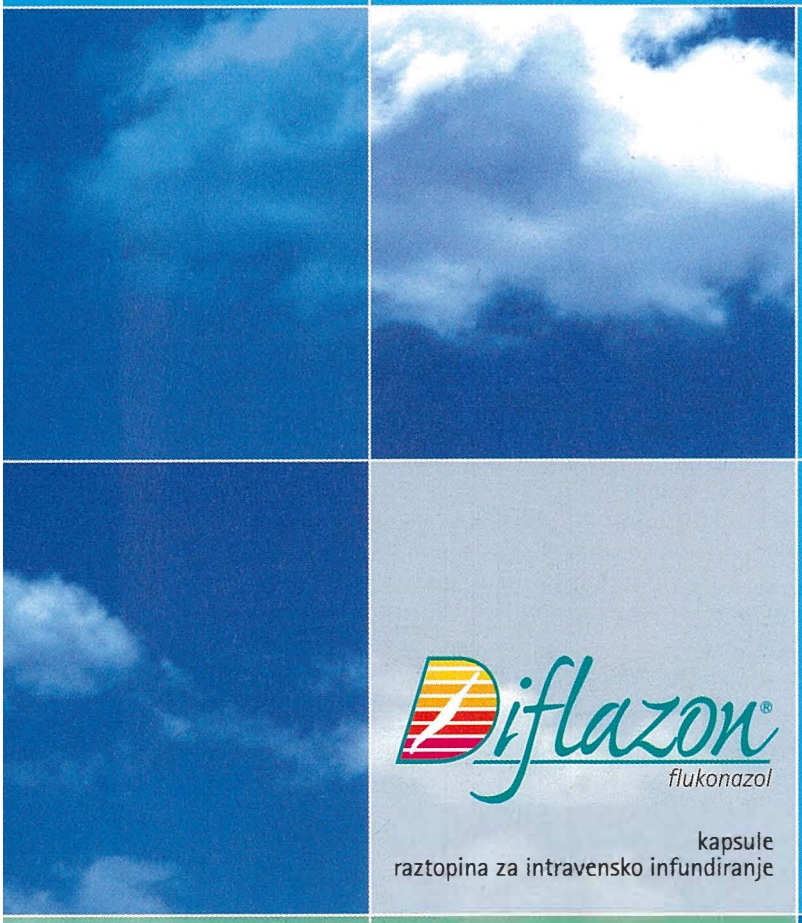

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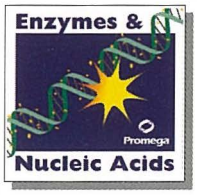



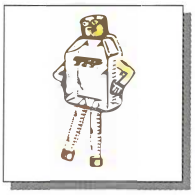


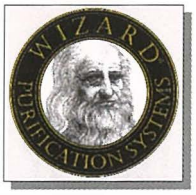



**IZDELKI ZA MOLEKULARNO BIOLOGIJO**

**DOKUMENTACIJA IN ANALIZA GELOV**

**PLASTIKA ZA CELIČNE KULTURE**

ELGA LABWATER

SANYO

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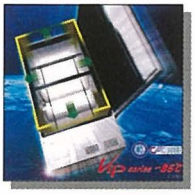

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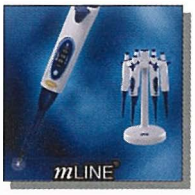


**ELEKTRONSKE IN MEHANSKE AVTOMATSKE PIPETE**

**DIAGNOSTIKA MIKOPLAZEM IN LEGIONEL**

**SEKVENATORJI**

**CAELYX**

doksorubicinijev klorid v pegiliranih liposomih

***upanje z zaupanjem***

- metastatski rak dojk pri bolnikih s povečanim tveganjem za srčna obolenja
- napredovani rak jajčnika, če prva platinska terapija ni bila uspešna
- z aidsom povezan Kaposijev sarkom

Schering-Plough CE AG **[bolnišnična enota]** Dunajska 22, 1000 Ljubljana, telefon: 01 3001070, faks: 01 3001080

**Odmerjanje in način uporabe:** Rak dojk in rak jajčnikov: 50 mg/m2 i.v. 1x na vsake 4 tedne. Kaposijev sarkom: 20 mg/m2 i.v. na vsaka dva do tri tedne. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero od pomožnih snovi; dojenje **Posebna opozorila in previdnostni ukrepi:** Pri vseh bolnikih je priporočljivo rutinsko pogosto spremljanje EKG. Incidenca mielosupresije je majhna, praviloma je blaga do zmerna in reverzibilna ter ni povezana z epizodami okužb zaradi nevtropenije ali s sepso. Pri bolnikih, ki imajo z aidsom povezani Kaposijev sarkom mielosupresija omejuje odmerek. Med zdravljejnjem je potrebno redno in pogosto opravljati preiskave krvne slike. Diabetiki: vsaka prebodna steklenička zdravila Caelyx vsebuje saharozo; odmerek dajemo v 5 % (50 mg/ml) raztopini glukoze za infundiranje. **Interakcije:** Previdnost je potrebna med sočasno uporabo drugih mielotoksičnih zdravil in med sočasno uporabo zdravil, za katera je znano, da medsebojno delujejo s standardnim doksorubicinijevim kloridom. **Neželeni učinki:** Levkopenija, anemija, nevtropenija in trombocitopenija. Lahko se pojavijo palmarno-plantarna eritrodizestezija, stomatitis, slabost, astenija, izpuščaj, bruhanje, alopecija, zaprtje, anoreksija, spremembe na sluznicah, driska, bolečine v trebuhu, zvišana telesna temperatura, perestezijek, bolečine, obarvanje kože, farinsgitis, suha koža, dispepsija in zaspanost. Redkeje se pojavijo periferni edemi, oralna kandidiaza, mrzlica, bolečije v prsih, gingivitis ter drugi. **Način in režim izdaje:** 1 viala s 10 ml razopine za intravensko infundiranje (2 mg/ml), 1 viala s 25 ml raztopine za intravensko infundiranje (2mg/ml), - samo na recept, uporaba samo v bolnišnicah. **Datum priprave besedila:** Februar 2004. Podrobnejše informacije so na voljo pri proizvajalcu.

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*Title page* should include a concise and informative title, followed by the full name(s) of the author(s); the institutional affiliation of each author; the name and address of the corresponding author (including telephone, fax and e-mail), and an abbreviated title. This should be followed by the *abstract page*, summarising in less than 200 words the reasons

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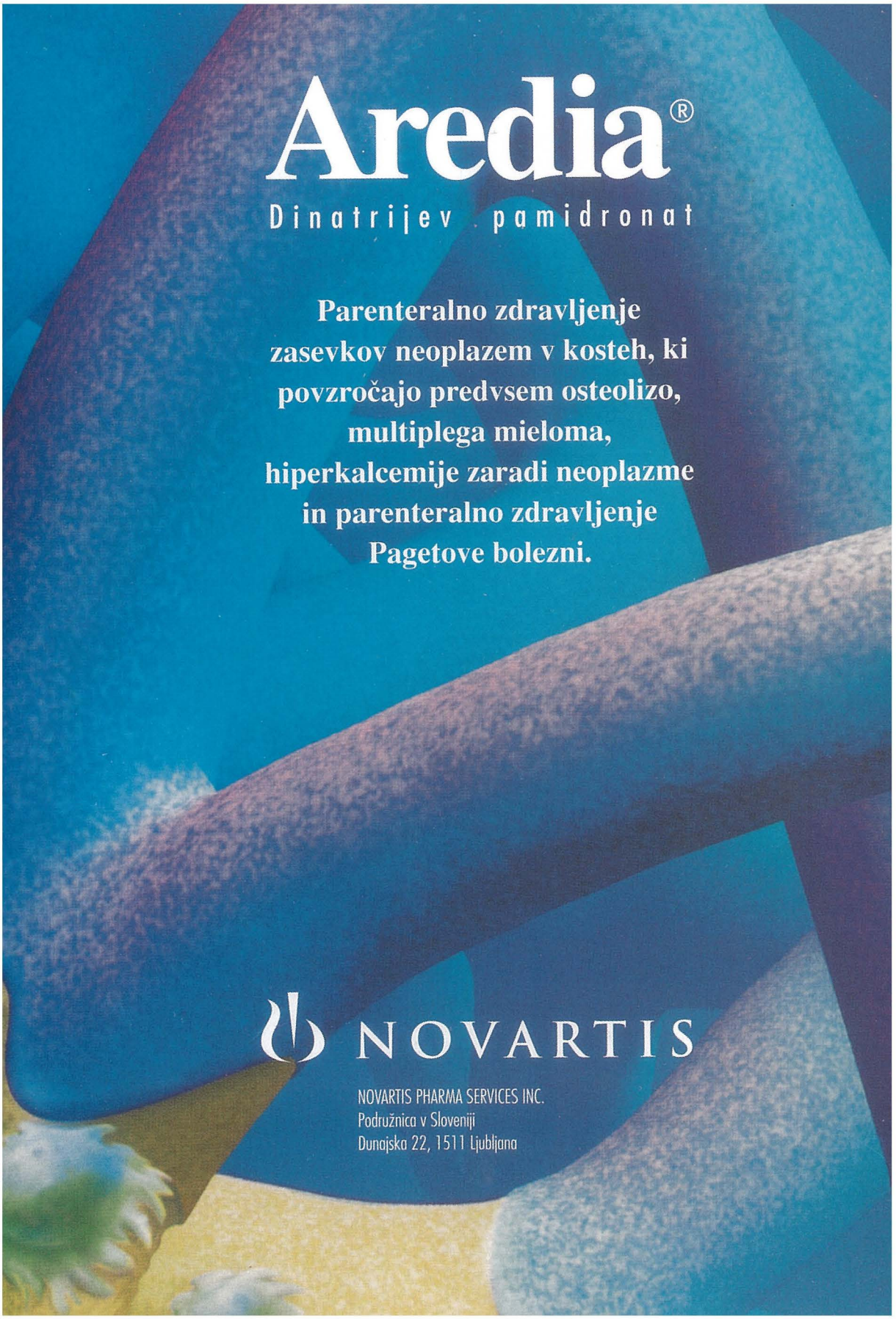
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