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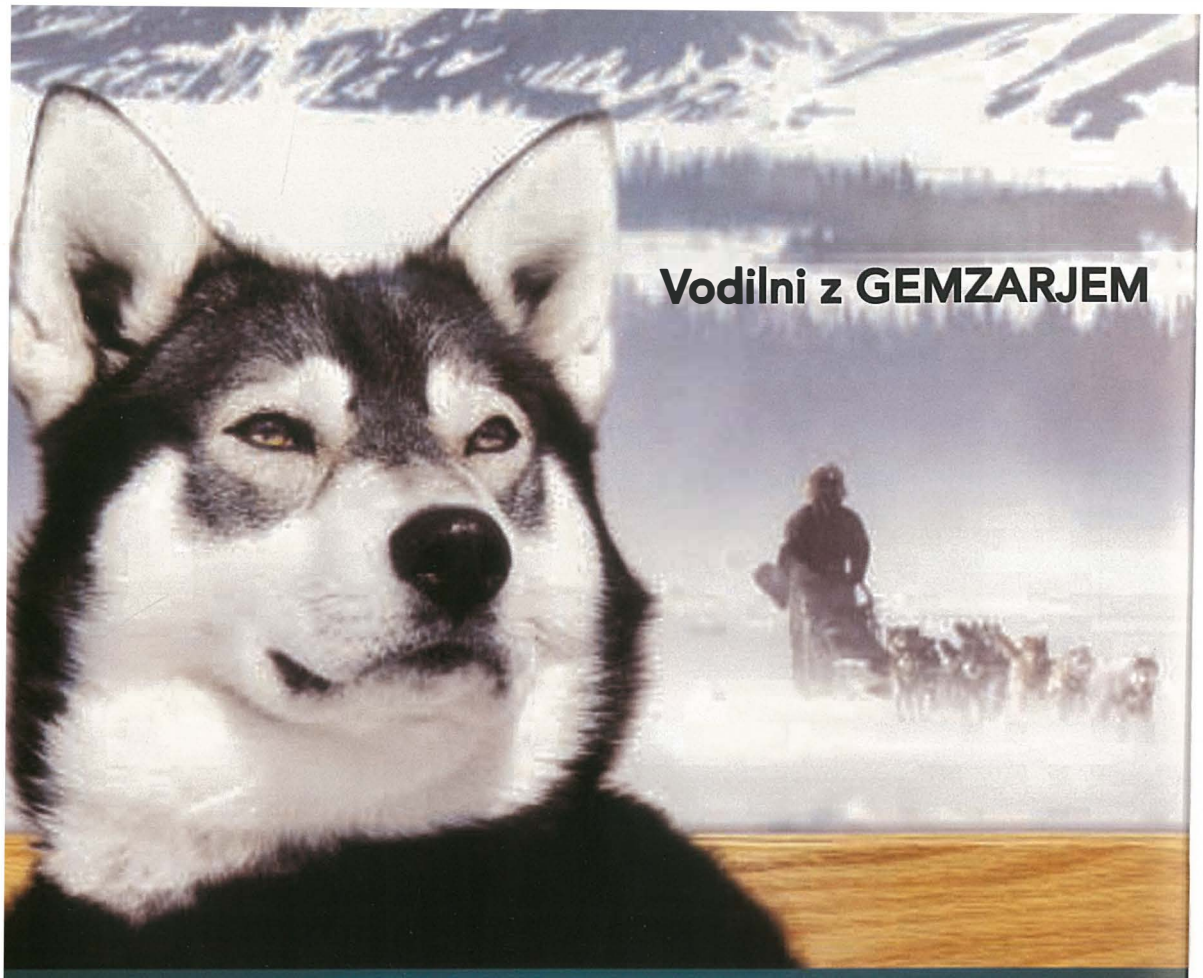

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Editorial office
***Radiology and Oncology***
*Institute of Oncology*
*Zaloška 2*
*SI-1000 Ljubljana*
*Slovenia*
*Phone: +386 1 5879 369*
*Phone/Fax: +386 1 5879 434*
*E-mail: gsersa@onko-i.si*

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*case report*

# Chronic nonischemic ileo-ileo-colic intussusception

**Goran Roić[1], Zvonimir Vrtar[2], Vesna Posarić[1], Igor Borić[1], Irenej Cigit[2]**

*[1]Department of Pediatric Radiology, [2]Department of Pediatric Surgery, Children's Hospital Zagreb, Zagreb, Croatia*

***Background.*** *Chronic intussusception is a prolapse of a portion of the bowel into the lumen of an immediately adjacent segment of the bowel; it lasts for 14 days or more. The aim of the article is to present a rare cause of nonacute abdominal pain.*

***Case report.*** *We report about 14-year-old girl who presented with a one-month history of intermittent cramping lower abdominal pain and change in bowel behavior. Plain abdominal x-ray, ultrasonography and CT were performed. Laparatomy revealed an ileo-ileo-colic intususscception (70 cm long); invaginated Meckel's diverticulum was a prevailing anomaly.*

***Conclusions.*** *Atypical clinical presentation of chronic intussusception often results in delayed or inadequate management of such cases because of the lack of suspicion of a correct diagnosis. Preoperative diagnosis of invagination was based on ultrasonography and computed tomography (CT) which proved again as the most effective and useful preoperative diagnostic method. Surgical intervention is always needed in adults and older children because of high incidence of underlying lesions in them.*

*Keywords: ileal diseases; intussusception; Meckel's diverticulum*

## Introduction

Intussusception (invagination) is a prolapse of a portion of the bowel into the lumen of an immediately adjacent segment of the bowel. The acute type does not present as great a diagnostic problem as does the chronic intussusception. The chronic intussusception is defined as intussusception lasting for 14 days or more.[1]

Adult intussusception is the cause of 1-5% of all bowel obstructions.[2] A vast majority (95%) of intussusceptions occurs in children, whereas only 5% occur in adults.[3]

In adults, 80%–90% of cases have a demonstrable cause. Approximately 65% are due to a neoplasm, whereas nonneoplastic causes compose the remaining 15%–25% of cases with a known cause and include adhesions and postoperative complications, Meckel's diverticulum, lymphoid hyperplasia and adenitis, trauma, celiac disease, duplications, and Henoch-Schönlein purpura.[4] Treatment always requires surgical excision.[5]

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Correspondence to: Goran Roić, M.D., Department of Pediatric Radiology, Department of Pediatric Surgery, Children,s Hospital Zagreb, Klaićeva 16, 10 000 Zagreb, Croatia; Phone: +385 1 4600231; Fax: +385 1 4600228; E-mail: goran.roic@zg.htnet.hr

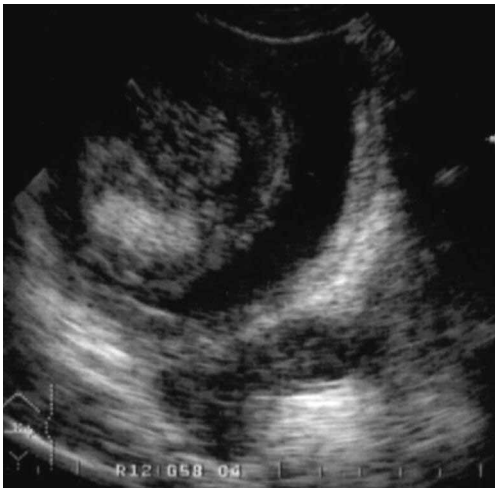

**Figure 1a.** Intussusception. Transverse sonogram through the lower abdomen demonstrates a rounded mass; peritoneal fluid is trapped between the serosal layers.

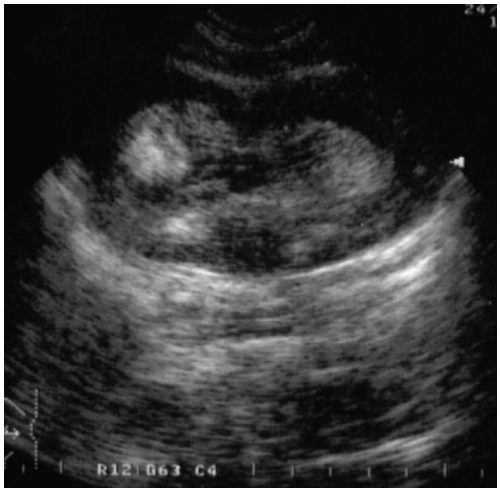

**Figure 1b.** Intussusception. In the longitudinal plane, the alternating hypoechoic and echogenic layers are called »sandwich« or »pseudokidney sign«.

## Case report

A 14-year-old girl presented with a one-month history of intermittent cramping lower abdominal pain and change in bowel behavior. Due to menstrual problems, the patient was initially treated as dysmenorrhea.

Abdominal ultrasonography revealed a soft-tissue mass with hypoechoic outer layer and central echogenic area; the peristalsis through invaginated ileum was active (Figure 1a). The characteristic US findings in a longitudinal plane were alternating hypoechoic and echogenic layers called the »sandwich« or »pseudokidney« sign (Figure 2b). Plain abdominal x-ray showed slightly dilated loops of the small bowel without air-fluid levels.

CT of the abdomen showed concentric rings (»*target*« sign) with the thickening of the affected bowel and intraluminal areas of fat attenuation due to mesentery and Meckel's diverticulum drawn into the intussusception (Figures 2a, 2b).

Laparatomy revealed an ileo-ileo-colic intususception (70 cm long); the prevailing anomaly was invaginated Meckel's diverticulum.

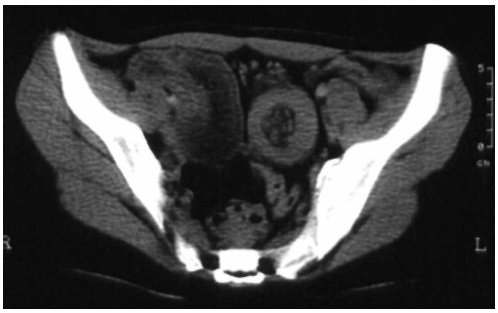

**Figure 2a.** Intussusception. CT scan shows a target sign in the region of the terminal ileum.

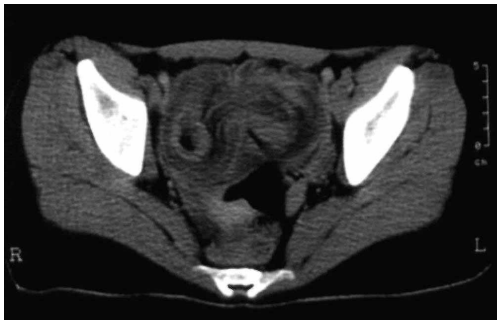

**Figure 2b.** Intussusception. CT scan obtained caudad to Figure 2A shows the presence of fat in the center of ileal intraluminal mass specific for inverted Meckel's diverticulum.

## Discussion

The classical presentation of intussusception consisting of pathognomonic triad of severe abdominal pain, bloody stool, and a palpable abdominal mass leads to the correct diagnosis in the majority of the patients. Intussusception can also be present in a subacute or chronic form with a long history of less severe symptoms.[1,6] This form of »*nonischemic*« intussusception is a distinct entity with atypical clinical presentation and often results in delayed diagnosis due to low index of suspicion.[6]

If one considers the possibility, chronic intussusception can be readily diagnosed by sonography; the CT appearances are pathognomonic.[7-9] Ultrasonography of transverse sections shows a mass with a swirled appearance of sonolucent and hyperechoic bowel wall of the loop-within-a-loop. The characteristic US findings in a plane transverse to intussusception are a sandwichlike or pseudokidney appearance of the intussuscipiens and the intussusceptum with a hypoechoic ring surrounding an echogenic center; it appears as if multiple layers would build the walls of the intussuscepted bowel loops.

Typical CT findings of intussusception are thickening of the affected bowel segment, areas of fat attenuation within the abnormal bowel loop, concentric rings (»*target*« sign), and an intraluminal soft-tissue mass at the leading end of the intussusceptum.[10,11] The »*target*« appearance is not specific for intussusception, and it may also be seen in neutropenic colitis and cystic fibrosis.[12] With intussusception, the mesentery invaginates the bowel and is trapped between the overlying layers of the bowel in the intussusceptum and intussuscipiens. In our case, CT and ultrasonography findings were typical.

Intussusception in adults must be managed by surgery, and intestinal resection is the procedure of choice.[13] The laparoscopic approach offers both a diagnostic and therapeutic option. Laparoscopy may be used as the final diagnostic or/and therapeutic tool for intussusception in adults.[2]

Chronic intestinal invagination is a rare cause of nonacute adult abdominal pain and Meckel's divertculum is a rare, though prevailing cause of intestinal invagination. Atypical clinical presentation of chronic intussusception often results in delayed or inadequate management of such cases because of the lack of suspicion of a correct diagnosis. Preoperative diagnosis of invagination was based on ultrasonography and computed tomography which proved again as the most effective and useful preoperative diagnostic methods. Surgical intervention is always needed in adults and older children because of high incidence of underlying lesions in them.

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Radiol Oncol 2005; 39(2): 95-9.

*case report*

# Osteosarcoma of the maxilla

**Bige Sayin, Nilgün Yildirim, Murat Vural, Doğan Dede**

*Department of Radiology, Ankara Numune State Hospital, Ankara, Turkey*

***Background.*** *Maxillofacial sarcomas are rare tumours and osteosarcoma of the jaws is an exceptionally rare entity. Unlike osteosarcoma of the long bones, maxillofacial osteosarcomas are reported to occur in the third or fourth decades.*

***Case report.*** *We report an 18-year-old female patient with the histopathologic diagnosis of osteoblastic osteosarcoma of the maxillary bone on the basis of computerized tomographic findings. Following the initial surgery and the adjuvant chemo-radiotherapy, a massive local recurrence developed in the facial region of the patient within two years.*

***Conclusions.*** *The radiographic evaluation of the osteosarcoma of the maxilla is important in the diagnosis and obtaining a complete surgical therapy. CT examination of this region after plain radiography plays a major role at the diagnosis.*

*Key words: maxillary neoplasms – radiography; osteosarcoma*

## Introduction

Osteosarcoma is the most common primary malignancy of bone although only 6% to 10% of osteosarcomas occur in the craniofacial region.[1] Within the craniofacial region the mandible is usually reported as the most common site of the involvement, followed by the maxilla and skull.[1,2] The average age at the onset of osteosarcoma of the maxillofacial region is about one or two decades later than that of osteosarcomas of other regions and the highest occurrence is found in the third to fourth decade of life.

The patient we present is much younger than those in the literature.

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Correspondence to: Bige Sayin MD, 96.sokak Yazikiri Sitesi B-2 Blok No:12, 06530 Ümitköy /Ankara, Turkey; Phone: +90 312 235 23 85; Fax: +90 312 363 22 89; E-mail: tamsay@hotmail.com

## Case report

An 18-year-old female patient was admitted to our hospital in September 2000 with the complaint of a painless swelling of her right cheek which was gradually enlarging for over two months. She also reported excessive tears in her right eye and loss of teeth on the right maxilla. By the physical examination, a 4 × 7 centimetre, hard, non-tender mass involving the right half of the maxillary region was found. No cervical lymphadenopathy was detected following the bilateral palpation

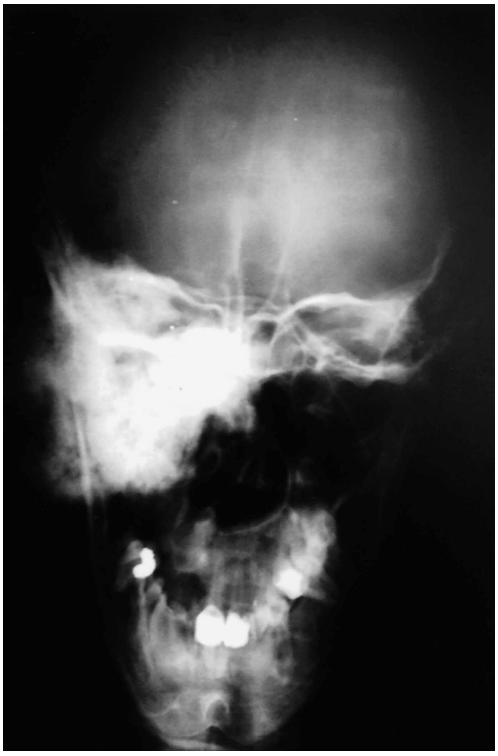

**Figure 1.** On Townes view plain film densely calcified and ossified mass can be appreciated.

of the neck. Her systemic examination did not reveal abnormal clinical findings. Chest X-ray, blood tests and abdominal ultrasonography were normal. A whole-body bone scan showed the increased activity in the right maxillary location. On the computerized tomography it was seen that the tumour exhibited the invasion into the upper palatinum and infero-lateral wall of the maxillary sinus, and caused a development of a centimetre defect in the base of the orbital cavity, however, there was no descent of the orbital structures. Although the tumour was in close relation to the medial wall of the maxillary sinus, this region appeared to be tumour-free. A punch biopsy of the lesion revealed the diagnosis of osteoblastic osteosarcoma of the maxilla.

After the evaluation, a surgical exploration was performed and the patient underwent a wide excision of the tumour with hemimaxillectomy of the right side. The histopathologic examination of the specimen confirmed the diagnosis of the punch biopsy of osteoblastic osteosarcoma and the margins of the surgical resection were negative for the tumour. The nearest margin of the resection to tumour was three millimetres away. The patient received a total of 57 Gy adjuvant irradiation therapy with $^{60}$Co teletherapy equipment. The combination chemotherapy (adriamicine 500 mg/m$^2$ and metotrexate 50 mg/m$^2$) was given in six cycles in an adjuvant setting.

In December 2001, she was free of symptoms and both the control X-ray and CT did not detect any recurrent tumour in the related region.

In June 2002, she was again admitted to our hospital with the complaint of a painful swelling in the operated area, difficulty in oral feeding and chemosis. Upon a clinical examination, a massive recurrent lesion at the operated site was noted. The plain radiography demonstrated a densely ossified mass in the right hemifacial region (Figure 1).

On CT scan examination, a 6 × 9 × 15 cm, mixed density, complex mass was seen at the primary site and also invaded the upper, lateral and inferior wall of the right orbita, the zygomatic bone, the infratemporal fossa, the masticatory muscles, and extended to ethmoid air spaces and narrowed the airway passage. The inferior border of the right ramus was disrupted and the right bulbus oculi was pushed anteriorly by the tumour. The right masseter muscle was seemed to be thickened and heterogeneous with respect to the contra lateral side. The right parapharengeal fat tissue and lateral recessus was obliterated and the right sided narrowing of the nasopharyngeal airway passage was noted. The mass had dense amorphous ossifications and showed the heterogeneous uptake of contrast material (Figure 2). We also constructed three-dimensional (3D) images so as to define the lesion more precisely (Figure 3).

The patient was evaluated for the possible

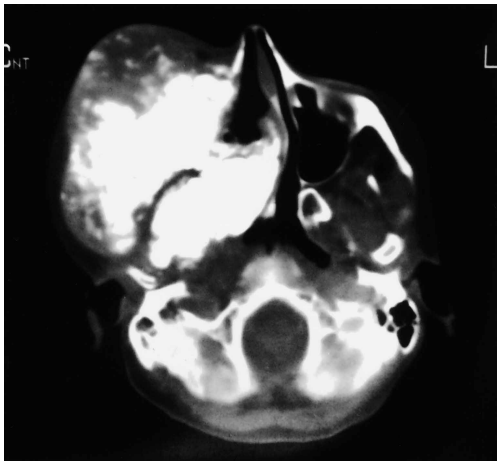

**Figure 2.** Axial computed tomography image. Mass composed of calcification and ossification.

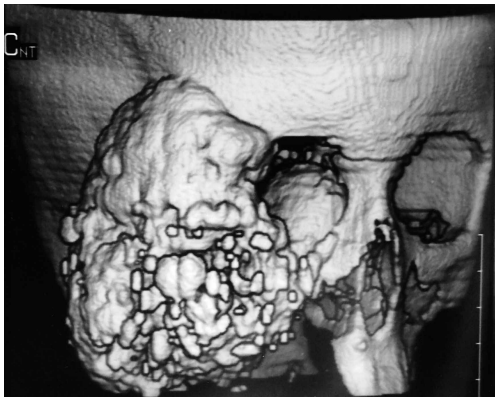

**Figure 3.** Three dimensional reconstructed image of the mass.

metastasis and was negative. Because of locally advanced and in-operable disease, a course of palliative external radiation therapy was administered with $^{60}$Co teletherapy equipment. Following a total dose of 20 Gy, there was an improvement in her symptoms but no regression of the lesion was noted.

## Discussion

Osteosarcoma is the most common primary malignancy of bone, although only 6% to 10% of osteosarcomas occur in the craniofacial region.[1] Osteosarcoma of the craniofacial region is a relatively rare disease.[2,3] The mandible is usually reported as the most common site of involvement although there are some reports that mandibulary and maxillary osteosarcomas have been seen in the equal frequency followed by the skull.[1,4,5] When compared with other locations, craniofacial osteosarcomas are less aggressive, occur in a more elderly population and prefer local invasion rather than distant metastases. The average age at the onset of osteosarcoma of the maxillofacial region is found in the third to fourth decade of life.[6] While a slight male predominance is reported by some authors,[1,4,7] some others propose it is more frequent in women.[5] There are also reports with equal gender distribution.[3] The histologic types are chondroblastic (41%), osteoblastic (33%) and fibroblastic (26%).[2]

The major risk factors for the development of osteosarcoma of the jaws are similar to those for osteosarcoma of the long bones, i.e., previous irradiation of facial region, Paget's disease and fibrous dysplasia. Other bone abnormalities, such as multiple osteochondromatosis, chronic osteomyelitis, myositis ossificans and trauma have also been proposed as risk factors.[3,7] Our patient had no known aetiology of osteosarcoma.

On plain radiographs, findings in osteosarcoma of the jaws are non-specific and these tumours have variable presentations, with the spectrum ranging from osteolytic through mixed osteolytic-osteoblastic to predominatly osteoblastic.[8] It may have a completely radio lucent appearance, but it is often presented as a poorly-defined mixed radio lucent-radiopaque lesion.[7,8] Plain radiography must be followed by the CT examination as the bone erosion, soft tissue infiltration and neoplastic tissue ossification can be showed superiorly.

CT has come to play a large role as osseous changes in the jaws, distinguishing the lesion from surrounding or superimposed structures, anatomy of the tumour and the degree

of ossification can be precisely evaluated. The CT appearance of our case has been reported as being a mass of mixed radiopacity with a predominant soft tissue component, central calcification/ossification, and the aggressive destruction of the structures involved. Three radiographic presentations of osteosarcoma of the jaw are identified.[5] The first is radiolucent, characterized by a total absence of bone formation within the tumour. In this type, the conventional radiology reveals a non-specific destruction of bone indistinguishable from the bone erosion caused by carcinoma. The second has a mottled appearance with small areas of amorphous ossification separated by non-ossified tumour tissue. In this type, the mottled ossification can be better or exclusively visualized by CT. The third, with lamellar ossification, is typically characterized by bony plates irradiating from a focus like a sunburst. In most cases, this type is visible with the conventional radiography; however CT separates fine lamellae from adjacent structures and makes the diagnosis easier in the less typical cases.

The presented patient's radiographic appearance was in accordance with the third type identified above. This trabecular sunburst pattern, resulting from bony spicules extending from cortex into the soft tissue, has been reported in 25% to 32% of jaw osteosarcomas.[1] The sunburst pattern of periosteal bone formation in relation to a large soft tissue destructive mass, is considered characteristic of the osteosarcoma but it is non-specific.[9,10]

It is clear that the complete resection of the primary lesion is ideal for the treatment of osteosarcoma. A total maxillectomy is recommended at the time of the initial diagnosis of osteosarcoma as was in the patient presented.[6] The surgical margin appears important in terms of prognosis. Patients with clear surgical margins of greater than 5 mm demonstrate a better survival, fewer local recurrences, and less metastatic disease than those with margins of less than 5 mm.[7] Although such a wide rim of normal tissue is impractical in the jaws, clear margins play a role in eradication of disease and limitation of intramedullary extension.[6,7] In our patient, clear surgical margins were obtained at the initial therapy, but one margin was close to the tumour as previously described. Osteosarcomas arising from the maxilla cannot always be resected with sufficiently safe margins as in the presented patient. This is reflected by a relatively high local recurrence rate in some series.[6] These tumours have usually a tendency to spread with local invasion.[2,3,5] Our patient had no detectable metastases in spite of the advanced, recurrent mass.

Adjuvant treatments are considered effective for preventing recurrence only when the primary lesion has been removed completely, although chemotherapy can be used for the control of occult distant metastases, as in osteosarcomas of extremities.[6,11] From available data, it appears that the introduction of chemotherapy for the treatment of craniofacial osteosarcomas did not lead to the improvement in the survival statistics as it did with osteosarcomas of extremities.[2] Some studies have shown radiation to be ineffective in the treatment of craniofacial osteosarcomas.[2,11] Delgado *et al* expressed that when surgical margins are not free of disease, the use of radiation does not improve the outcome.[9] On the other hand, the ability of these tumours to spread through bone marrow dictates the establishment of surgical margins extending beyond the clinical and radiological presentation of the disease.[2] Therefore, early diagnosis and radical surgery with wide surgical margins should be the most important part of primary treatment, as the residual tumour may show the aggressive local invasion of the tissues of the head and neck, as in our patient.[1,4,12] High histological grade and incomplete resection or local recurrence support a poor prognosis.[2]

In our view the presented case is interest-

ing in terms of relatively early age onset of the tumour. Secondly, although the patient was free of symptoms and local recurrence with X-ray and CT 1.5 years after the therapy, she presented with a local, massive recurrence in 6 months time. That's why we believe that the careful follow-up of these patients for local recurrence is mandatory.

In conclusion, osteosarcoma of the maxilla has an aggressive biological behaviour even in the case of applying adjuvant therapies. Therefore, early diagnosis and radical surgery with wide surgical margins are the keys to a good outcome. CT has an important role in the early diagnosis and the evaluation of its extent for the surgical planning.

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# Multislice computed tomography of pulmonary embolism: spectrum of findings

**Šerif Bešlić, Faruk Dalagija, Vesna Đurović**

*Institute of Radiology, Clinical Center, University of Sarajevo, Bosnia and Herzegovina*

***Background.*** *The purpose of this study is to analyse the contribution of multislice computed tomography (MSCT) as a diagnostic method in the diagnosis of pulmonary embolism (PE) and spectrum of findings in our material.*

***Methods.*** *During the period of one and a half year, we found PE in 25 patients (15 males and 10 females). The average age of the patients was 54.4 years (25 - 74). The examination was performed by »Somatom Volume Zoom« Siemens CT machine with four row detectors, with retrospective ECG gating, collimation 4 x 2.5 mm and reconstructed section with 0.8 mm. Contrast medium (130 ml) and 10 ml of saline was applied, administered with a flow rate of 3.5 ml/s and with time delay of 22 seconds.*

***Results.*** *During the examination, we found embolism of the main branches of pulmonary artery in 14 (56%) patients, at the right branch in 10 (40%), at the left one in 4 (16%), and bilateral pulmonary embolism in 11 (44%) patients. Subsegmental pulmonary emboli were noticed in 8 (32%) patients. Pulmonary infarct was found in 12 (48%) patients, and was followed up with ipsilateral pulmonary artery dilatation in 11 (44%) cases, redistribution of the circulation and pulmonary artery branches dilatation in infarct zone in 9 (36%) cases, contrast enhanced consolidation of pulmonary parenchyma in 10 (40%), rag zones of ground glass attenuation in 15 (60%), haemorrhage in 21 (84%), striped and reticular pulmonary drawing in 11 (44%), and mosaic olighemy in 3 (12%)cases. Thrombi were rare, found only in the R/L atrium in 2 (8%)cases, pericardial haemorrhage in 1 (4%), mediastinal lymph nodes in 1(4%) case, sudden cut off of peripheral branch leading to infarct apex in 1 (4%), and haemoptysis in 1 (4%) case. In addition to deep vein thrombosis, heart failure was found as aetiology factor in 7 (28%) and malignancy in 3 (12%) cases.*

***Conclusions.*** *MSCT is an excellent non-invasive method for visualization of thrombus in the pulmonary artery. In our study, we have more often found embolism of the right branch of pulmonary artery, and pleural effusion, infarct contrast enhanced consolidation of pulmonary parenchyma, ground glass attenuation zone, ipsilateral pulmonary artery dilatation, circulation redistribution with pulmonary artery branches dilatation nearby infarct zone. This diversity of findings cannot be noticed by any other method, with the possibility of making alternative diagnosis, which has led MSCT in the foreground when pulmonary embolism diagnostics is at stake.*

*Key words: pulmonary embolism – diagnosis; X-ray computed - methods*

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Correspondence to: Prof. Šerif Bešlić, MD, PhD, Institute of Radiology, Clinical Center University of Sarajevo, Bolnička 25, Bosnia and Herzegovina; Fax +387 33 444 553; E-mail: sbeslic@bih.net.ba

## Introduction

Pulmonary embolism (PE) is an obstruction of any pulmonary artery branch by clot which could be brought from varicose veins in legs, tendency to blood clotting (because of existing malignancy, after prostate gland operation, in gynaecologic diseases, in heart failure and arrhythmias, etc).[1]

It is a frequent disease in risk hospitalized patients. An embolus tears off from the deep leg veins, divides in fragments in the right heart, from where it is rinsed in the lung, where the emboli of different size splash the lung.[2,3]

PE can cause immediate death or the patient is breathless, has chest pain, his face and body become blue, neck veins swell up, his breathing is low and rapid, has palpitations, coughs and coughs up white pus mixed with blood (sputum).[1,4,5]

Thrombosis can cause pain and swelling of the leg, red colouring, warmth and tension could occur, but clinical evaluation is mostly unreliable and can cause serious mistakes, and most of people with deep vein thrombosis (DVT) have no any symptoms.[6]

Sudden dyspnoea without changes on plain chest radiography could be one of the manifestations.[1]

PE prevalence found on autopsy is 15-26%, and it is greater than the one found in hospitalized patients.

Owing to organs hypoxia, especially brain, 1/6 patients lose consciousness (syncope). The embolism attacks can repeat several times, so high blood pressure in pulmonary circulation appears (pulmonary hypertension), with bad prognosis and most patients die after 5 years.[1]

Due to the above, all cases of pulmonary embolism must be taken seriously.

Vein thrombosis is a frequent disease, with an incidence of 1-2 persons/ per 1000/ per year. Approximately 3000 persons get vein thrombosis in Slovenia every year. Non-treated thrombosis of popliteal and/or femoral vein will lead to PE in approximately 50% patients, of whom 10% patients die of pulmonary embolism.[3]

PE is the third most frequent cause of death in US with almost 50 000 deaths every year, with annual frequency of 300 000 to 600 000 (on average about 500 000) accidents. Many of PE events passed undiscovered because clinical indications and PE symptoms are non-specific. A fast and accurate diagnosis can save 100 000 lives every year. An accurate diagnosis is therefore a great challenge.[7,8]

The mortality caused by PE is high, partly because of relapse. The mortality in non-treated patients is 30%, and in the patients with anticoagulation therapy, 10%. Repeated PE appears in 0.4-0.5% patients with acute PE. Access to the treatment of patients with PE has to be fast and interdisciplinary. Clinical suspicion of PE has to be confirmed or denied by diagnostic methods, preferably with non-invasive, precise and easily accessible methods.

It is important to exclude PE, because of the haemorrhage which can occur during anticoagulant therapy. The haemorrhage risk increases by 2% every day during the anticoagulant therapy.[3]

It is known that 20% of DVT of the calf will have propagation proximately, but sometimes thrombosis staying in the calf should not lead to embolism. Should we wait and look at the insurance policy in situation like that, or should we start with diagnostic imaging of the affected extremity?

Differential diagnosis of PE is very wide and includes many conditions, from life-endangered diseases to anxiety.[3]

There is no any warning signs, symptoms or laboratory tests, which suggest PE.[2]

In 2/3 of patients with the suspicion of PE, other diseases were diagnosed.[9]

PE diagnosis is clinical, laboratory (simple test in bed D-Dimmer essay), ECG, plain ra-

diography of chest (RTG), gas analysis in arterial blood, lung scintigraphy with technetium 99, transthoracic or transesophageal US of the heart and veins, angiography of pulmonary artery, which until recently, was the most reliable diagnostic method, and sometimes the therapy method as well.[1,3,8]

The chest angiographies were normal in 10% cases, and most of its abnormalities were non-specific. Non-specific shade, pleural effusion, atelectasis or elevation of hemidiaphragm, and vascular alternation, i.e. focal ipsilateral pulmonary artery enhancement (Fleschner's sign or so called the ankle sign) could be found. The pulmonary artery branch embolism can be seen as the lung infarct, a wedge shaped shadow with its top oriented centrally and base peripherally. Usually, the right interlobar pulmonary artery is affected. Because of the clot presence, focal olighemy may occur, but is very rare and results from the vascular obstruction (Westermarks sign).

Lung infarct can develop immediately or in 2-3 days after embolism, usually peripherally or in the lower lung zones, frequently associated with small pleural effusion. At the beginning, it is ill-defined, but with time, it becomes sharp, the so-called Hampton's hump in the peripherally wedge-shaped shade with curvy peak headed to the hilus. The infarct healing, or the so-called »melting«, demonstrates as keeping its shape and, with time, reducing in size. Pneumonia and oedema usually »disappear – fade away« gradually.[1,2,10]

In big branch embolism, the whole lobe of the lung can »fall out« of function, so, the pulmonary-blood vessel bed or pulmonary tissue cannot be seen with chest X-ray.[1]

The lung scintigraphy with technetium 99 (V/Q) has been preferred for a long time as screening test for detecting clinically significant pulmonary embolism was. It shows »fall out« of lobe of a lung or part of it. A segmental or greater perfusion defect is present with normal ventilation in that zone (V/Q discord) indicates a high possibility of pulmonary embolism.[1,10]

V/Q scanning findings are indirect indicators of a clot, not visualized directly, so it has a high sensitivity, but low method specificity, especially in the patients with other lung diseases. Because of that, the interpretation of perfusion scintigraphy results is difficult.[2,3,10]

PIOPED study results show that only 41% PE can be confirmed with this method, also the accordance in the interpretation of findings among different examiners is poor (30%).[2,3]

Until recently, the most reliable method has been diagnostic pulmonary angiography, sometimes it is therapeutical as well (local thrombolysis, fragmentation, embolectomy).[1,11]

Angiography has been considered the most precise examination, but it is invasive (morbidity 6%, mortality 0.5%), and it is not available everywhere.[3]

The pulmonary angiography findings were considered a gold standard; however, they show 25% false negative results for small subsegmental emboli, and the accordance in interpretation of findings among different examiners is poor (<30%). This investigation is rarely performed in clinical practice.[2]

The technology revolution in diagnostic approach to suspicious pulmonary embolism has been happening in the last 10 years by introducing spiral computed tomography (SCT).[2,12]

In 1978, Sinner was the first who described PE diagnosed with CT. In 1980, Godwin and co-operators showed directly endovascular emboli. In 1992, the first comparative analysis of SCT and PA was made, and in the next years, Teigen and co-operators used electron beam CT (EBCT).[7]

In the last 10 years, CT reached a high accuracy in the pulmonary embolism evaluation.[7]

Spiral or electron beam CT findings have revolutionized the pulmonary embolism diag-

nosis and made possible the direct visualization of a clot in the central pulmonary artery.[2] CT provides, with high sensitivity and specificity (>90%), a direct visualization of obstructing emboli together with their vascular and pleuroparenchymal sequels (cardio pulmonary status). An insufficient contrast bolus, hilar limphadenopathy and hilar calcifications, respiration artefacts can cause diagnostic problems, e.g. subsegmental emboli can be overlooked, oblique arteries may demand oblique reconstructions for better visualization, etc. It can be combined with the pelvis and extremities scanning for analyzing sources of thromboembolism (CT flebography). The consequences of a negative CT angiogram are favourable, with DVT or PE in 0.5%, and fatal embolism occurs in 0 to 0.7% cases.[2,13]

The comparisons of SCT pulmonary angiographies (SCTPA) with V/Q scans proved higher punctuality of SCTPA than V/Q; SCT was correct in 92%. CT, in comparison with V/Q scan, shows a reliability of 90% to 54%, respectively. SCT has a higher sensitivity (77-81%) than V/Q (41%), and a similar proportion has been observed in specificity. In total, SCT is more punctuate than V/Q. Various studies in several European centres proved a higher specificity of CT than that of V/Q, and better accordance in the interpretation of CT findings between different examiners.

In that way, SCT has put into question the role of ventilation-perfusion scintighraphy and has thrown suspicion on pulmonary angiographies as a gold standard.[8]

Moreover, CT allows the visualization of other changes in the thorax, which may be the cause of patient's condition and symptoms. In 65% of patients, various changes are discovered by CT, upon which an alternative diagnosis was made in the patients suspicious for PE. Neither scintigraphy nor angiography has these possibilities.

The introduction of the multislice CT (MSCT) has brought significant advantages, such as the possibility to examine dyspnoeic patient in an emergency situation in a few seconds, covering broad volumes with a low collimation, the possibility of a precise analysis of peripheral pulmonary arteries and of a detailed whole lung exploration. The combined CT venography and pulmonary CT angiography, using one injection of contrast medium, reduces the examination time and excludes additional examinations. Finally, by the evaluation of the right heart, the load and distension of the right-side cavities can be estimated. In that way, the multislice CT exposed one of its most important applications.[6,12]

Risky and symptomatic patients are often exposed to ascendant venography, which is considered as a gold standard fort he detection of small deep thrombi in the vein system, but this technique is invasive, so radiologists are looking for a replacement.

Ultrasound (US) B mod and Colour Doppler are fast and reliable methods, but need experienced examiners. MRI is also a promising method, but so far, it has not been used widely in urgent situations and in seriously ill patients, mostly because of long-term examination, monitoring problems, high costs and limited availability.[7,11]

The time of flight and phase contrast imaging proved to be highly accurate in some research studies on imaging of the blood circulation in the proximal vein system, and also provides a direct visualization of a clot in the pulmonary artery or extremities veins. In pregnant women and the patients with plaster cast, the acute clot can be differentiated from the chronic clot and from imitating pathology. MRI is an expensive screening method. It has some deficiencies, e.g. every patient cannot fit in the machine (overweight), and for the time being, the clot visualization below the knee is not satisfactory.[6]

The treatment of PE presumes usage of anticoagulants and fibrinolitics.[2]

The therapy of blood clotting lasts usually

6-12 months and is accompanied by hemorrhagic complications in 2-15% cases; a thrombotic vein can be surgically separated from the thrombosis place, or a special device is inserted (IVC filter) in which the clots are kept not to go in the right heart, more exactly, in the pulmonary circulation.[1]

They are used when the contraindication for anticoagulation therapy is present. Pulmonary thromboendarterecotmy can be used in vitally endangered patients.[13]

The prognosis is good with adequate therapy. However, there is a high level of suspicion on fatal result (about 20%) in non-treated subjects. Hardly noticed subsegmental emboli present a problem. The consequences for non-treated subsegmental emboli are unknown, while the consequences of following up the negative pulmonary angiograms or SCTPA are favourable.[2]

The goal of this study is to analyze the contribution of MSCT in the detection of pulmonary artery embolism in our material, as well as to review the frequency of findings spectrum that follows it, and which can be diagnostically important.

## Methods

In the period of one year and a half, we found PA embolism in 25 patients (15 male and 10 female) during MSCT scanning. The youngest patient was 25 and the oldest one was 74. Average age of patients was 54.4 years.

After the native CT serial, which included the whole thorax and upper abdomen, the contrast serial was made in the area from the arcus of the aorta to 2 cm below the mouth of the lower pulmonary veins.

Scanning was performed on the »Somatom Volume Zoom« Siemens device, MSCT with 4 rows of detectors, with retrospective ECG-gating, thick layer of 3 x 2.5 mm and section width of 0.8 mm.

The contrast medium (CM) 130 ml and 10 ml of physiological solution were injected by automatic syringe in the cubital vein with a flow rate of 3.5 ml/s and with a delayed time, determined mostly empirically and ranging from 22 to 25 sec, depending on the cardiac status and patient's age.

The analysis of the following findings was made: embolism frequency and dilatation of central and segmental branches, frequency of pulmonary circulation redistribution, infarct, contrast enhanced consolidation of pulmonary parenchyma, zone opacification type ground glass, olighemy mosaic, septal bumps and reticular drawing, pleural reaction and pericardial effusion, the right heart dilatation, heart failure signs, frequency of clots in the heart, haemoptysis, appearing of enhanced mediastenal lymph nodes, and frequency of malignant process coincidence and pulmonary embolism.

## Results

During the examination we found pulmonary artery embolism in 25 (100%) patients. Among them, 15 (60%) were male and 10 (40%) female. The spectrum and frequency of CT findings in examined patients are shown in Table 1.

From the given chart, we can see that PE was more often followed by pleural effusion, which was found in 21 (84%) patients, zone opacification ground glass found in 15 (60%) patients, central pulmonary artery branches embolism in 14 (56%) patients, pulmonary infarct in 12 (48%) patients, bilateral PE, ipsilateral pulmonary artery enhancement, and striped and reticular pulmonary drawing in 11 (44%) patients, contrast enhanced pulmonary parenchyma consolidation and PE of the right branch of pulmonary artery in 10 (40%) patients. Other CT findings were rare, or harder to notice.

**Table1.** Patient data: spectrum of findings in pulmonary embolism

| Features | Number of patients |
|---|---|
| Bilateral PE | 11 (44%) |
| Central branches embolism | 14 (56%) |
| PE R.Branch | 10 (40%) |
| PE L.Branch | 4 (16%) |
| Subsegmental PE | 8 (32%) |
| Ipsilateral pulmonary artery enhancement | 11 (44%) |
| Dilation R.Branch | 8 (32%) |
| Dilation L.Branch | 3 (12%) |
| Circulation redistribution and branch dilation in infarct zone | 9 (36%) |
| Sudden failure of peripheral pulmonary artery leading to infarct apex | 1 (4%) |
| Infarct | 12 (48%) |
| Contrast enhanced pulmonary parenchyma | 10 (40%) |
| United Infarct and contrast enhanced consolidation pp | 6 (24%) |
| Rag zone of ground glass opacification | 15 (60%) |
| Olighemy mosaic | 3 (12%) |
| Striped and reticular pulmonary drawing | 11 (44%) |
| Effusion and adjacent pleura reaction | 21 (84%) |
| Presence of previous heart failure indications | 7 (28%) |
| Clot in R/L atrium | 2 (8%) |
| Malignance (1 Ca. Recti,2 Ca pulmo) | 3 (12%) |
| Haemoptysis | 1 (4%) |
| Pericardial effusion | 1 (4%) |
| Boundary lymph nodes in mediastinum | 1 (4%) |

## Discussion

Obstruction of any pulmonary artery branch, mostly with blood clot, is called pulmonary embolism.

The pulmonary embolism is the final result of thrombosis in the peripheral veins of lower extremities and is considered the third most frequent cause of death.

The risk factors are prolonged staying in bad, varices in lower extremities, trauma, recent surgical treatment, obesity, pregnancy, deficiency of antithrombin III, deficiency of S protein, increased blood clotting in the patients with malignant disease, migrant thrombophlebithis, deep vein thrombosis in pelvis, acute heart attack, serious heart impairment, central vein catheters, congestive heart disease, arrhythmias, atrial fibrillation, etc.[1,2,10,11,14]

Sudden death occurs most frequently when the obstruction happens at the bifurcation of the pulmonary artery. When the distant branches are occluded, the patient is breathless, becomes blue in the face and body, the veins of the neck are swollen, breathing is superficial and accelerated (>21/min), the blood flow rate through the lung is decreased, all organs suffer from ischemia, especially the brain, so, in 1/6 of patients, syncope develops. If the patient stays alive, acute pulmonary heart will develop, with strong chest pain bellow the sternum. The prognosis is dependent on the heart condition and quick intervention.

The embolus in the intermediate artery causes the deterioration of the patient's condition, chest pain, cough, blood-stained cough up, feeling of choking, tachypnea and superficial breathing.

Symptomatology can be divided in few

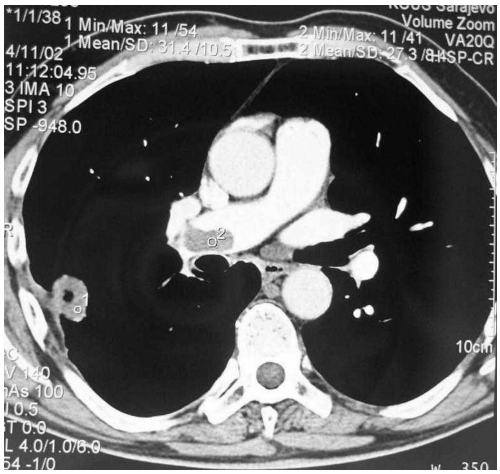


**Figure 1.** Pulmonary embolus in the right central branch.

phenomena, such as the pulmonary infarct syndrome (pleural pain or haemoptysis), isolated dyspnoea syndrome (dyspnoea in absence of pleural pain, haemoptysis or circulatory collapse) and circulatory collapse syndrome (losing consciousness or blood pressure <80mmHg) and can be met in 65%; 22% and 8% patients, separately.

The emboli in the central branches are most often and most easily detected (Figure 1).

In this study, it was found in 14(56%) cases; PE of the right branch in 10(40%), in the left branch in 4(16%), and bilateral PE in 11(%). The average age of the patients was 54.4 years. It was more frequent in men (60%) than in women (40%).

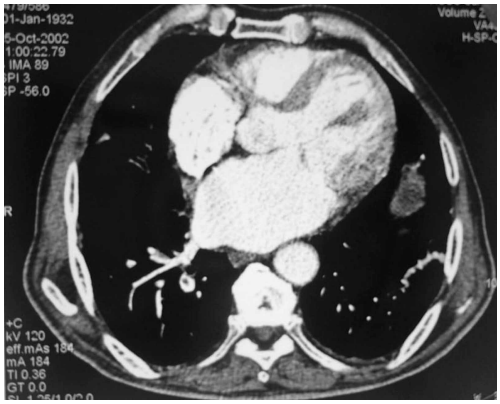

**Figure 2.** Pulmonary emboli of subsegmental artery.

As shown in Table 1, PE in the subsegmental artery were found in 8 (32%) examined patients (Figure 2).

PE divides in 3-11 parts, on average, when it comes in the heart. One or few fragments are big enough to be detected.[3]

One third of PE causes or contributes to the patient's death where clinical diagnosis of suspected PE is unreliable; so, over 70% of cases are not clinically suspected. These results have not changed for 3 decades in spite of the progresses in medicine and prophylaxis. Approximately 10% of the patients do not survive the initial stage of PE. PE is fatal if it is not treated in 30%, and this can be reduced to 2-10% if diagnostic and treatment with anticoagulants are quick enough. This therapy is accompanied with complications in 10-30%.

The estimation frequency of isolated subsegmenal PE is very significant because they can be indicator of a silent deep vein thrombosis (DVT), which potentially indicates harder embolic accidents. The detection of a small embolus can be relevant for a chronic pulmonary hypertension diagnosis in the patients with thromboembolism disease, and may represents a »tip of the iceberg«. This problem may not be solved for a long time.

The only solution to solve the problem of these small missed or potentially missed clots is to evaluate consequences of patients with negative SCT pulmonary angiographies (SCT-PA), in other terms, to determine the subsequent PE rate (negative predicting value).

Different authors cite different results for the main, lobar, segmental and subsegmental branches: sensitivity 88-91%, specify 81.5-86%, positive 75.81.5% and negative predicting value 91-94%.[20]

Some authors reported the sensitivity of 90%; specificity 94%, positive and negative predicting value 90 and 94%.[4]

According to certain authors, the sensitivity at segment level is 91-96% and specifity 78-100%, the subsegment sensitivity 63% and specificity 89% and, recently, the sensitivity

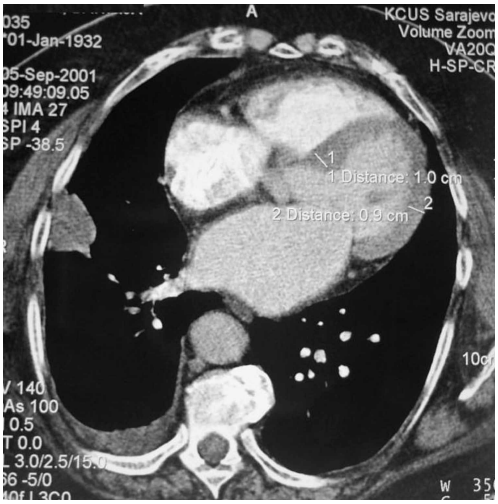


**Figure 3.** Pulmonary infarct (Humptons hump).

and specifity ranges of 88-96% and 94-100%, repsectively. In that way, CT is kept busy with angiographies on subsegmental level.

According to these authors, angiographies have some lower results at subsegmental level, so it cannot be used as a reference method for success evaluation.[3]

A one-mm breath hold collimation results with significant greater percentage of embolism detection in subsegmental pulmonary arteries, and greater harmony between different readers than using thicker cross sections. Using one-mm cross vs. opposite 3mm ones, the number of indefinite cases reduces to 70%.[21]

Also 54% subsegmental arteries are identified after using pulmonary window, and they are correctly visualised using mediastinal window.[18]

The prevalence of isolated subsegmental embolism, according to different studies, is between 5 and 30%. If satisfied, the subsegmental branches don't show during examination. The pulmonary diagnosis can be predicted in 5-30%. This is especially important in the patients with accompanying lung and heart diseases, in whom they may be warning signs for developing recurrent potentially mortal embolism.[3]

Only relatively specific PE finding is wedge shaped pulmonary consolidation, which most probably represents pulmonary infarct, although in PE patients, this finding is very rare and, according to some authors, varies between 10%, 25% and 62%.[3,13]

A similar image may appear in 5% of patients who have not PE (It is often seen in pneumonia, tumours, pulmonary fibrosis, haemorrhage, oedema).[3]

In this investigation, pulmonary infarct was found in 12 (48%) patients. We believe that it is more frequent than reported in literature and that the advance of diagnostic methods will contribute to a more frequent revealing (Figure 3).

Pulmonary infarcts can be any shape or size, like peripheral opacification, lobular or wedge-shaped image, irregular polyhedral, depending on the number and location of affected secondary pulmonary lobules with cut apex, when the lobules lay just right opposite embolus and they are divided adequately from bronchial collateral vessels.

The infarct can include central regions of low attenuation, which show the combination of opaque glass shade and reticulation below and that represent no infarct secondary pulmonary lobules, which in time of embolism cannot be per funded. Alternatively, they can be supplied from nonembolised pulmonary arteries, retrograde circulation from pulmonary veins, or from bronchial collateral vessels.

The contrast enhancement of lesion after the fourth injection of contrast medium is connected with pulmonary haemorrhage (76%), and non-enhanced lesion suites pulmonary infarct. However, a drop in enhancement in the collapsed lung is not a specific sign of pulmonary infarct, because it can be seen in some kinds of pneumonia.[7]

The contrast enhanced consolidation of pulmonary parenchyma was, in this investigation, found in 10 (40%) cases. In 6 (24%) cases it was related to the infarct (Figure 4). In

radiology literature, these two categories are not adequately distinguished.

The presence of vascular sign, associated with the vessel bump leading to shade apex, increases the possibility that the lesion represents infarct, but this sign is not frequent and therefore hard to recognize.

The enhancement of ipsilateral pulmonary artery in this investigation was found in 11 (44%) cases, 8 (32%) on the right and 3 (12%) on the left branch. Circulation redistribution and branch dilation in the infarct region are found in 9 (36%) cases, and a sudden break of the peripheral pulmonary artery leading to infarct apex only in 1 (4%) case. This sign is difficult to recognize and requires a meticulous analysis.[10,13,15]

The obstruction exceeding 30% of pulmonary circulation causes a sufficient increase in pulmonary vascular resistance to produce significant pulmonary hypertension which results in overloading the right ventricle (RV), which increases and dilates. The interventricular septum moves to the left, compressing the left ventricle (LV). It was found that small acute pulmonary embolism was related to short axis (RV/LV) under 1.1/1. In all serious acute PE cases, the relation was greater than 1.5/1. Straightening or left movement interventricular septum and contrast reflux in the vena cava inferior (VCI) can be seen, but it is more difficult to quantify. An acute dilation of RV can be a useful sign to evaluate physiology effect PE difficulty, because revealing vasoactive agents can increase pulmonary vascular resistance to a reflexive pulmonary vasoconstriction followed by mechanical obstruction with intravascular clots.[3]

Chemodynamic consequences are the reduction >50% vascular trough leads to pulmonary hypertension and failure right-site heart, and 1% ill patients with acute pulmonary embolism will become chronically ill.[2,15]

An earlier diagnosed heart failure as infarct source is often present, and in our study, it was found in 7 (28%) cases, of which the clot was found in left/right atrium in 2 (8%) cases. A malignant process as infarct source, found in 3 (12%) cases, was not significant in this small serial.

Accompanying effusions develop suddenly and usually are small and unilateral, reaching the maximum length in the first three days. These effusions are often hemorrhagic and connected with inflammatory response, following pulmonary necrosis. High effusion frequency was also confirmed in this investigation. It was found in 21 (84%) patients; in only one patient (4%), pericardial effusion was found. Incremental mediastinal lymph nodes were rare, too, only 1 (4%) case.

Pleural effusion, as it has been reported, is the most frequent in the group with pulmonary embolism, and segment consolidation which morphology easily can represent pulmonary infarct, until mosaic sample and enhanced mediastinal lymph nodes can meet rarely.

Except the mentioned parenchymal and pleural changes, pulmonary thromboembolism can result in haemorrhage without infarct, and on CT, the haemorrhage is viewed as a ground glass opacification, or as an air ways consolidation, not differing from pneumonia or oedema.[13]

Vascular occlusion of small arteries, which supply secondary pulmonary lobules, makes inhomogeneous pulmonary parenchyma attenuation on CT. This is called mosaic oligohemy. These limited regions of changed pulmonary parenchyma attenuation (mosaic sample) are a specific sign of perfusion obstacle and are helpful in diagnosing pulmonary embolism.[3,13]

Our investigation showed the existing ground glass opacification in 15 (60%) cases, and in 3 (12%), mosaic oligohemy. The detection of this sign takes a lot of patience.

When we talk about diagnostic approach, a relatively great number of indefinite investigations stand out, especially in the patients

with chronic pulmonary diseases or parenchyma abnormalities on chest radiography. Chest X-Ray (RTG) is mostly non-specific and normal only in 10%.[2,10]

Although CT is more sensitive for additional signs than RTG, the absence of abnormalities on CT does not exclude PE, because 29% of patients with PE had no pleuropulmonary abnormalities described on CT.[7]

The majority of late PE occurs in the first weeks after treating or excluding PE: 50% of PE have relapse, and 90% of PE are fatal within the first 1-2 weeks. So, an average follow-up of 3 months is acceptable to differentiate the missed PE. A vein fatal PE occurs in 0-0.9%. In CT examinations with the 3mm collimation, the vein thromboembolism frequency (VTE) was 0.5% and fatal PE 0.3%.[3]

The lower extremities investigation on DVT can be used as an alternative method in some patients with adequate cardiopulmonary reserve or low or moderate clinical suspicion on VTE.

Pulmonary vessels analysis is based on different algorithms depending on accessible equipment quality.

As it is mentioned in the introduction part, beside chest x ray in PE diagnostic, other methods are used, such as SCT angiographies (SCTA), which came into the first imaging line in PE studies, followed echocardiography and ventilation/perfusion (VQ) scinthigraphy, pulmonary angiographies (PA), venography and often D-dimmer test.[16]

Normal V/Q scanning excludes PE, and consequently, V/Q scanning diagnoses of PE with possibility over 90%. However, investigations show that 60-70% V/Q scanning are not diagnostic and ask for additional tests. Studies, which compare V/Q scanning and SCTPA, show that, in scintigraphy, the diagnosis has been made in 74% and on CT in 92% samples.[7,8]

It has been published that unsuccessful or indefinite SCTPA rate is between 2 and 13%. This is in contrast to V/Q scanning rate without diagnosis, which vary a lot (30-80%), and in the same range, it is not diagnostic for PA (0-17%).[3]

CT showed itself superior to V/Q scintigraphy in the estimation of embolus maturity.[7]

The duration of investigation in SCT is approximately 10min, and in V/Q scanning 45 min, which can be extremely important in seriously ill patients who need special care and monitoring.

CT has better results than scintigraphy, and in many things, it is equal to angiographies. It is non-invasive, fast, widely accessible, especially in the institutions where pulmonary scintigraphy and angiographies are not accessible, and presents imaging method of choice, if it is carefully composed as a whole diagnostic procedure. When CT is optimal to subsegmental branches, angiographies are not necessary.[3]

Studies reported on 2002 RSNA meeting found a significant decrease in using ventilation-perfusion (V/Q) pulmonary scintigraphy and pulmonary angiographies during the last decade. The usage of CT pulmonary arteriography did not only increase during the same period, but it replaced V/Q scanning as a standard test.[9,12]

Negative SCT can exclude clinically suspected pulmonary embolism as precisely as normal pulmonary scintigraphy or negative pulmonary angiographies.[17]

Pulmonary angiography was a method of choice for a long time, high sensitive and specific (gold standard) for pulmonary embolism detection, such as intraarterial defect of filling or sudden break (totally obstruction) of pulmonary vessels.

It is indicated when the radionucleid scan is indefinite or indirectly possible when the patient is candidate for operation (for embolectomy) or in extremely high risk of using anticoagulants.[2,10]

Angiographies are indicated in case of high PE suspicion, in normal CT and negative

extremity US, and in low-quality CT image of peripheral pulmonary circulation.[3]

In recent studies SCTPA found more subsegmental PE than PA (92 to56%). In this role, SCTPA proved to be better than PA.[7]

Depending on slice thickness, the literature cites different results about SCTPA effect, from 53 to 100%. The comparison of SCTPA with the 1 mm collimation and pulmonary angiographies showed that both techniques were comparative for discovering subsegmental size emboli. Thinner slice has an advantage in CT. The 1mm-thick reconstructive scan allows detection 14 to 40% additional subsegmental PE comparing with 2 and 3mm-thick reconstructive cross sections.[7]

Spiral CT gives possibility for making alternative diagnosis; its findings percentage varies from 11-85%.

Alternative diagnoses in the patients without PE included pneumonia, atelectasis, pneumothorax, pneumomediastinum, pericardial or pleural haemorrhage, aortal dissection, cardiovascular disease, interstitial pulmonary disease, traumatic changes, postoperative changes, abscess, esophagitis, mycosis cork, bronchial infection, chronic obstructive pulmonary disease, bronchopleural fistula, mediastinitis, pulmonary artery hypertension, aspirate pneumonia, septical embolism, diaphragm hernia, oesophageal rupture and malignant tumours. Alternative finding can be met with or without PE.

Other SCTPA advantages are that it is a strategy with the lowest rate of mortality, with the lowest total price per saved life, usually in combination with leg examination by US-Doppler. The chipper approach was using leg US, followed with SCTPA.[7,8]

SCTPA is a routine widely spread 24-hour technique, more accessible than nuclear studies, which is one of the main reasons that SCT is the first choice in diagnosing PE at many institutions.[3]

Researches and technology progress made multislice SCT (MSCT) de facto a gold standard for imaging pulmonary embolism. CT has become accepted as the first-line method for imaging pulmonary circulation in the patients with suspective pulmonary embolism in daily clinical practice.

However CT has not accepted yet universally as gold standard, especially in internists and pulmologists, although these CT critics prefer to send patients regularly on CT than on V/Q.

However, many clinicians do not accept SCTPA as definitive method for excluding PE because of some interpretation mistakes. But, minimum experience and knowledge in interpretation mistakes (technical, anatomical, connected with patients, inadequate parameters of injection, flow rate, concentration and time delay, or insufficient apnoea lasting, what could have result as pseudo defects of loading) are needed.

The best compromise must be found among high longitudinal space resolution and short time apnoea. Breath hold artefacts can result in an inhomogeneous opacification of pulmonary arteries, with hypodense doubling or steaming up of vessel contours. Artefacts beams from contrast in the vena cava superior (VCS) can create defects of pseudo-loading in pulmonary arteries of right upper slice. These artefacts can be reduced with the saline thrust right after the injection of contrast medium, which rinses the contrast into VCS. Anatomical limiting factors and variants should be known for accurate interpretation.

VCS obstruction, cardiomiophaty, focal or global enhancement pulmonary and cardiac resistance, or pulmonary shunts can request longer delay time, until circumferential per vascular oedema or mycosis corks of small bronchi can simulate PE. Changing windows and levels can increase the confidence in interpretation of suspect loading defect, but that also can increase obvious artefacts caused by image noise, solid beam and moving.

An additional follow-up of the patient's

condition is also possible with CT, usually with perfusion pulmonary scans. The changing of perfusion image can be unnoticeable in some patients with central clots. Dissolving and fragmentation of central embolus with peripheral migration can lead to obvious deterioration of perfusion defects with chest pain and missing repeated PE diagnosis. With CT venography, stratifying contrast medium advances from slow blood circulation in varicose veins, proceeds to the obstacles and hardening artefacts, which can be made from bones, orthopaedic material and calcifications, thus averting accurate diagnosis.[6]

Contrast extravasation can appear on the injection place, as undesired reactions to contrast; teophilinum can be given as prophylactic therapy.[3]

Technical problems, which could lead to investigation without conclusion, were met in less than 3% of patients, and usually they are connected with breathing artefacts (hard dyspnoeic patients), bad relation signal-noise, and insufficient opacification of pulmonary arteries, which may occur in 1-10% cases.[7]

CT provides a quantitative estimation of PE effects on tissue perfusion, with an additional direct embolus visualization, which has a significant influence on treatment planning.[9]

As it has been seen in the last years, CT has become a method of choice for central pulmonary embolism (PE) diagnosis to the level of segmental arteries. Multiplanar and 3D reconstruction and colour delineation of perfusion defect, ROI measuring of arterial proceeds for pulmonary blood circulation estimation, 1 mm collimations, axial and 3D SSD image reconstruction and analysis of sub segmental arteries by mediastinal and pulmonary window, contribute those.[13,14,18,19]

On the basis of these experiences, the patients with negative CTPA made with 3 mm collimation, can be without anticoagulant therapy if they are not seriously ill and if they have no limited cardiopulmonary reserve and/or if there is no high clinical suspect on PE.[22]

For those who can't keep breathing is suggested to breath low; however, the survey of segmental and subsegmental emboli is not optimal.[3]

Using monitoring reading became important for pulmonary arteries analysis, using cine-mod scanning, resulted in an enhanced detection PE rate. Monitors are also helpful for Multiplanar reconstruction (MPR) to differentiate infra and extra vascular structures and to improve diagnostic reliability. Double-screen monitors show simultaneously the mediastinal and parenchymal window, thus providing a more precise diagnosis; preventing false-positive may cause respiratory or vascular artefacts. Windows sets also should be adapted according to vascular reinforcement, intending not to miss small emboli. Large number of images is a problem, because it slows down the work. The total number of SCTPA images is in range from 100-200 for single SCT (SSCT) and 500-1000 for MSCT.[7]

With reference to irradiation quantity, it must be said that SCTPA is responsible for high effective radiation dose, larger than the radiation dose in chest X ray and venography.

Today, SCTPA is the most used primary method in suspected PE in Austrian hospitals.[16]

It is a diagnostic procedure of choice in clinical practice with high accordance among different examiners for main, lobar and segmental zones.[11,20]

For exclusion of pulmonary embolism, SCT is used as a transitive step, leaving pulmonary angiographies for cases with no reliable results. The following protocol was suggested: when CT is positive, stop; when it is negative, lower than subsegmental branches, other examinations are not needed.[8]

In the arsenal of diagnostic examinations, except the mentioned ones, echocardiography in bed is obviously appropriate initial di-

agnostic test to evidence the overloading of RV, which is frequently united with massive PE, and to show clots in the heart cavities or central pulmonary arteries or other disorders, as pericardial tamponade, acute valvular disease, infarct of myocardium or aorta dissection. US examination is also priceless with classical flexography for examining the vein system of lower extremities.[7]

MRI has significant role in diagnostic arsenal, too.[23]

Which of these diagnostic procedures will triumph at the end, will be seen, taking into consideration a permanent technological innovation.

## Conclusions

MSCT is easily accessible and excellent non-invasive method for the clot visualization in pulmonary artery. As the investigations show, it has become effective at the subsegmental level, and in many respects, surpassed pulmonary angiographies. It provides information about the whole spectrum of findings which can be seen in pulmonary embolism; so far, no other method could provide it. Moreover, it also allows alternative diagnosis. Pulmonary artery embolism is, in most cases, associated with the changes in the pulmonary parenchyma and with indications for heart failure. In this investigation, pulmonary embolism was mostly followed by the findings of pleural effusion, enhanced attenuation ground glass type, pulmonary infarct, contrast enhanced consolidation pulmonary parenchyma, and striped and reticular septal bumps. The right pulmonary artery embolism was found more often than the left branches embolism. It is harder to detect other signs described in literature or they are very rare. An investigation on greater serials with new MSCT devices with 16, 32 and 64 detector lines will probably bring new significant information.

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# Characterization of lung cancer patients, their actual treatment and survival: experience in Slovenia

**Lučka Debevec[1], Andrej Debeljak[1], Janez Eržen[2], Viljem Kovač[3], Izidor Kern[1]**

[1]*University Clinic of Respiratory and Allergic Diseases Golnik, 4204 Golnik, Slovenia*
[2]*Department of Thoracic Surgery, Clinical Centre, 1000 Ljubljana, Slovenia*
[3]*Institute of Oncology, 1000 Ljubljana, Slovenia*

***Background.*** *The aim of the study was to establish characteristics of lung cancer patients diagnosed at the University Clinic of Respiratory and Allergic Diseases Golnik in 1996, their selected and realized therapy, and survival.*

***Methods.*** *The retrospective study comprises 345 patients aged from 37 to 90 years (mean 65), 285 males and 60 females. Performance status (Karnofsky): > 80 in 171 patients, 60-80 in 130 and <60 in 44 patients. Microscopically confirmed tumour in 97%: by bronchoscopy 281, transthoracic needle biopsy 23, peripheral lymph nodes biopsy 12, sputum cytology 7, pleural (effusion) cytology 4, distant metastases biopsy 2, mediastinoscopy 1, autopsy 4 patients. Histology and/or cytology: squamous 131, adenocarcinoma 86, large cell 63, small cell 51, non-small cell 1, unclassified 2. Clinical staging of non-small cell lung cancer (NSCLC): stage I 63, stage II 32, stage IIIA 48, stage IIIB 59, stage IV 77, undeterminable 2 patients. Staging in small cell lung cancer (SCLC): limited disease 24, extended disease 27 patients.*

***Results.*** *The selected primary oncological therapy was changed in 11%. Realized primary therapy: radiotherapy 102 (30%), surgery 77 (23%), chemotherapy 47 (14%), supportive treatment 111 (33%). In resected patients staging was correct in 46%, underestimated in 44%, overestimated in 10%. The overall five-year survival was 7.8% (median 6.2 months) and the five year survival of resected patients was 41.9% (median 33 months). The median survival of irradiated patients was 5.7 months, of supportively treated patients 2.5 months. The survival was significantly different according to the performance status and stage.*

***Conclusions.*** *The selected oncological therapy was actually realized in 89%. In our patients there was a low percentage of NSCLC treated by chemotherapy. Among five-year survivors there were 26 resected and one supportively treated patient, that confirms surgery as the most effective therapy in our lung cancer patients.*

*Key words: lung neoplasms – diagnosis – therapy; survival analysis*

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Correspondence to: Lučka Debevec, M.D., University Clinic of Respiratory and Allergic Diseases Golnik, 4204 Golnik, Slovenia; Phone: +386 4 2569 171; Fax: +386 4 2569 117; E-mail address: lucka.debevec@klinika-golnik.si

## Introduction

In recent years there were among 2 million inhabitants in Slovenia approximately one thousand new primary lung cancer patients per year. The data of Cancer Registry of

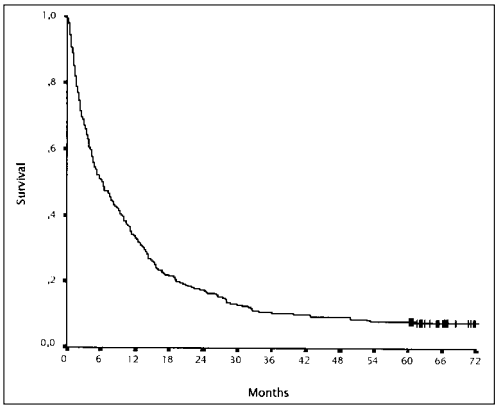


**Figure 1.** Overall survival of 345 patients

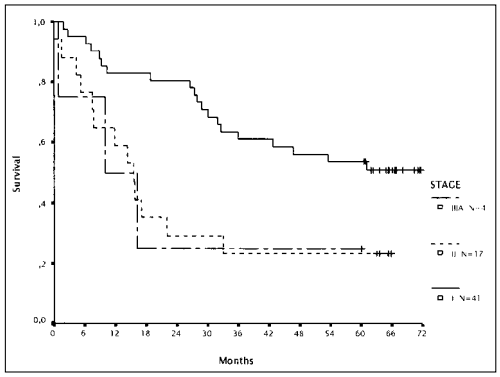


**Figure 2.** Survival of resected patients according to clinical stage

Slovenia presented 958 new cases in 1996, with the incidence rate of 82 per 100.000 population for men and 17 per 100.000 population for women. During that year the lung cancer was the most common cancer in men and the sixth most common cancer in women (after cancer of the breast, skin, corpus uteri, colon and cervix uteri).[1] More than a third of lung cancer patients were diagnosed at the University Clinic of Respiratory and Allergic Diseases Golnik. The study presents the evaluation of routine management and survival of 345 lung cancer patients. This number involves all lung cancer patients diagnosed in 1996, and among them some were also treated by chemotherapy at this institution. Surgery was applied at the Department of Thoracic Surgery, Clinical Centre, Ljubljana, and radiotherapy at the Institute of Oncology, Ljubljana.

The purpose of the study was to establish characteristics of patients and their tumours, the selected and realized therapy, and the survival.

## Methods

The retrospective study comprises 345 patients. The characteristics of patients and their tumours are evident in Table 1 and Table 2.

After the diagnostic procedure 337 of 345 patients were presented at a lung cancer meeting (pulmologist, surgeon, radiation oncologist, pathologist, radiologist) where a treatment modality for each patient was se-

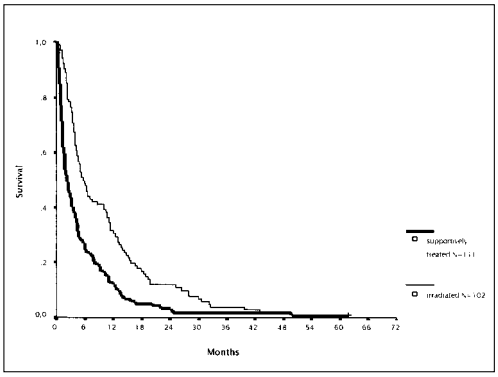


**Figure 3.** Survival of irradiated and supportively treated patients.

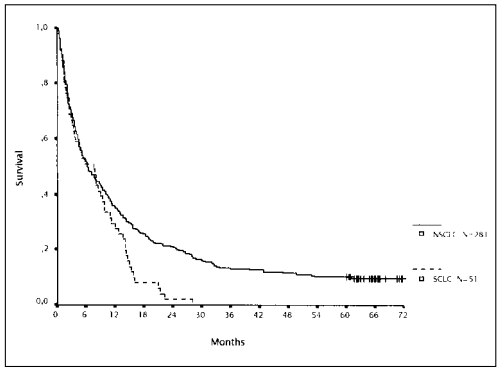


**Figure 4.** Survival of NSCLC and SCLC patients.

**Table 1.** Characteristics of patients

| | |
|---|---|
| Number of patients | 345 |
| Gender | |
| male | 285 |
| female | 60 |
| Age (years) | 37 – 90 (mean 65) |
| Predominant symptoms and signs at the time of admittance | |
| cough, dyspnoea, with or without hemoptysis | 119 |
| bronchitis, pneumonia | 83 |
| haemoptysis, haemopthoe | 30 |
| chest pain | 30 |
| brachialgia | 11 |
| bone pain | 10 |
| Syndrome venae cavae sup., dysphagia, paresis n. recurrentis | 13 |
| central nerve system symptoms | 14 |
| weight loss, weakness | 13 |
| digestive disorders | 8 |
| peripheral lymph nodes enlargement | 4 |
| asymptomatic | 10 |
| Performance status (Karnofsky) | |
| >80 | 171 (49%) |
| 60 - 80 | 130 (38%) |
| <60 | 44 (13%) |
| Clinical stage (332 patients with classified tumour) | |
| Non-small cell cancer | |
| stage I | 63 (22.5%) |
| stage II | 32 (11.5%) |
| stage III.A | 48 (17%) |
| stage III.B | 59 (21%) |
| stage IV | 77 (27%) |
| Small cell cancer | |
| limited disease | 24 (47%) |
| extended disease | 27 (53%) |
| Undeterminable | 2 (1%) |

**Table 2.** Characteristics of tumours

| | |
|---|---|
| Microscopically confirmed tumour | 334 (97%) |
| Not confirmed | 11 (3%) |
| Diagnostic investigations for verification | |
| bronchoscopy | 281 |
| ransthoracic needle biopsy | 23 |
| peripheral lymph node needle biopsy | 12 |
| sputum cytology | 7 |
| pleural (effusion) cytology | 4 |
| distant metastases biopsy | 2 |
| mediastinoscopy | 1 |
| autopsy | 4 |
| Histology and/or cytology | |
| squamous cell | 131 (39%) |
| adenocarcinoma | 86 (26%) |
| large cell | 63 (19%) |
| small cell | 51 (15%) |
| non-small cell | 1 (0.3%) |
| unclassified | 2 (0.6%) |

**Table 3.** Selected and realized primary treatment modality of patients

| Primary treatment | Selected | Realized |
|---|---|---|
| Surgery | 93 (28%) | 77 (23%) |
| Radiotherapy | 110 (32%) | 102 (30%) |
| Chemotherapy | 50 (15%) | 47 (14%) |
| Supportive treatment | 84 (25%) | 111 (33%) |
| Total | 337 (100%) | 337 (100%) |

| | |
|---|---|
| No therapy (death before selection) | 8 / 345 |

lected. Thereafter it was presented to the patient. For various reasons the actual primary treatment in some patients was changed.

Staging of non-small cell lung cancer (NSCLC) was made according to TNM classification,[2] while the one of small cell lung cancer (SCLC) was made according to limited disease (LD) and extended disease (ED). The diagnostic procedure from admittance day to microscopic verification took 1 to 75 days, mean 7 days.

The zero time for the calculation of the survival was the date of admittance to the institution until death or until the end of the follow-up period on December 31st 2001. All living patients were confirmed to have been alive at this date. The minimal follow-up time for all patients was 5 years. The survival was calculated according to Kaplan-Meier's method, differences were confirmed by the log-rank test.

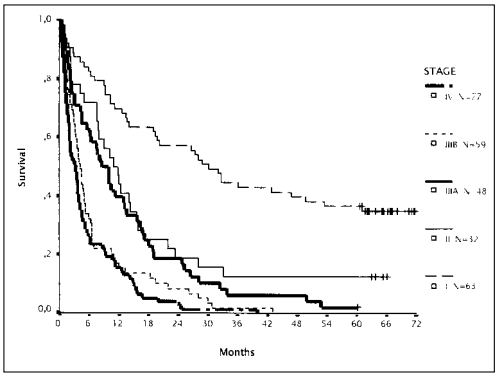


**Figure 5.** Survival of NSCLC patients according to stage.

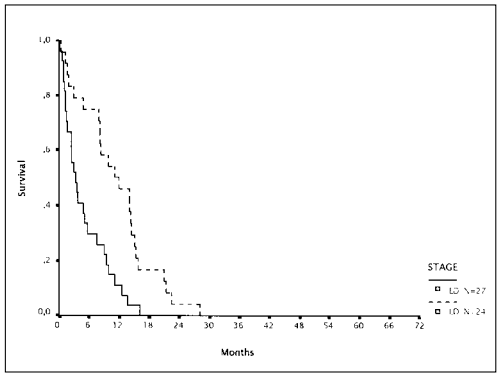


**Figure 6.** Survival of SCLC patients according to stage

## Results

The selected and realized primary treatment modality is evident in Table 3. The therapy was most frequently not realized in patients selected for surgery. The overall primary oncological therapy was changed in 27 of 253 (11%) patients.

The overall survival of 345 patients is presented on Figure 1. The median survival was 6.2 months. After five years 27 (7.8%) patients were still alive.

There was no difference in survival according to gender (p=0.127).

Eighty-eight of 93 patients selected for surgery were admitted for thoracic surgery. Afterwards 4 patients refused the intervention while 7 patients were rejected by the surgeon. In 77 surgically treated patients 35 had lobectomy, 5 bilobectomy, 22 pneumonectomy, 9 exploratory thoracotomy, 6 mediastinoscopy (mediastinotomy). In 62 resected patients staging was correct in 46%, underestimated in 44% and overestimated in 10%. The survival of resected patients is presented on Figure 2. Their median survival was 33 months. The five-year survival of resected patients was 41.9%, stage I 51.2%, stage II and IIIA 23.5% and 25% respectively, considering the clinical TNM staging. In patients with exploratory thoracotomy the median survival was 14.1 months.

In irradiated patients the median survival was 5.7 months and in supportively treated patients 2.5 months (p=0.0001), Figure 3.

In NSCLC patients the median survival was 6.3 months, in SCLC patients 7.5 months, however, the long-term survival was significantly better in NSCLC patients (p=0.0153), Figure 4.

The survival according to the stage was significantly different in NSCLC (p<0.0001), Figure 5, and in SCLC patients (p=0.0004), Figure 6.

The survival according to the performance status is different as well (p<0.0001), Figure 7.

## Discussion

Of registered predominant symptoms and signs the pulmonary ones were present in two thirds of our patients. Only 3% of patients were asymptomatic. Hawson *et al*.[3] reported 15% asymptomatic patients in NSCLC and 5% in SCLC among 1024 lung cancer patients. Haber[4] established the increase of asymptomatic patients in Queensland of 7% in 1964 to 13% in 1990. Lee *et al*.[5] established 7.2% asymptomatic in 3794 Korean lung cancer patients. The frequency of discovery of patients still at an asymptomatic stage could indicate the efficiency of detection.

Bronchoscopic samples most commonly

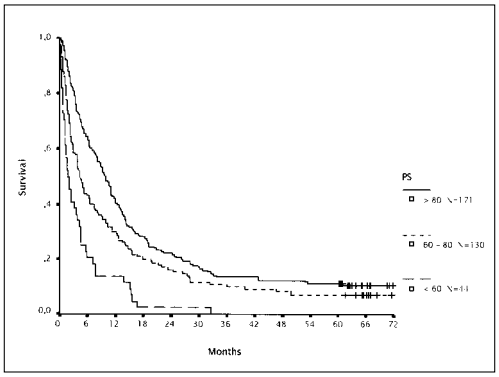


**Figure 7.** Survival of 345 patients according to performance status.

enabled the microscopic confirmation of tumour. In 4 patients tumour was proven by autopsy. In 11 (3%) patients tumour was microscopically not confirmed. These were patients with a low performance status, not capable for diagnostic procedures or capable for a supportive treatment only. The Cancer Registry of Slovenia in 1996 reported 92% microscopically confirmed lung cancer in male and 91% in female.[1] The percentage of unconfirmed lung cancer, named also radiological lung cancer, is rarely reported. Lung[6] published a study of 16 Turkish centres and 3.8% radiological cancer among 11849 lung cancer patients. Juhasz *et al.*[7] reported 11% of unconfirmed tumours in 499 NSCLC patients, so they concluded that there were no SCLC among their patients.

Squamous cell is the most common type of lung cancer, 30%[8] to 50%[9] of all lung cancer. The increase of adenocarcinoma in some countries over the last two decades is most likely to be attributable to the increased use of milder, filter-tip cigarette, the smoke from which is inhaled deeply, causing adenocarcinoma of the periphery of the lung.[10] Small cell lung cancer is less frequent, 15%[11] to 30%.[12] In our patients there were 39% squamous cell and only 15% small cell, 26% adenocarcinoma and 19% large cell, meanwhile the Cancer Registry of Slovenia published 32% squamous, 17% small cell, 24% adenocarcinoma and no specified data for large cell carcinoma in 1996.[1]

The valid TNM classification since 1997 range T3N0M0 tumours in IIB stage, it was already considered in the analysis. It was not possible to distinguish A and B in I and II stage. Based on the present data we were able to determine the clinical stage in 99% of patients. Only in resected patients it was possible to compare clinical TNM and postsurgical-pathomorphological TNM stage that has a better survival.[13] Clinical TNM stage was correct in almost half of our patients, very similar to the published data.[14,15,16] In our patients 13% had exploratory thoracotomy, also as a consequence of tendency to enable the resection for all patients without the proven inoperability. As exploratory thoracotomy yields no benefit to the patient in terms of survival or palliation, the goal of thoracic surgeons should be to eliminate such intervention.[17] Consistent and precise staging enabled diminishing of exploratory thoracotomy from 15.1 to 2.1%.[16]

The duration of a diagnostic procedure in our patients was mostly about one week and did not essentially influence a therapy delay. The realization of therapy depends on the patient's motivation for therapy, confidence in the doctor, fear of therapy modality, access to the treatment and financial possibilities. The latter is not the case in Slovenia, because all citizens have health insurance that includes the whole cancer management. The difference between the selected and realized therapy was mostly the consequence of waiting for the radiotherapy up to two weeks and for the surgery about one month. During the waiting time the patient's situation can deteriorate and a primarily selected therapy may not be suitable any more. It can be also considered that the selected therapy modality was not always adequate.

All of 110 patients referred to radiotherapy came to the Institute of Oncology[18] and 93% of them were irradiated, i.e. 30% of all pa-

tients. This percentage included primarily irradiated patients with curative and palliative intent, but not irradiated after thoracotomy or chemotherapy. Hawson *et al.*[3] reported 40%, Skričkova *et al.*[19] 32.2% irradiated cancer patients, both in NSCLC only.

Of 93 patients selected for surgery 83% of them were operated (cervical mediastinoscopy and parasternal mediastinotomy as the initiation of surgical intervention included). Five percent of patients refused the surgery after coming to the thoracic surgeon, while 9% were rejected because of signs of inoperability or deterioration of a general condition.

Chemotherapy was performed in 44/47 selected SCLC and 3/3 selected NSCLC patients. That minimal use of chemotherapy in NSCLC (1%) was also due to the insufficient payment of modern expensive drugs by the health insurance. Hawson *et al.*[3] reported the same use of chemotherapy in 873 NSCLC, but in 1990.

Of 337 treated patients 111 (33%) were getting a supportive care. One of them, peripheral large cell carcinoma stage I, without symptoms, unfit for the resection, survived for more than five years. A similar percentage of a supportive treatment is reported by others.[3,19]

The presented survival figures are factual and not calculated. They do not exclude perioperative and general mortality. Almost 8% of patients survived for 5 years, all but one were resected.

## Conclusions

The selected oncological therapy was actually realized in 89%. In our patients there was a low percentage of NSCLC treated by chemotherapy. Among five-year survivors there were 26 resected and one supportively treated patient, that confirms the surgery as the most effective therapy in our lung cancer patients.

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# Surgical treatment of malignant pleural mesothelioma. Experience in the interdisciplinary approach in Slovenia

**Janez Eržen[1], Stanko Vidmar[1], Miha Sok[1], Andrej Debeljak[2], Peter Kecelj[2], Viljem Kovač[3], Marjeta Stanovnik[3], Tomaž Rott[4], Izidor Kern[3]**

*[1]Department of Thoracic Surgery, Clinical Centre, 1000 Ljubljana, Slovenia*
*[2]University Clinic of Respiratory and Allergic Diseases Golnik, 4204 Golnik, Slovenia*
*[3]Institute of Oncology, 1000 Ljubljana, Slovenia*
*[4]Institute of Pathology, Medical Faculty, University of Ljubljana, 1000 Ljubljana, Slovenia*

***Background.*** *The aim of the study was to identify perioperative morbidity and mortality, the category and mode of adjuvant treatment, local recurrence and survival in patients treated by extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma (MPM).*

***Methods.*** *From 2000 to 2003, 18 patients with MPM were referred to the Department of Thoracic Surgery in Ljubljana, and 17 of them were operated on. Two patients underwent explorative thoracotomy, and 15 patients were evaluated. Five female and nine male patients (aged 52-68 years) were treated by EPP and one male patient by pleurectomy. Eight patients received both adjuvant chemotherapy (ChT) and radiotherapy (RT), with cisplatin 100 mg/m$^2$ + mitomycin C 6-10 mg/m$^2$ or gemcitabine 1000 mg/m$^2$ and external beam radiation with 24 Gy - 58 Gy respectively, three patients received no adjuvant therapy, three patients were treated by adjuvant ChT, two of them were given cisplatin 100 mg/m$^2$ + mitomycin C 6-10 mg/m$^2$, and one patient cisplatin 100 mg/m$^2$ on the first day and gemcitabine 250 mg/m$^2$ in prolonged 6 hours infusion on the first and on the eighth day. One patient was treated only by adjuvant RT.*

***Results.*** *There were no perioperative deaths and the postoperative morbidity was 42%. Of the 15 evaluable patients, and in the median follow up of 40 months (28-64), we noticed nine (60.0%) recurrences, seven local and two abdominal. Eight (53.3%) patients died, all because of the local progress of disease. Of the 3/15 patients without adjuvant treatment, one patient (T1bN0M0) is well 46 months after the operation, one patient (T2N0M0) got recurrence in abdomen, was treated with ChT and reoperation, and is still alive 31 month after the first surgical treatment. One patient (T2N0M0) died two months after the surgery due to local recurrence. In ChT+RT group, 6/8 patients died: the patient at stage T1aN0M0 died after nine months, the patient at stage T1bN0M0 died after nine months, two patients at the stage T2N0M0 died after four and 23 months respectively, the patient at stage T3N0M0 after 11 months, and the patients at stage T3N2M0 died seven months after the operation. Two out of eight patients are alive: the patient at stage T1bN0M0 is alive 43 months, and the patient at stage T2N0M0 is alive 28 months after the operation. In the ChT group, 1/3 patient (T2N0M0) died 6 months after the operation, 2/3 patients (T2N0M0 and T3N0M0) are well after 43 and 20 months respectively. The patient treated with adjuvant RT only is well 50 months after the surgical treatment. The median survival time was 20 months for the whole group of patients operated on, the 1-year survival rate was 53.3% and 2-year survival rate was 46.7%.*

***Conclusions.*** *In selected patients with MPM, complete surgical resection is indicated, followed by chemotherapy and radiotherapy. The operation could be performed safely with acceptable mortality and morbidity. Our group of patients is too small, the adjuvant therapies were too different to favour any of the treatment mode applied. Further randomised studies and standardised protocols are needed to evaluate the best mode of treatment for each patient.*

*Key words: pleural neoplasms; mesothelioma – surgery – drug therapy - radiotherapy*

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Correspondence to: Assist. Janez Eržen, MD, MSc, Clinical Department for Thoracic Surgery, Clinical Centre, Zaloška 7,1525 Ljubljana; Phone +386 1 522 21 64; E-mail: janez.erzen@mf.uni-lj.si

## Introduction

Malignant pleural mesothelioma (MPM) is a rare disease and it is rarely curable. Most frequently the patients with mesothelioma had been exposed to asbestos. Recently, the presence of a DNA tumour virus (simian virus 40) in tumour cells has suggested a connection between the simian virus 40 and human mesothelioma.[1,2] Mineral oils, liquid paraffin, recurrent pulmonary infections, tuberculous pleuritis, exposure in leather and petrochemical industry, environmental exposure to copper, nickel and glass fibres are cited as non-asbestos risk factors.[3]

MPM grows from the visceral or parietal pleura. For a long period of time it can be localised at the pleura, but later it infiltrates the lung parenchyma, the diaphragmatic muscle, the endothoracic fascia, the mediastinal fat, the soft tissues of the chest wall, and even the ribs and the pericardium. It usually involves the lower part of thoracic cavity and the lower pulmonary lobe.[4]

MPM is more frequent in males, who usually fall ill between the ages 50 and 70 years. In 80% of patients, the illness starts with dyspnea, chest pain and pleural effusion.[5] Patients often suffer from irritating cough and fever.

MPM grows up from multipotential mesothelial or subserous cells. The tumour histology affects the survival prognosis, which makes it important to diagnose the epithelial, mixed or sarcomatous type of tumour.[3] Occasionally the mesothelioma is hard to distinguish from metastatic adenocarcinoma and the early stage of the benign mesothelial hyperplasia.[3] Immunohistochemical studies are required, and in same cases even electron microscopy, to establish a conclusive diagnosis.

Due to slowly evolving symptoms and non-specific clinical picture, the diagnosis is frequently delayed. The average time interval between the first symptoms of the disease and the diagnosis is from three to six months.

A sufficient amount of tissue is needed for diagnosis, and it is obtained by thoracoscopy, videothorascopic procedure or needle puncture. An invasive diagnostic procedures may causes a malignant seeding.[6]

The prognosis of the disease is poor. Median survival of untreated patients is four to twelve months.[7,8] Nevertheless, it can stretch up to five years for 10-15% of patients, in whom the progression of the disease is, for unknown reasons, slow.[3]

Surgical treatment promises the most, but only for selected patients. It is appropriate for patients with the epithelial tumour, stage I or II. The prognosis is more favourable for patients who are in good condition, younger than 50 years and not in pain.[4] The nature of the tumour, which spreads over anatomically large and heterogeneous area, makes the microscopically complete resection rarely possi-

ble.[9] The operation alone is usually not sufficient. Additional methods are applied prior to, in the course of, or after the surgical removal of the tumour. Postoperative irradiation,[5,10,11] systemic[12,13] and intrapleural chemotherapy[14-16] are very common. Modern methods of treatment, such as photodynamic therapy,[17,18] immunotherapy, genetic treatment and intracavitary chemotherapy with heat, seem promising, but are yet to produce permanent improvement.[19]

For the majority of patients, the surgical treatment of MPM is not viable and it is hardly ever successful. Only 10-15% of patients with MPM are operated on. A typical candidate for the operation is a patient in stage I or II of the disease, with the epithelial type of MPM. Two methods of surgical treatment are used: pleurectomy and extrapleural pneumonectomy (EPP).

Pleurectomy is the more frequent of the two methods, with less complications, and lower postoperative mortality rate. This operation is less radical, and localised recurrences are more common.[3,20] Nevertheless, the operation is equally successful, if the tumour can be completely resected.[21]

EPP is a more radical operation than pleurectomy, more difficult for the patient, with higher postoperative mortality and morbidity rates. Its long-term survival prognosis improves when combined with radiotherapy and chemotherapy.[22] The surgical procedure involves a complete resection of the lungs, parietal pleura, pericardium, and diaphragm. Regional lymph nodes are removed as well. The early postoperative mortality should not exceed 10%.

## Methods

The four-year period of surgical treatment of MPM has been retrospectively analysed at the Clinical Department of Thoracic Surgery of the Clinical Centre in Ljubljana. The data were obtained from the medical records provided by the University Clinic of Respiratory and Allergic Diseases Golnik, by the Department of Thoracic Surgery of the Clinical Centre, and by the Institute of Oncology in Ljubljana. The data pertaining to survival were obtained from the Cancer Register at the Institute of Oncology, and through telephone contacts with patients and their family physicians.

During the period between the years 2000 and 2003, the Clinical Department of Thoracic Surgery, Clinical Centre Ljubljana, admitted 18 patients diagnosed with MPM. They were aged between 32 and 68 years, the average age was 58.5 years. Seven of them were females, eleven were males.

Ten patients had been exposed to asbestos, or had been diagnosed with asbestosis of lungs. All of them came from the region of Gorica, four of them from Kanal, a place with merely 1500 inhabitants.[23]

All but three patients had been diagnosed with MPM prior to the admission to our department. In nine cases the diagnosis was based on needle biopsy, in five cases additional thoracoscopy[24] was performed to confirm the inconclusive needle biopsy-based diagnosis. The diagnosis based on thoracoscopy was always conclusive. One patient was diagnosed by thoracoscopy, without previous needle biopsy. Two patients were diagnosed by minithoracotomy at our department, one with the help of video-thoracoscopy.

All patients had a history of chest pain on the affected side and/or dyspnea. Other symptoms were: irritating cough (3), general discomfort and fatigue (3), loss of weight (2) and fever. All except one had thoracic effusion.

Surgical treatment was chosen in the case of epithelial type of tumour, stage I, II or III according to IMIG (International Mesothelioma Interest Group) classification,[3] if the patient's status made the procedure possible.

In addition to usual blood tests and ECG, bronchoscopy, pulmonary function tests, the ultra-sound of liver, and computerised tomography (CT) of the thorax and of the upper abdomen were performed in all patients.

## Results

Of the 18 patients chosen for the operation, one female patient did not undergo it due to her rapidly deteriorating general condition. In two patients, only explorative thoracotomy was performed, the other 15 patients were evaluated. EPP was performed on 14 patients, one patient underwent pleurectomy.

None of the patients died in the first 30 days after the operation. Six of the radically operated patients (42%) developed minor postoperative complications, which were not life-threatening, nor did they affect further treatment or length of hospitalisation (Table 1).

Most of the radically operated patients had major posterolateral thoracotomy performed, with the removal of the $6^{th}$ rib, and in three patients double thoracotomy was indicated. Goratex fabric was used for the reconstruction of the diaphragm and of the pericardium, except in one patient, whose diaphragm was replaced with a Vycril net.

The patients remained in hospital from 6 to 14 days, 10 days on the average.

Thirteen radically operated patients had the epithelial, and two the mixed type of mesothelioma. Most of them were at stage I and II of the disease (Table 2).

**Table 1.** Type and number of operative complications in patients with malignant pleural mesothelioma, treated by the extrapleural pneumonectomy and pleurectomy

| Type of complications | Number |
|---|---|
| Tahiarrythhmia | 3 |
| Unexplained fever | 1 |
| Chylothorax | 1 |
| Bronchial fistula | 1 |

**Table 2.** Stage in radical operated patients with malignant pleural mesothelioma

| Stage – IMIG classification | Number |
|---|---|
| T1aN0M0 | 1 |
| T1bN0Mo | 6 |
| T2N0M0 | 4 |
| T3N0M0 | 3 |
| T3N2M0 | 1 |

None of the patients received neoadjuvant treatment. The patients who underwent explorative thoracotomy and not the operation were treated differently. One of them received chemotherapy and radiotherapy, the second one just chemotherapy. The patient who was not operated was treated for symptoms only. Three operated patients in stage I had no adjuvant treatment. Eight patients underwent chemotherapy and radiotherapy, three patients just chemotherapy, one patient only radiotherapy (Table 3).

Of the patients who took cytostatic drugs after the operation during the first three years, four were given mitomycin C 6-10 mg/m$^2$ and cisplatin 100 mg/m$^2$ each three weeks. The treatment was often adjusted to the patien's condition, side effect of drugs, and the response to treatment. On the average, it lasted three months, in one case only a month, and in another case five months. One of the patients was given cisplatin, metotraxat, adriamycine and gemcitabine because of an early extensive progression.

In the course of further treatment, three patients were given gemcitabine 1000 mg/m$^2$ instead of mitomycin C during the last year,

**Table 3.** Mode of the treatment and survival

| Mode of the treatment | Number of patients | Median survival in month | Alive |
|---|---|---|---|
| OP + CT + RT | 8 | 10 | 4 |
| OP + CT | 3 | 20 | 2 |
| OP | 3 | 31 | 2 |
| OP + RT | 1 | 50 | 1 |
| Total | 15 | 20 | 7 |

OP = operation; CT = chemotherapy; RT = radiotherapy

**Table 4.** Type and mode of adjuvant treatment of the operated patients

| Patient | Start of CT | Completed CT | CT | Start of RT | Completed RT | Tumour dose in Gy |
|---|---|---|---|---|---|---|
| F.K. | 17.04.00 | 07.09.00 | Mito C+Cispl | 23.10.00 | 22.11.00 | 40 |
| E.S. | 26.06.00 | 24.09.00 | Cispl+MTX+Adria+Gemz | 07.07.00 | 04.10.00 | 58 |
| S.B. | | | | 08.05.01 | 08.06.01 | 54 |
| B.P. | 13.11.01 | 13.03.02 | Mito C+Cispl | 18.03.02 | 27.03.02 | 27 |
| F.Z. | 26.01.02 | 20.03.02 | Mito C+Cispl | | | |
| J.B. | 07.01.02 | 09.04.02 | Mito C+Cispl | 02.07.02 | 31.07.02 | 50 |
| V.K. | 25.02.02 | 14.05.02 | Mito C+Cispl | 29.07.02 | 08.08.02 | 41 |
| A.M.M. | 15.10.02 | 02.12.02 | Mito C+Cispl | 06.02.03 | 12.03.03 | 50 |
| I.L. | 25.09.02 | 23.12.02 | Mito C+Cispl | | | |
| D.S. | 23.04.03 | 01.07.03 | Cispl+Gem | 21.07.03 | 19.09.03 | 54 |
| I.P. | 12.06.03 | 27.08.03 | Cispl+Gem | 15.10.03 | 06.11.03 | 24 |
| B.R. | 08.12.03 | 03.02.04 | Cispl+Gem in prolong inf. | | | |

KT = chemotherapy; RT = radiotherapy; Mito C = mitomycin C; Cispl = cisplatin; MTX = Methotrexat; Adria = adriomycine; Gem = gemcitabine

while the dosage of cisplatin remained the same.

The above eight patients had postoperative radiotherapy of hemithorax, at the dosage from 24 to 58 Gy.

Three patients took cytostatic drugs without radiotherapy. Two patients were administered cisplatin 100 mg/m$^2$ and gemcitabine 1000 mg/m$^2$, one patient cisplatin 100 mg/m$^2$ and gemcitabine 250 mg/m$^2$ in prolonged 6-hour infusion on the first and on the eighth day. One female patient underwent radiotherapy and no chemotherapy (Table 4).

The median survival of all operated patients, regardless the adjuvant treatment, was 20 months. One-year survival rate was 53.3%, and two-year survival rate was 46.7%.

The median survival of the patients who received postoperative chemotherapy and radiotherapy, as well as of those treated with chemotherapy without radiotherapy, was 11 months, while the patients without adjuvant treatment had median survival of 31 months. The female patient who underwent radiotherapy after the operation (Table 3) survived longest (50 months). The patients with explorative thoracotomy and adjuvant ChT and RT, as well as the patient treated for symptoms only, survived for a little over 8 months.

## Discussion

The exposure to asbestos and lung asbestosis were definitely established in 10/18 (55%) patients, and very probable in two other cases (65%). It is especially distressing that most of them came from a geographically small region of Gorica, and that Kanal, a small place with about 1500 inhabitants, drastically stands out.[23] Asbestos, a primary etiological agent of MPM, was present in 66% of patients, which is a little lower than the percentage reported by other authors.[1-3] Other etiological factors, such as the infection with the simian virus 40, were not explored. Two of the patients, however, had been employed in petrochemical industry.

The symptoms had been present for several months, up to half a year, on the average. Only in one female patient had the x-ray examination revealed changes a year before, and adenocarcinoma of lungs had been initially diagnosed.

The disease affects males more than females. Other studies report ratios even more detrimental for males[3,5] than is the case in our study (1 : 2.4).

The disease usually starts with dyspnea and pleural effusion, as well as chest pain in

the affected side.[3,5,7] All patients had the history of one or more of these symptoms.

The diagnosis is not easy, since symptoms such as chest pain, dyspnea, fatigue and cough are non-specific, and, on the other hand, histopathologist can find it difficult to distinguish MPM from adenocarcinoma.[3,5] In our group, needle biopsy was in five cases insufficient for a definite diagnosis.

In order to determine the stage of the disease, the CT of the thorax and of the upper abdomen was performed on all candidates for the operation. The CT was underestimated only in two patients (13.3%). In both cases the tumour had spread to mediastinal organs and was consequently inoperable. No MRI was performed, although it is recommended, since it is more precise than CT in determining the penetration of the tumour in the mediastinum and in the diaphragm.[5]

In the course of the four years, EPP was performed on 14 patients, which is more than in the previous period of time. In the analysis of the MPM patients in Slovenia between 1980 and 1977, Debevec *et al* report that only 24 of 156 patients with MPM were operated on. Explorative thoracotomy was done for half of them, and EPP only for five patients.[25]

In most cases, extensive posterolateral thoracotomy was performed, with the resection of a rib. Double thoracotomy was performed in three patients, which was mostly the surgeon's choice. The approach must provide grounds for a safe and radical surgery on extensive area involving vital and sensitive structures such as functional pulmonary veins, the heart and the inferior vena cava.

When performing EPP, we try to resect parietal pleura, lungs, pericardium and diaphragm in one piece, without opening the pleural cavity. This is achieved only rarely because of its adhesion to the thoracic wall, mediastinum, pericardium and diaphragm, as well as due to previous diagnostic procedures in the pleural cavity. The defect of the pericardium and of the diaphragm was in all but one patients restored with a Goretex patch. This fabric is very suitable, it causes no complications, but it is very expensive. A Vycril net used in one operated patient proved satisfactory as well, and is frequently being used. In each operation, the canal made by previous diagnostic biopsies was radically resected, either as a separate procedure or during the thoracotomy.

None of the operated patients died during the early postoperative period, which is a very good result. At present, the early postoperative mortality is 5-10%.[3,5,10,22,26] Early postoperative deaths are mostly due to sudden drop of blood pressure because of the dislocation of mediastimun and blood in-put disorders, haemorrhage, infection of the remaining pulmary lobes, bronchial fistula and the subsequent empyema in the pleural cavity, and mediastinitis. Herniation of the heart can result from the defect of the pericardium, unless it has been meticulously reconstructed.[5]

Various postoperative complications are reported for EPP. They occur in 50% and even more patients. In our group, 42% of patients experienced complications, but none of them was extensive. Only one female patient had to be readmitted because of a bronchial fistula.

Pleurectomy is a less demanding procedure, with fewer complications and low early postoperative mortality, but it is also less radical than EPP. The median survival after this operation is from 9 to 20 months, as reported by different authors.[7] Radical resection from the visceral pleura, where the disease usually recurs, is problematic.[9] Local recurrence is 10% for EPP, and 52% for pleurectomy.[27] Decortication always indicates adjuvant treatment. It was performed in only one female patient at the stage T1aN0M0. After the operation, she underwent adjuvant treatment involving chemotherapy and radiotherapy. The patient died nine months after the operation due to local progress of mesothelioma.

Most authors agree that EPP alone is not sufficient, and that adjuvant treatment is nec-

essary.[3,5,11,20] Median survival after EPP is from 9 to 19 months,[7] not unlike the survival after decortication. This is due to the fact that decortication is more frequently indicated at lower stages of the tumour.

Not all of the authors report such optimistic results. Mattson reports that 100 operated patients, who underwent adjuvant treatment involving five different modes of irradiation and systemic chemotherapy, had the median survival of 8 months and only 20% had two-year survival.[11]

Adjuvant treatment most frequently involves chemotherapy and irradiation of complete hemithorax at high tumour dose,[5,11] or only irradiation of hemithorax at high tumour dose.[10]

Median survival of the whole group of our operated patients was 20 months, which is significantly better than the survival of patients in the same period and who were not operated on[28] and whose median survival was 11 months. The groups were not randomised. Patients who were not operated on were probably at a higher stage of the disease, had different histological type of tumour, and were in worse performance status than the patients operated on, so that the two groups cannot be validly compared.

Most of our patients (12/15) received adjuvant treatment after the operation, but not in the same mode. They were prescribed different cytostatic drugs, different dosages, different number of cycles, as well as different radiation doses. Five recent patients were treated with a cytostatic drug of the 3rd generation, which shows better results.[29-31] The IMRT method of irradition, which could be very effective,[32,33] was not available in our case. A small number of patients (3) had no adjuvant treatment. The small size of the sample of treated patients makes any evaluation of the efficiency of individual methods of treatment unreliable. There are indications that the results tend to be the same as those reported by DaValle[34] that in a group of 17 patients the survival length showed no correlation with the adjuvant treatment. His study, however, was not controlled and randomised. At least one more year of follow-up observation would be needed for a valid evaluation of our methods of treatment.

Different and multiple methods of treatment indicate that the MPM disease is still unmanageable, fatal for most patients, irrespective of how it is treated. In spite of aggressive local treatment, loco-regional recurrences of the tumour are almost inevitable, if the rest of the pleural cavity, pericardium and abdomen are considered loco-regional. Better results are obtained in carefully selected patients at initial stage, who are treated with a radical local resection of the tumour and adjuvant radiotherapy.

In future, neoadjuvant cytostatic treatment, applied and recommended by Stamatis,[35] who reports 31% of three-year survival, will have to be considered. The same author points out that the use of cytostatic drugs after EPP can be detrimental to the other side of the lungs. For that reason he recommends that the treatment starts with three cycles of cisplatin and gemcitabine medication, radical resection after three to four weeks, and radiotherapy of hemithorax after four to six weeks.

## Conclusions

The incidence of MPM has been growing. In patients with epithelial tumour at stage I and II, surgery is indicated besides the oncological treatment. If sufficient, or if the disease is strictly localised, pleurectomy is performed. EPP is a more radical procedure, relatively safe and with acceptably low postoperative mortality and morbidity. It is crucial that the best method of neoaduvant and/or adjuvant treatment after a radical operation is agreed upon.

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# Managing anemia with epoetin alfa in patients with rectal cancer

**Vaneja Velenik[1], Irena Oblak[1], Veronika Kodre[2]**

[1]*Department for Radiotherapy, Institute of Oncology, Ljubljana, Slovenia*
[2]*Janssen-Cilag Slovenia, Division of Johnson & Johnson d.o.o., Ljubljana, Slovenia*

***Background.*** *Anemia is one of the most challenging problems in clinical oncology due to its high prevalence among the patients with malignant diseases. The purposes of our study were: (1) to assess the potential of epoetin alfa therapy to prevent the decline in Hb concentrations that typically accompanies chemotherapy/radiotherapy (ChT/RT) of the patients with rectal cancer; (2) to test the hypothesis that the use of epoetin alfa significantly reduces the transfusion requirements in the patients with rectal cancer treated with ChT/RT after surgery, and (3) to evaluate the safety profile of the administration of epoetin alfa in the clinical setting.*

***Methods.*** *Sixty patients who underwent surgery for rectal cancer were prospectively enrolled. Group A consisted of 39 patients with Hb concentrations ≤13 g/dl at the start of ChT/RT following surgery, and group B of 17 patients with Hb concentrations >13 g/dl at the start of ChT/RT following surgery, but whose Hb concentrations fell below 13 g/dl during the ChT/RT protocol. The starting dose of epoetin alfa in both groups was 10,000 IU subcutaneously (sc) three times a week (tiw). The following major parameters were evaluated: (1) change in Hb concentrations relative to the baseline as measured at 4-week intervals, (2) allogenic blood transfusion requirements in relation to Hb concentrations, and (3) incidence and severity of adverse events and their potential relationship to epoetin alfa administration.*

***Results.*** *The study protocol was completed in 56/60 patients. In group A, a statistically significant increase in Hb concentration ($p<0.001$) was observed after the first 4 weeks of epoetin alfa treatment compared to the baseline values, with the mean increase of Hb concentration of 1.97 g/dl ± 0.91 g/dl and Hb concentrations remained significantly increased through the whole study ($p=0.0017$). In group B, a continuous decrease in Hb concentrations was observed during the first weeks of therapy, reaching the level of statistical significance after 3 weeks of postoperative treatment. After the initiation of epoetin alfa treatment, an increase of Hb concentrations and their maintenance at ≤12 g/dl was observed also in group B. Not a single patient enrolled in the study needed transfusion. None of described adverse events was connected to the epoetin alfa treatment.*

***Conclusions.*** *The results of the present study show that epoetin alfa is safe and effective in maintaining Hb concentrations during the adjuvant therapy in rectal cancer patients. It significantly increases Hb concentrations and reduces transfusion requirements in the patients receiving chemoradiotherapy after surgery for rectal cancer.*

*Key words: rectal neoplasms – radiotherapy – drug therapy; anemia – drug therapy; epoetin alfa*

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Correspondence to: Vaneja Velenik, M. D., Department of Radiation Oncology, Institute of Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia; Phone: +386 1 232 3063; Fax: +386 1 431 41 80; E-mail: vvelenik@onko-i.si

## Introduction

Anemia is one of the most challenging clinical problems in clinical oncology due to its high prevalence among the patients with malignant diseases.[1,2] It is now recognized as an independent prognostic factor for patient's survival[3-12] and can also have a considerable negative effect on patient's quality of life.[7,13-17]

Generally, clinical studies have shown that recombinant human erythropoietin (epoetin alfa) administered once weekly or three times a week improves hemoglobin (Hb) levels, decreases transfusion requirements,[1,4,7,12-20] improves quality of life,[14-17,21-24] and may also improve the survival in the patients with cancer-related anemia.[4,7,25-27] However, despite such efficient approach to the anemia management, a comprehensive survey[28] indicated that only 36% of patients with solid tumors who were anemic received treatment for their anemia. Moreover, treatment of anemia was initiated at lower Hb levels than recommended (mean Hb level of 9.6 g/dl for solid tumors).[28]

Accordingly, it is mandatory to assess the feasibility and safety of the administration of epoetin alfa in each individual type of cancer. The purposes of our study were: (1) to assess the potential of epoetin alfa therapy to prevent the decline in Hb value that typically accompanies chemotherapy/radiotherapy (ChT/RT) of the patients with rectal cancer; (2) to test the hypothesis that the use of epoetin alfa significantly reduces the transfusion requirements in the patients with rectal cancer treated with ChT/RT after surgery, and (3) to evaluate the safety profile of administration of epoetin alfa in the clinical setting.

## Methods

Sixty patients who underwent rectal cancer surgery were prospectively enrolled in the study between March 2002 and December 2003 (Table 1). The following inclusion criteria were used:

- histologic confirmation of adenocarcinoma of the rectum (pathohistological stage II and III) that were amenable to postoperative ChT/RT;
- age above 18 years;
- WHO performance status 0-2;
- Hb level ≤13 g/dl;
- serum transferrin saturation (TSAT) >20%.

Exclusion criteria were: uncontrolled or severe cardiovascular disease, including recent (<6 months) myocardial infarction; uncontrolled hypertension (diastolic blood pressure >95 mm Hg); congestive heart failure; uncontrolled or unexplained seizures; major illness

**Table 1.** The study population

| Group | N | Description | Mean age/Range (years) | Gender (male/female) |
|---|---|---|---|---|
| A | 39 | Hb level ≤ 13 g/dl at the start of the Cht/RT treatment following surgery; enrolled at the start of the Cht/RT | 64.8±14 | 19 M/20 F |
| B | 17 | Hb level >13 g/dl at the start of Cht/RT treatment following surgery; enrolled during the Cht/RT | 68.5±9.5 | 11M/6F |
| All | 56 | Patients with Hb≤13 g/dl treated for rectal cancer with Cht/RT after surgery | 66.6±11.7 | 30 M/26 F |

ChT/RT – chemo-radiotherapy; N – number of patients

or infection within the preceding month, history of thrombotic or other vascular events during the preceding 6 months; known hypersensitivity to epoetin alfa or one of its components; pregnancy, lactation, or inadequate method of contraception in females with childbearing potential.

Surgical procedures were as follows: abdominoperineal resection (APR; 23 patients), low anterior resection (LAR; 28 patients), anterior resection (RRA; 6 patients), Hartman's palliative resection (2 patients) and coloanal anastomosis (CA; 1 patient).

After surgery, all patients were treated on adjuvant setting at the Institute of Oncology in Ljubljana, Slovenia, following the protocol outlined below and approved by the Protocol Review Board and Committee for Medical Ethics at the Institute of Oncology. All patients were informed about the study protocol.

At the enrolment, baseline data (history, physical and laboratory tests) were collected in all patients, including complete blood cell count, reticulocyte count, levels of serum iron, folate and vitamin B12, transferin saturation (TSAT) and ferritin.

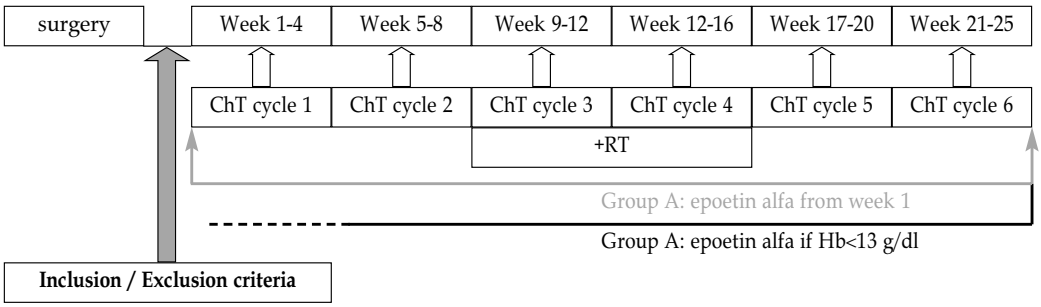
On the basis of Hb concentration, the patients were divided into two groups. Group A consisted of 39 patients with Hb level ≤13 g/dl at the start of the ChT/RT, and group B of 17 patients with Hb level >13 g/dl at the start of the ChT/RT following surgery, but whose Hb fell below 13 g/dl during the ChT/RT.

*Chemo-radiotherapy protocol*

The patients were treated following the combined ChT/RT protocol as shown in Figure 1. During 25 weeks, the patients received 6 cycles of chemotherapy with 5-fluorouracil (5-FU), 425 mg/m$^2$/day intravenously (iv), and Ca-folinat, 50 mg/day iv both during the days 1-5. Because of concomitant irradiation during the 4th cycle of ChT, the doses of 5-FU and Ca-folinat were reduced to 75% level for this cycle only. The cycles were repeated every 28 days. The patients were irradiated with 10-15 MV linear accelerator photon beams to a tumor dose of 50.4 Gy and daily fractions of 1.8 Gy, applied five-times/week.

*Epoetin alfa administration protocol*

In group A, the treatment with epoetin alfa started on day 1 of ChT/RT, whereas in group B, epoetin alfa was administered during the course of ChT/RT when a patient's Hb concentration decreased below 13 g/dl. The starting dose of epoetin alfa was 10,000 IU subcutaneously (sc) three times a week (tiw). Hb concentration was monitored regularly at monthly intervals during chemotherapy and weekly during ChT/RT. If the Hb concentration increased by less than 1 g/dl from the baseline after 4 weeks of initiating epoetin alfa, the dose of the drug was increased to 20,000 IU sc tiw. In case of the increase of Hb concentration by more than 2 g/dl per month, the dose of epoetin alfa was reduced to 10.000 IU biw.




ChT cycle: Chemotherapy cycle; RT: Radiotherapy

**Figure 1.** Protocol of the study

The administration of epoetin alfa was interrupted when Hb concentration increased above 14 g/dl and was initiated again when it fell below 12 g/dl at a dose of 10.000 IU twice a week (biw).

The application of epoetin alfa was abolished if the treatment with epoetin alfa was not effective (no expected rise in Hb level after dose escalation) or in cases of developing a severe adverse reaction related to epoetin alfa.[29]

All patients included in the study would be transfused if Hb concentration was <10 g/dl.

*Iron treatment, transfusion requirements and concomitant therapy*

The patient's iron status, including transferrin saturation-TSAT (serum iron/iron binding capacity x 100; %) and serum ferritin (μg/L) was evaluated on weekly basis during ChT/RT, and on monthly basis during ChT. To avoid iron depletion of available stores and to support adequately erythropoiesis, stimulated by epoetin alfa, the patients with TSAT <20% and/or serum ferritin <100 μg/L required supplemental iron (300 mg elemental iron orally per day).

*Follow up*

In the postoperative phase, the patients were followed on weekly basis for a total of 25 weeks. Safety evaluations were carried out by clinical laboratory tests and by assessing the incidence and severity of treatment-related side effects.

*Statistical analysis*

The following parameters were evaluated: (1) change in Hb concentration relative to the baseline as measured at 4-week intervals, (2) blood transfusion requirements in relation to Hb level, and (3) incidence and severity of adverse events and their potential relationship to epoetin alfa administration. Hb concentration was presented as mean ± standard deviation (SD). Statistical analysis was performed using the two-sided paired t-test. A probability value of <0.05 was considered statistically significant.

## Results

The study protocol was completed in fifty-six of sixty patients (56/60; 93.3%). The remaining four patients (4/60; 6.7%) included in the study were not included in statistical evaluations due to insufficient data. Forty-five of fifty-six patients (45/56; 80.3%) completed all six cycles of chemotherapy and radiation therapy as specified in the protocol. Eleven patients (11/56; 19.7%) received less than six cycles of ChT (5 cycles- 3 patients; 4 cycles- 5 patients; 2 cycles- 3 patients) due to the appearance of adverse events (ileus, dehydration, nausea, leucopoenia, febrile neutropoenia, infection, cardial decompensation, radioproctitis, mucositis).

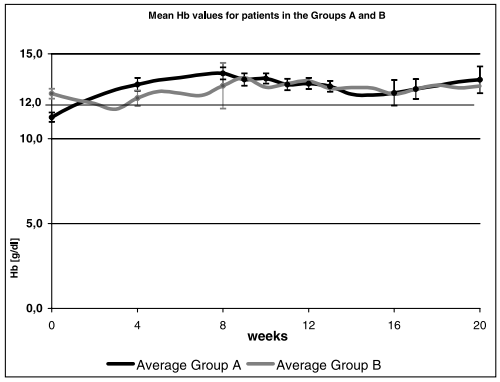



**Figure 2.** Mean hemoglobin (Hb) concentrations in the patients treated with epoetin alfa in groups A and B. In group A, Hb levels were statistically increased from the enrolment in the study onwards. In group B, an initial decrease in Hb concentrations (weeks 0 through 3) was observed. After the initiation of the treatment with epoetin alfa, mean Hb concentrations in group B also reached the level of 12 g/dl till the end of the treatment.

*Hematological response*

In group A, a statistically significant increase in Hb concentration ($p<0.001$) was observed after the first 4 weeks of epoetin alfa treatment compared to the baseline values, with the mean increase of Hb concentration of 1.97 g/dl ± 0.91 g/dl. As shown in Figure 2, Hb concentrations remained significantly increased from the initial values through the rest of the treatment ($p=0.0017$). In group B, a continuous decrease in Hb concentrations was observed during the first weeks of the therapy, reaching the level of statistical significance after 3 weeks of postoperative treatment, ($p=0.006$). After the initiation of epoetin alfa treatment, an increase of Hb concentrations (on average 0.7 g/dl ± 0.4 g/dl/4 weeks) and their maintenance at ≥12 g/dl were observed (Figure 2).

Figure 3 illustrates the frequency of Hb readings <13 g/dl in the patients from group A compared with those from group B during RT part of the protocol. In group A, a progressively smaller share of patients with Hb values <13 g/dl was registered during RT. None of the patients had Hb concentrations <13 g/dl at the 6th week of the irradiation. On the other hand, in group B, the share of patients with Hb concentrations <13 g/dl progressively increased during RT. In this subgroup, epoetin alfa was typically initiated during the 3rd week of RT.

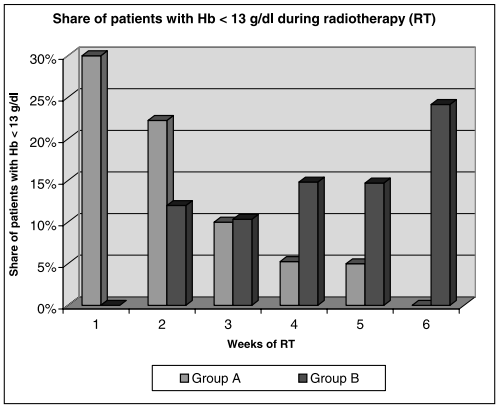



**Figure 3.** Prevalence of patients with hemoglobin (Hb) concentration <13 g/dl during the RT part of the protocol. In group A, a progressively smaller share of patients with Hb concentrations <13 g/dl during RT was observed and with none of the patients with Hb values 13 g/dl at the end of RT. In group B, the share of patients with Hb concentration <13 g/dl progressively increased during RT.

*Transfusion requirements*

Not a single patient enrolled in the study needed transfusion.

*Safety and tolerability of epoetin alfa*

Nine adverse events that occurred in 6 patients who completed the study were recorded: ileus, dehydration, nausea, leucopoenia, febrile neutropoenia, infection, cardial decompensation, radioproctitis, and mucositis. None of the described adverse events was connected to the epoetin alfa treatment.

## Discussion

In the present study, we tested the efficacy and feasibility of epoetin alfa administration in the patients receiving chemo-radiotherapy after surgery for rectal cancer. Our results demonstrate that, also in the patients with this type of cancer, epoetin alfa effectively increases and maintains Hb concentration during ChT/RT at the clinically requested level. None of the patients enrolled in our study required transfusion despite the aggressiveness of the treatment protocol.

The results of our study corroborate the findings of randomized controlled trials with epoetin alfa in the treatment of anemia in other solid and hematological malignancies. These studies have consistently shown an increase in Hb concentrations, a decrease in transfusion requirements, and an improvement in patient's energy level, their ability to maintain daily activities, and their overall quality of life.[1,4,7,13-19,21-24]

Our results also confirmed an excellent safety profile of epoetin alfa. Although

thrombotic/vascular events and hypertension have been reported previously in the patients treated with epoetin alfa,[27] no such events were observed in our population of patients.

Recent studies on ovarian and lung cancer patients receiving cisplatin-based chemotherapy have demonstrated that higher Hb concentrations exerted a positive effect on patient's tolerability of chemotherapy.[30-32] The patients with low Hb-concentrations due to either the disease itself or myelotoxicity of chemotherapy had a lower capacity to compensate for treatment toxicity.[30]

In addition, our results indicate that the epoetin alfa treatment is particularly beneficial in combined treatment protocols. The major challenge remains how to identify the patients who would most likely develop anemia during the combined therapy and who are candidates for prophylactic epoetin alfa treatment. The benefits of epoetin alfa prophylaxis in the context of current clinical guidelines, which recommend starting with epoetin therapy at the Hb concentration range of 10-11 g/dl,[33,34] are yet to be defined.

Anemia is a major cause of fatigue which is clinically manifested in 40-80% of patients with malignancies[15,20,35-37] and usually critically influences the quality of their lives. Indeed, fatigue is at least as common among the most reported bothersome symptoms in the patients with cancer as the pain is.[13,15,17] On the other hand, many authors have reported that the problem of cancer-related fatigue is frequently not assessed adequately because it is not mentioned by patients, assessed by physicians, or not addressed to as an integral part of the treatment evaluation protocols.[38] Obviously, it is of critical importance to identify the fatigue in each individual patient and to offer him appropriate therapeutic option to alleviate it.

Hypoxia in the tumor has been recognized as a key regulator of tumor growth. Sustained hypoxic environment in a growing tumor may trigger changes that can result in a more aggressive phenotype of tumor cells.[39-41] Many studies have demonstrated a reduced probability of local control and worse survival results in the patients with hypoxic tumors, treated with ChT and/or RT.[42] In case of RT, the reduction in radiosensitivity of tumor cells should be seriously considered when the oxygen partial pressure in a tumor decreases below 25-30 mmHg. In general, a two- to threefold higher radiation dose is required to kill completely the hypoxic cells, compared with well-oxygenated cells, a difference referred to as the oxygen enhancement effect.[43] The increase in Hb concentrations, which improves the oxygen-carrying capacity of blood, is also correlated with better response to chemotherapy.[44]

To conclude, the results of the present study show that epoetin alfa is safe and effective in maintaining Hb concentrations during the adjuvant therapy of rectal cancer patients. It significantly increases Hb concentrations and reduces transfusion requirements in the patients receiving chemoradiotherapy after surgery for rectal cancer.

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*case report*

# Metastatic thymoma: a case report of an isolated, intra-abdominal metastasis causing asymptomatic spinal cord compression

**Douglas G. Gold, Robert C. Miller**

*Division of Radiation Oncology, Mayo Clinic, Rochester, Minnesota, USA*

***Background.*** *Although thymomas are characterized histologically by a benign appearance, they have the potential for aggressive local invasion, and occasionally they metastasize.*

***Case report.*** *We describe a 47-year-old woman who recently presented to our clinic with asymptomatic spinal cord compression due to an intra-abdominal metastasis of a thymoma arising as the first site of metastasis 21 years after the primary tumour was resected.*

***Conclusions.*** *For the patient presented here, radiotherapy and surgery were chosen over systemic therapy as the primary treatment modalities at the time of recurrence for two reasons. First, the patient had a single, isolated metastasis that occurred after a 2-decade disease-free interval; thus, preoperative radiotherapy followed by resection was potentially curative. Second, it was thought, on the basis of the retroperitoneal location of the recurrent tumour immediately below the diaphragm, that it possibly was not a haematogenously disseminated metastasis but a local pleural and lymphatic migration.*

*Key words: thymoma; neoplasm metastasis – radiotherapy; spinal cord compression*

## Introduction

Thymomas are unusual tumours that typically arise in the anterior mediastinum and are derived from thymic epithelial cells. Although the tumours are characterized histologically by a benign appearance, they have the potential for aggressive local invasion, and occasionally they metastasize.[1] A 47-year-old woman recently presented to our clinic with asymptomatic spinal cord compression due to an intra-abdominal metastasis of a thymoma arising as the first site of metastasis 21 years after the primary tumour was resected.

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Correspondence to: Robert C. Miller, MD, MSc, Division of Radiation Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; E-mail: miller.robert@mayo.edu



## Case report

In March 1983, when the patient was 25 years old, invasive thymoma of the anterior mediastinum was diagnosed. At her most recent evaluation in 2004, only partial records were available about the evaluation and treatment in 1983. However, according to the existing

medical records, the primary tumour, which involved the anterior mediastinum, had been resected piecemeal. She was referred for postoperative external beam radiotherapy because of concern about residual tumour within the operative bed. A total radiation dose of 39.6 Gy in 22 fractions was administered to the mediastinum using opposed photon beams delivered by a 10-MV linear accelerator. A boost was delivered to a smaller volume within the mediastinum for a total dose in that area of 54.0 Gy in 30 fractions. The maximum spinal cord dose was 40.2 Gy.

The patient tolerated radiotherapy well and had no evidence of recurrence or treatment toxicity for more than 20 years. In March 2003, she noted a lower abdominal mass after a year of menorrhagia and sought medical evaluation. She subsequently underwent simple hysterectomy. At the time of hysterectomy, an omental mass, 18×12×9 cm, was resected along with the uterus. Pathologic evaluation of the uterus demonstrated a subserosal, 0.5-cm leiomyoma; no other abnormality was noted. The omental mass was found to be an inflammatory myofibroblastic tumour. Immunohistochemical staining of the omental mass for anaplastic lymphoma kinase and smooth muscle actin was negative.

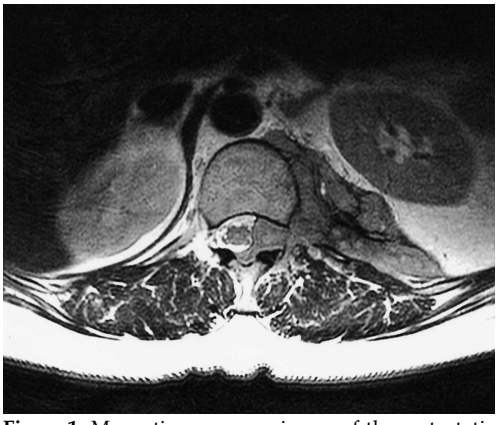

**Figure 1.** Magnetic resonance image of the metastatic lesion at the level of vertebral body T12 before radiotherapy. Note the proximity of left kidney to the mass and the relation of the mass to the spinal cord.

Progressive left hip pain developed in early 2003. This worsened in 2004, and in October 2004, magnetic resonance imaging (MRI) showed an epidural mass that extended from vertebral body T11 to L1, with compression of the left lateral thecal sac. A left paraspinal mass was also present, extending from the T11-12 interspace to L2. The two lesions were connected at the T12-L1 neural foramen. There were no abnormalities of the vertebral bodies. The intimate relation between the tumour and spinal cord is shown in Figure 1. Subsequent computed tomography (CT) of the chest, abdomen, and pelvis did not show abnormalities of concern other than a soft tissue mass arising in the left retroperitoneum near the origin of the left psoas muscle and contiguous with an epidural mass extending through the left T12 neural foramen. No bony destruction was apparent. The state of the tumour before radiotherapy is shown in Figure 2a. No evidence of local recurrence or new primary tumour was detected in the thorax. A nuclear bone scan did not show any abnormality. An incidental MRI finding was an incompletely imaged T2 hyperintense thyroid nodule, 1.8×2.2×2.7 cm.

A CT-guided needle biopsy was performed in October 2004 at an outside institution and repeated at a different site within the tumour at Mayo Clinic in early November 2004. Both biopsy specimens revealed metastatic thymoma. Immunohistochemical stains showed that the tumour contained a mixture of cytokeratin-positive epithelial cells and CD3-positive T cells. CD20 staining showed only a few reactive lymphocytes. Staining for S100 protein was negative. This staining pattern was thought to be consistent with the diagnosis of metastatic thymoma, presumably related to the tumour resected from the chest in 1983. The original pathology slides from 1983 were not available for comparison with the metastatic lesion found in 2004. The omental tumour identified in 2003 was compared with the new lesion and the two tumours were his-

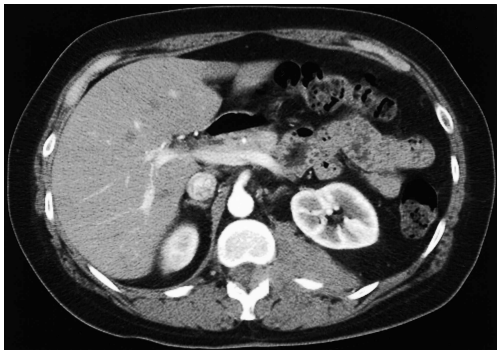

**Figure 2a.** Computed tomographic images showing the paraspinal mass before radiotherapy.

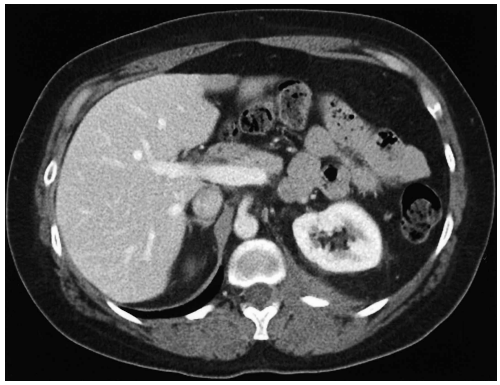

**Figure 2b.** Computed tomographic images showing the paraspinal mass approximately 4 weeks after radiotherapy.

tologically different. A biopsy specimen from the thyroid lesion demonstrated a benign thyroid nodule.

The patient was in excellent health, with no major symptoms other than occasional mild left hip pain. Her past medical history was unremarkable. A detailed neurologic evaluation did not document a clinical myelopathy. No other neurologic deficits were present except for minimal loss of sensation over the left iliac crest in the region where she was experiencing pain.

Optimal surgical management of the recurrent thymoma would entail an en bloc resection. However, because of the location of the tumour, its apparent adherence to the spinal cord, and its local invasion of surrounding bony and muscular structures, the patient was referred for preoperative radiotherapy. After a medical oncology evaluation, it was thought that chemotherapy was not indicated at that time.

The patient received 50.4 Gy in 28 fractions of external beam radiation delivered with intensity-modulated radiotherapy. The gross target volume was determined from the patient's MRI, which was fused with a treatment-planning CT scan. The clinical target volume was considered the gross tumour volume as demonstrated on MRI plus areas where bone invasion was suspected on the basis of the CT scan. The patient's previous radiotherapy fields were reconstructed to ensure no overlap between those fields and the current treatment. The patient was carefully counselled about the potential risk of myelopathy from overlap of the two radiotherapy treatments. Intensity-modulated planning priorities were assigned to minimize the dose to the kidneys, followed by the small intestine (Figure 3). The spinal cord was not avoided because of the proximity of the tumour to the cord as well as the convex shape of the tumour, which surrounded one-half of the circumference of the spinal cord in some areas. Ninety-nine percent of the planning

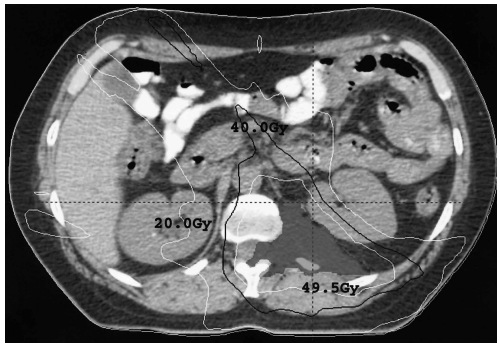


**Figure 3.** Isodose distribution from the intensity-modulated radiotherapy plan showing the gross target volume (shaded structure, which indicates macroscopically evident tumor by fusion of the computed tomographic and magnetic resonance imaging data sets) and the 49.5-Gy, 40-Gy, and 20-Gy isodose lines. (The clinical and planning target volumes have been deleted for clarity.)

target volume, consisting of the clinical target volume plus a 1.0-cm margin, received a dose of 48.5 Gy or greater. The minimal planning target volume dose was 43.2 Gy. The maximal spinal cord dose was 50.9 Gy. Also, 17.6% of the right kidney and 37.3% of the left kidney were treated beyond the normal tissue tolerance limit of 20 Gy.

The patient tolerated the treatment well, without experiencing acute gastrointestinal tract or other toxic effects. Her hip pain resolved during the final weeks of radiotherapy, suggesting an early response to radiotherapy as the left neural foramen at the T12-L1 level was decompressed.

In January 2005, restaging studies were performed preoperatively, including MRI of the thoracic and lumbar spine and CT of the chest and abdomen. MRI demonstrated a marked decrease in the size of the paraspinal mass. CT also showed a decrease in the size of the lesion, with less encroachment on the spinal canal as compared with the imaging studies before radiotherapy (Figure 2b). No evidence of malignant disease was found elsewhere.

In February 2005, laminectomy of T11-L1, posterior instrumented fusion of T5-L4, left thoracotomy with en bloc resection of the paraspinal metastasis, and T11-L1 corpectomies with titanium cage strut grafting were successfully performed. Pathologic evaluation of the resected specimen showed a 5.0×4.0×2.5-cm mass containing extensive fibrosis and metastatic thymoma. All surgical margins were negative for tumour.

## Discussion

The histologic classification of thymomas, which are derived from thymic epithelial cells, has been debated, and several classification systems have been proposed. However, it is generally accepted that the clinical degree of invasion of the tumour, not the presence of benign or malignant histologic features, determines prognosis. This observation led to the formulation of the Masaoka staging system, currently the most commonly used staging system.[2] Masaoka stage I consists of encapsulated tumours. Stage II includes tumours with macroscopic invasion of the surrounding mediastinal tissues or microscopic invasion of the capsule. Stage III includes tumours with macroscopic invasion of nearby organs. Stage IVA includes pleural or pericardial dissemination, and stage IVB includes lymphatic or haematogenously disseminated metastases.[1,2]

Surgical resection is the treatment of choice for most thymomas confined to the thoracic cavity, where the success of surgery and adjuvant therapy depends on the extent of resection and stage of disease.[3] According to one report, the frequency of recurrence for stage I disease may be less than 5% after complete resection, whereas for stages II and III disease, the frequency of recurrence is 7% and 16%, respectively.[4] Postoperative radiotherapy is often administered for stages II and III tumours because of the apparent local control and survival benefit reported in retrospective series.[5-7] Preoperative radiotherapy has been used for stage III disease to facilitate total or subtotal resection.[8] Our current practice is to consider adjuvant radiotherapy for resected Masaoka stage II tumours that penetrate the capsule and for resected stage III tumours. However the decision depends on several factors, including the potential sites of tumour adherence or invasion, surgical expertise and technique, and the patient's underlying medical condition.

Thymomas typically spread by direct invasion of nearby organs. Metastases may occur in the thorax as pulmonary nodules, pleural-based implants, diaphragmatic masses, or malignant pericardial or pleural effusions. Extrathoracic metastases are rare but may involve the kidney, bone, liver, and brain. Disease may spread directly from the thorax

to the abdomen or retroperitoneum, as has been documented for mesotheliomas.[1,3,4,9]

Chemotherapy may be considered for unresectable and metastatic thymomas. Single-agent chemotherapy, with various agents, has been studied, with ifosfamide appearing to be a promising agent. Multiagent chemotherapy regimens, with combinations of cisplatin, doxorubicin, cyclophosphamide, and vincristine, have produced response rates in excess of 50%. Chemotherapy has also been given neoadjuvantly as part of combined modality therapy involving surgery and radiotherapy.[10-13]

For the patient presented here, radiotherapy and surgery were chosen over systemic therapy as the primary treatment modalities at the time of recurrence for two reasons. First, the patient had a single, isolated metastasis that occurred after a 2-decade disease-free interval; thus, preoperative radiotherapy followed by resection was potentially curative, whereas systemic therapy would not offer the possibility for a durable cure. Second, it was thought, on the basis of the retroperitoneal location of the recurrent tumour immediately below the diaphragm, that it possibly was not a haematogenously disseminated metastasis. It was hypothesized that the spread of the tumour from the mediastinum to the retroperitoneum occurred through very slow-growing microscopic tumour deposited in the pleural space before or at the time of surgery in 1983. These microscopic tumour cells eventually migrated through lymphatic channels across the diaphragm, in a manner similar to that described for mesotheliomas. The absence of other identifiable sites of distant metastatic disease lends support to this hypothesis. However, even if the underlying method of spread in this case was from an isolated, blood-borne metastasis rather than through local pleural and lymphatic migration, the treatment strategy would have been the same because of the very long disease-free interval between the initial diagnosis and the development of the metastasis.

Postoperatively, this patient did well. Adjuvant systemic therapy will not be administered because of the absence of known residual malignant disease. Close observation with serial history and physical examinations and periodic CT of the chest and abdomen are planned for follow-up.

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# Rapid detection of most frequent Slovenian germ-line mutations in BRCA1 gene using real-time PCR and melting curve analysis

**Srdjan Novaković and Vida Stegel**

*Unit of Molecular Biology, Institute of Oncology Ljubljana, Slovenia*

***Background.*** *Detection of inherited mutations in cancer susceptibility genes is of great importance in some types of cancers including the colorectal cancer (mutations of APC gene in familial adenomatous polyposis - FAP, mutations in mismatch repair genes in hereditary nonpolyposis colorectal cancer – HNPCC), malignant melanoma (mutations in CDKN2A and CDK4 genes) and breast cancer (mutations in BRCA1 and BRCA2 genes).*

***Methods.*** *This article presents the technical data for the detection of five mutations in BRCA1 gene in breast cancer patients and their relatives. The mutations - 1806C>T, 300T>G, 300T>A, 310G>A, 5382insC - were determined by the real-time PCR and the melting curve analysis.*

***Results and conclusion.*** *In comparison to direct sequencing, this method proved to be sensitive and rapid enough for the routine daily determination of mutations in DNA isolated from the peripheral blood.*

*Key words: breast neoplasms – genetics; genes, BRCA1; mutation; polymerase chain reaction*

## Introduction

General screening for unknown mutations in the large genes such as *BRCA1* and *BRCA2* is time consuming and expensive. There is a whole range of procedures that should be performed prior to the final confirmation of the mutation. Habitually, the screening is started by using the methods that provide information about the region of the gene where the mutation is positioned (e.g. protein truncation test - PTT, single-strand conformational polymorphism analysis - SSCP, denaturing gradient gel electrophoresis - DGGE).[1-3] Direct sequencing and determination of specific changes in the nucleotide sequence aims at the final confirmation and identification of mutation.

Yet, when the mutation is well determined and precisely described, then the detection can be performed in a less complicated and less expensive manner. One group of these methods comprises the analysis based on the determination of differences in the melting

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Correspondence to: Srdjan Novaković, PhD, Unit of Molecular Biology, Institute of Oncology, Zaloška 2, 1000 Ljubljana, Slovenia. Tel. + 386 1 522 5118; Fax: +386 1 433 74 10; E-mail: snovakovic@onko-i.si

temperatures of perfectly matched base pairs and mutated variants.[4-6] This article reports the determination of known *BRCA1* mutations - 1806C>T, 300T>G, 300T>A, 310G>A, 5382insC using the real time PCR on Light Cycler and melting curve analysis. The system is programmed to monitor the melting curve analysis of the allele specific fluorescent resonance energy transfer - FRET probes after the PCR, allowing direct typing of the sample without any further processing.

## Methods

DNA was isolated from the peripheral blood using the DNA blood isolation kit (Quiagen, Hilden, Germany). The primers and probe sets for the detection of specific mutations were designed in our laboratory applying the Light Cycler Probe Design Software, Version 1.0, and synthesized by TIB Molbiol (Berlin, Germany).

The real-time PCR and melting curve analysis at the Light Cycler instrument (Roche Molecular Biochemicals, Mannheim, Germany) was applied for the detection of mutations. PCR was performed according to the manufacturer's instructions (Light Cycler Fast Start master hybridization probes, Roche Molecular Biochemicals). Briefly, the DNA templates were selectively amplified in the PCR reaction (annealing temperature 52°C, 45 cycles) using specific primers described in Table 1. Beside specific primers, the specific hybridization probes conjugated with LC Red640 (Light Cycler Red 640 fluorescent dye) were added to the mastermix. At the end of PCR reaction, the melting curve analysis was performed through heating the mix to 95°C for 1 min followed by cooling in steps (58°C, 48°C, 40°C, 35°C) to 35°C and repeated gradual heating to 85°C. The data were collected during the gradual heating phase (35°C - 85°C).

## Results and discussion

Several cancers appear to be related to *BRCA1* and *BRCA2* mutations including breast, ovarian, pancreatic, prostate, fallopian tube, la-

**Table 1.** The primers and probes used for the detection of mutations in *BRCA1* gene.

| Mutation | Primer and probe names | Type and length of nucleotide sequence* |
|---|---|---|
| 1806C>T | *BRCA1* F | primer – forward (23bp) |
| | *BRCA1* A | primer - reverse (24bp) |
| | Senzor | probe - senzor–FL (30bp) |
| | Anchor | probe - LC Red640-anchor–PH (34bp) |
| 300T>G | *BRCA1*in4 F | primer - forward (22bp) |
| 300T>A | *BRCA1*in5 B | primer - reverse (20bp) |
| | C61G Sen G | probe - senzor–FL (23bp) |
| | C61G Anch | probe - LC Red640-anchor–PH (32bp) |
| 310G>A | *BRCA1*in4 F | primer - forward (22bp) |
| | *BRCA1*in5 B | primer - reverse (20bp) |
| | C64Y Sen G | probe - senzor–FL (29bp) |
| | C64Y Anch | probe - LC Red640-anchor–PH (30bp) |
| 5382insC | *BRCA1*in19 F | primer - forward (21bp) |
| | *BRCA1*in21 S | primer - reverse (22bp) |
| | 5382insC Sen | probe - senzor–FL (22bp) |
| | Ex20 Anchor | probe - LC Red640-anchor–PH (28bp) |

*the sequences of primers and probes are available through E-mail of corresponding author
LC - Light Cycler Red 640 fluorescent dye, FL - Fluorescein, PH – phosphate

ryngeal cancer, as well as adult leukemias and lymphomas.[7] However, women with germ-line heterozygous mutations in *BRCA1* or *BRCA2* are primarily at increased risk of developing breast or/and ovarian cancer. The mutations in *BRCA1* and *BRCA2* predict the likelihood of breast cancer development by the age of 70 years of 45% to 87% and 26% to 84%, respectively. The odds of ovarian cancer for *BRCA1* and *BRCA2* mutation carriers are 16% to 63% and 10% to 27%, respectively.[8] Even though the breast and ovarian cancers related to inherited mutations in cancer susceptibility genes represent a small proportion of all cancers (less than 10%), it is of great importance for the clinician to detect the patients who are carrying these mutations. Consequently, the determination of potential risk among the family members of the mutation carrier can be estimated and prevention measures can be undertaken. The criteria for the genetic testing of patients and relatives are based on the most common risk factors in hereditary cancer syndromes – early age cancer onset, presence of the same cancer in multiple relatives, occurrence of multiple primary cancers in one individual, development of an unusual type of cancer (e.g. breast cancer in male), being a member of a specific ethnicity.[9,10] Considering the facts, that Slovenian population is ethnically relatively closed and that the breast cancer in Slovenia is the most common cancer type affecting women, we started, at the Institute of Oncology Ljubljana in 2001, with genetic counseling and testing of individuals from families with multiple histories of breast and ovarian cancer.

Laboratory of Medical Genetics - Vrije University Brussels, provided general mutation screening of *BRCA1* and *BRCA2* genes for Slovenian patients. From these results, it was evident that the most frequent mutations in hereditary breast (and ovarian) cancer were the Slovenian founder mutations IVS162A>G in *BRCA2* and 1806C>T, 300T>G, 300T>A, 310G>A, 5382insC in *BRCA1* gene. Almost 80% (precisely 77%) of all determined mutations in Slovenian patients were covered by this mutation profile. With the purpose of simplifying the detection of mutations in *BRCA1* gene, we applied the real-time PCR followed by melting curve analysis using hybridization probes. The primers and probes were designed on the sequences of *BRCA1* gene covering the reported mutations - 1806C>T, 300T>G, 300T>A, 310G>A, 5382insC. For each type of mutation, the optimal conditions were settled and the positive inner control was used.

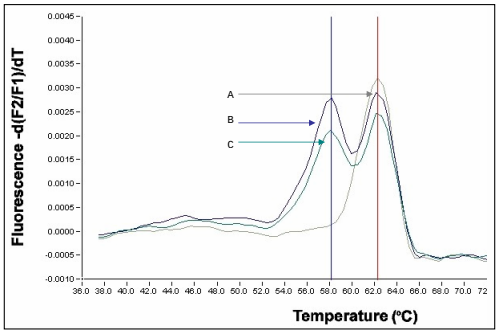


**Figure 1.** Detection of 1806C>T mutation in *BRCA1* gene by real-time PCR and melting curve analysis. DNA was isolated from the blood of a normal person and of a carrier of mutation. A - normal DNA (wild-type); B - positive control (mutant DNA); C - patient's DNA; wild type peak at 62°C; mutant peak at 58°C.

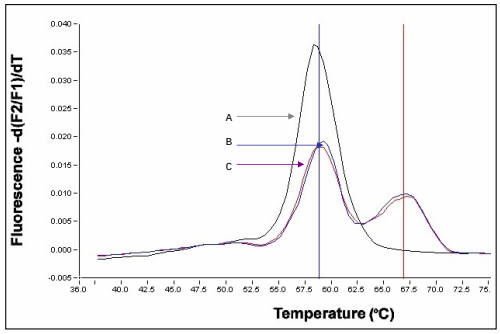


**Figure 2.** Detection of 300T>G mutation in *BRCA1* gene by real-time PCR and melting curve analysis. DNA was isolated from the blood of a normal person and of a carrier of mutation. A - normal DNA (wild-type); B - positive control (mutant DNA); C - patient's DNA; wild type peak at 58.5°C; mutant peak at 67°C.

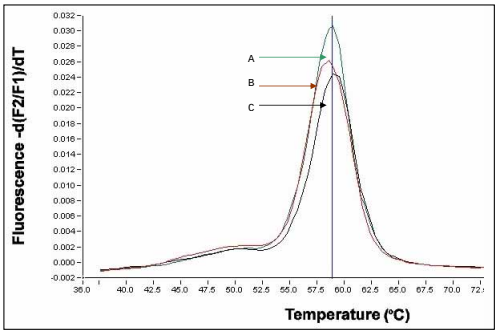


**Figure 3.** Detection of 300T>A mutation in *BRCA1* gene by real-time PCR and melting curve analysis. DNA was isolated from the blood of a normal person and of a carrier of mutation. A - normal DNA (wild-type); B - positive control (mutant DNA); C - patient's DNA; wild type peak at 58°C. Heterozygous mutant product for 300T>A mutation did not show any additional peaks.

The homozygous (wild-type) PCR product designed for the detection of 1806C>T on *BRCA1* gene showed a single peak at 62°C, whereas the heterozygous products (mutant) showed an additional peak at 58°C (Figure 1).

The homozygous (wild type) PCR product designed for the detection of 300T>G on *BRCA1* gene showed a single peak at 58.5°C, whereas the heterozygous products (mutant) showed an additional peak at 67°C (Figure 2). Unfortunately, the heterozygous product for 300T>A mutation did not show any additional peaks, thus making the mutation undetectable by this method (Figure 3). The reason for that was a too small difference (less than 2°C) between the melting temperatures of the wild type and mutated DNA sequence.

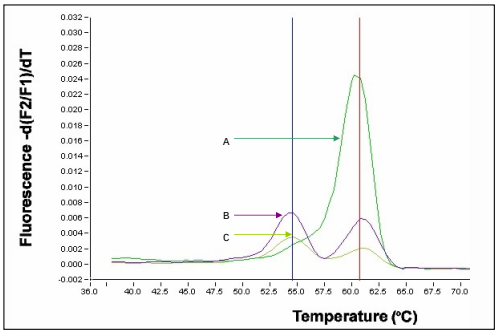


**Figure 5.** Detection of 5386insC on *BRCA1* gene by real-time PCR and melting curve analysis. DNA was isolated from the blood of a normal person and of a carrier of mutation. A - normal DNA (wild-type); B - positive control (mutant DNA); C - patient's DNA; wild type peak at 62.5°C; mutant peak at 67.5°C.

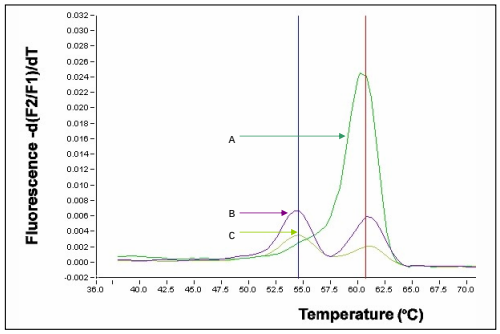


**Figure 4.** Detection of 310G>A on *BRCA1* gene by real-time PCR and melting curve analysis. DNA was isolated from the blood of a normal person and of a carrier of mutation. A - normal DNA (wild-type); B - positive control (mutant DNA); C - patient's DNA; wild type peak at 60.5°C; mutant peak at 54.5°C.

The homozygous (wild type) PCR product designed for the detection of 310G>A on *BRCA1* gene showed a single peak at 60.5°C, whereas the heterozygous products (mutant) showed an additional peak at 54.5°C (Figure 4).

The homozygous (wild type) PCR product designed for the detection of 5386insC on *BRCA1* gene showed a single peak at 62.5°C, whereas the heterozygous products (mutant) showed an additional peak at 67.5°C (Figure 5).

The majority of mutations detected with the real-time PCR and melting curve analysis were further subjected to direct sequencing. The number of tested individuals and of mutation positive individuals is listed in Table 2. An absolute correlation between the direct sequencing and the real-time PCR and melting curve analysis was obtained – the real-time PCR and melting curve analysis actually gave no false positive outcomes. The patient's DNA that was negative for mutations by real-time PCR and melting curve analysis was not subjected to sequencing in all cases, which precludes any conclusions concerning the false negative results of the method.

**Table 2.** Mutations in Slovenian patients detected by real-time PCR and melting curve analysis.

| Type of mutation | Number of tested patients | Number of detected mutations | No. LC positive/No. direct sequencing positive* |
|---|---|---|---|
| 1806C>T | 87+90 | 12 | 10/10 |
| 300 T>G | 5 | 2 | 2/2 |
| 300T>A | 5 | 0 | 0/2 |
| 310G>A | 2 | 1 | 1/1 |
| 5382insC | 3 | 2 | 2/2 |

* number of positive samples detected by real-time PCR and melting curve analysis using Light Cycler (LC)/number of samples confirmed to be positive by direct sequencing

However, positive misleading results may be obtained because of unknown polymorphisms or a mutation within the target region affecting hybridization of probes and binding of primers, and consequently, the melting temperature of the product. It should also be mentioned that careful optimization of the reaction for each mutation is necessary before the analysis of the patients' DNA samples is performed in order to achieve an optimal sensitivity and specificity for the method. Especially important is to bear in mind that not only the physical features during the reaction, but also the nucleotide structure in the dimmer (e.g. higher melting temperature of the fragments that have higher percentage of GC) and the length of the dimmer fragment (the melting temperature of longer fragments is higher) affect the melting temperature. In this study, the PCR was optimized in respect to annealing temperature, concentration of Mg2+, and number of polymerization cycles; the reaction during the melting curve analysis was optimized in respect to the time and temperature differences in the intervals of cooling and heating steps.

In view of the present results, it could be concluded that the primers and probes for the detection of 1806C>T, 300T>G, 310G>A and 5382insC mutations in *BRCA1* gene were designed successfully. After the optimization, the real-time PCR and melting curve analysis using hybridization probes showed out to be an extremely sensitive method for the detection of known mutations. Even though the designed primers and probes were specific for the mutation 300T>A, the method was not sensitive enough for this type of mutation. However, for the final conclusions about the sensitivity and specificity of the method, a larger number of samples should be included. Prior to this, possible false negative and positive results should be taken in consideration.

## Acknowledgment

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# Cytogenetic analysis of peripheral blood lymphocytes after arteriography (exposure to x-rays and contrast medium)

**Ljubomira Popova[1], Valeria Hadjidekova[1], Georgy Karadjov[1], Savina Agova[2], Danail Traskov[3], Vassil Hadjidekov[4]**

*[1]National Center of Radiobiology and Radiation Protection, Sofia 1756, Bulgaria*
*[2]Department of Medical Genetics, Medical University, Sofia 1431, Bulgaria*
*[3]Coordinated Science Laboratory, University of Illinois, IL 61801, USA*
*[4]University Hospital Alexandrovska, Department of Radiology, Sofia 1431, Bulgaria*

***Backgrounds.*** *The purpose of our study is to investigate the cytogenetic analysis findings in peripheral blood lymphocytes of 29 patients who had undergone diagnostic radiography.*
***Methods.*** *Peripheral blood samples were taken from 22 patients submitted to renal arteriography and 7 patients submitted to cerebral arteriography (17 male and 12 female, aged between 13-68 years). Cytogenetic analyses of peripheral lymphocytes were performed before the procedure, immediately after and 24 hours later. The entrance skin dose obtained during the whole diagnostic X-ray exposure was measured by thermoluminescent dosimeters and varied between 0.03-0.30 Gy. Both low and high osmolarity contrast media were used. Chromosomal aberrations and micronuclei frequency were used as biomarkers of genotoxicity.*
***Results.*** *The estimated frequency of chromosomal aberrations and micronuclei in the peripheral blood lymphocytes of patients after arteriography examination was significantly higher than the level before the diagnostic exposure. The mean frequency of cells with chromosomal aberrations was nearly double after examination and proved to be constant in the analysis after 24 hours.*
***Conclusions.*** *Radiological diagnostic procedures involving iodinated contrast media as arteriography may cause a significant increase in cytogenetic damage in peripheral blood lymphocytes.*

*Key words: angiography – adverse effects; lymphocytes; chromosome aberrations; micronucleus tests*

## Introduction

Iodinated contrast media are largely needed in diagnostic radiology. In angiography and interventional radiology, especially high diagnostic doses are obtained - relatively long fluoroscopy time plus serial radiography (several frames per second). Cytogenetic analysis findings of diagnostic doses of ×-rays and contrast media were investigated in experimental studies on cell cultures *in vitro*.[1,2] Parallel clinical investigations showed an increased genotoxicity in the peripheral blood lymphocytes of the patients undergoing angiography.[2-4] The results indicate that some contrast media can

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Correspondence to: Vassil Hadjidekov, MD, PhD, University Hospital Alexandrovska, Department of Radiology, Sofia 1431, Bulgaria; Phone: +359 888940801; E-mail: hadjidekov@yahoo.com

induce genotoxic effects alone, and when applied in combination with X-rays, can increase, even double the radiation induced genetic damage. Radiological contrast media do not only increase the absorbed dose, but may also enhance the sensitivity of blood cells to the radiation induced cell damage.[2-4]

Cytogenetic analysis results are of great concern as they are involved in the mechanism of cancer genesis. It is generally accepted that chromosomal mutations are causal events in the development of neoplasia and it has been postulated that an increased cytogenetic damage may be an indication of an enhanced cancer risk.[5]

The aim of the present study is to investigate the effects of contrast media and diagnostic radiation on cytogenesis of the peripheral blood lymphocytes of the patients undergoing arteriography. Chromosomal aberrations (CA) and micronuclei (MN) in the peripheral blood lymphocytes are used as cytogenetic biomarkers.

## Methods

### *Subjects investigated*

Twenty-nine patients with limited history of previous medical radiation exposures and undergoing angiography examination [22 renal arteriographies (RAr) and 7 cerebral arteriographies (CAr)] were selected for this study. In the selected group of patients, 17 were males and 12 females, ranging in age from 13 to 68 years (average age 41.6 years).

A Philips Medical Systems angiographic equipment »PolyDiagnost C« was used with DSI viewing console and Easy Vision workstation. The unit was operated at 60 - 90 kV range and up to 250 mA with a filtration of 2 mm Al.

Blood samples were collected in sterile vacationers with Li-heparin. Three samples were taken: (1) before angiographic run, (2) immediately after, and (3) 24 hours after the examination. The radiation exposure assessment was made by thermoluminescent dosimeters. The radiation exposure varied from 0.03 to 0.30 Gy (Table 1) and was estimated as skin entrance dose. The type and the volume of contrast material used are given in Table 1. For all subjects, a questionnaire was completed to assess their general physical condition, life style, previous ×-ray examinations, diets, use of medications.

### *Cytogenetic endpoints*

Lymphocyte cultures were prepared in 5 ml RPMI-1640 medium supplemented with 10% fetal calf serum and phytochaemaglutinin P.

For chromosomal aberration analysis, Colchicine 0.5 mkg/ml was added to the cultures 48 hours after incubation. The cells were harvested two hours later.[6] Twenty-eight subjects were analyzed for chromosomal aberrations (CA). The cells scored per sample for structural chromosomal aberrations after staining with 10% Giemsa ranged from 100 to 400.

For cytokinesis blocked micronucleus test, Cytochalasin B was added 44 hours after incubation. The cells were harvested after 72 hours (7). Ten patients were analyzed for the presence of micronuclei (MN) in binucleated lymphocytes immediately before (1) and after (2) radiodiagnostic examination. Two thousand cells per each sample were analyzed.

### *Ethics*

Informed consent was obtained from all investigated subjects after they had received an explanation of the study. The reports were reviewed and approved by the local ethics committee. The volume of the samples (1) and (2) is the blood collected during the air trapping prevention and catheters flushing.

### *Statistical analysis*

Student t- test and $\chi^2$- test was applied before and after arteriography of patients to analyze

statistical significance of the difference between the frequencies of chromosomal aberrations and micronuclei formation, respectively.

## Results

A total of 29 subjects submitted to angiography were investigated cytogenetically. Chromosomal aberrations were analyzed in 28 of them, and in 10 subjects, micronuclei formation in binucleated lymphocytes was investigated (Table 2).

The frequency of chromosomal aberrations was increased in most of the patients immediately after the examination and remained constant at the sampling after 24 hours (Table 2). Dicentric chromosomes, which are the most sensitive indicators of radiation exposure, were found in 7 cases. It must be noted that, despite selection, some of the patients underwent some kind of radiodi-

**Table 1.** Characteristics of the investigated patients undergoing arteriography

| Nº | Case | Age | Sex | Smoker | Type* of examination | Contrast agent (mg J/ml) | Total volume (ml) | Entrance skin dose (Gy) | Ro-exam. in last 1 year | Sampling time** CA | MN |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | GI | 28 | M | yes | CAr | iodixanol 320 | 80 | | Head CT | 1; 2 | 1; 2 |
| 2. | KG | 45 | F | | CAr | iodixanol 320 | 80 | | Head CT | 1; 2 | 1; 2 |
| 3. | DG | 56 | F | no | CAr | iopromide 300 | 50 | | Head CT | 1; 2 | 1; 2 |
| 4. | RF | 44 | F | | RAr | iopromide 370 | 40 | | IVU | 1; 2 | 1; 2 |
| 5. | DS | 39 | M | yes | RAr | iohexol 350 | 40 | | no | 1; 2 | 1; 2 |
| 6. | SM | 49 | M | yes | CAr | iohexol 350 | 50 | | Head CT | 1; 2 | 1; 2 |
| 7. | DK | 36 | M | yes | CAr | iohexol 350 | 50 | | Head CT | 1; 2 | 1; 2 |
| 8. | ED | 64 | F | no | CAr | iohexol 350 | 50 | | Head CT | 1; 2 | |
| 9. | MP | 50 | M | | CAr | iopromide 300 | 80 | | Head CT | 1; 2 | 1; 2 |
| 10. | PD | 35 | M | yes | RAr | diatrizoate 370 | 58 | 0,09 | IVU | 1; 2; 3 | |
| 11. | II | 65 | F | no | RAr | diatrizoate 370 | 52 | 0,08 | Abdominal | CT | 1; 2; 3 |
| 12. | EL | 60 | F | no | RAr | ioxaglate 320 | 50 | 0.20 | IVU | 1; 2; 3 | |
| 13. | PX | 42 | M | | RAr | diatrizoate 370 | 46 | | no | 1; 2; 3 | |
| 14. | HI | 33 | M | no | RAr | diatrizoate 370 | 46 | 0,20 | no | 1; 2; 3 | |
| 15. | SV | 13 | F | no | RAr | diatrizoate 370 | 48 | 0,19 | IVU | 1; 2; 3 | |
| 16. | HS | 17 | F | no | RAr | diatrizoate 370 | 18 | 0,05 | no | 1; 2; 3 | |
| 17. | ML | 33 | F | no | RAr | diatrizoate 370 | 50 | 0,15 | no | 1; 2; 3 | |
| 18. | VI | 18 | M | no | RAr | diatrizoate 370 | 60 | 0.3 | IVU | 1; 2; 3 | |
| 19. | TG | 38 | F | no | RAr | diatrizoate 370 | 40 | 0.03 | no | 1; 3 | |
| 20. | PP | 58 | M | yes | RAr | diatrizoate 370 | 30 | 0.11 | RA | 1; 2; 3 | |
| 21. | AD | 29 | M | no | RAr | diatrizoate 370 | 36 | 0.15 | no | 1; 2; 3 | |
| 22. | VY | 68 | M | no | RAr | iopromide 300 | 50 | 0.19 | no | 1; 2 | 1; 2 |
| 23. | DZ | 46 | M | yes | RAr | diatrizoate 370 | 50 | | no | 1; 2; 3 | |
| 24. | SD | 44 | F | | RAr | diatrizoate 370 | 35 | 0.26 | IVU | 1; 2 | |
| 25. | ID | 21 | M | yes | RAr | diatrizoate 370 | 40 | 0.08 | no | 2; 3 | |
| 26. | ME | 68 | F | | RAr | diatrizoate 370 | 14 | | Abdominal CT; IVU | 1; 2 | |
| 27. | GV | 64 | M | | RAr | diatrizoate 370 | 45 | | | 1; 2 | |
| 28. | HP | 52 | M | | RAr | diatrizoate 370 | 45 | | | 1; 2 | |
| 29. | TZ | 34 | M | no | RAr | iopromide 300 | 50 | 0.03 | no | 1; 2 | |

* CAr - Cerebral arteriography, RAr - Renal arteriography; **1 - before arteriography, 2 - after arteriography, 3 - 24 hours after arteriography

**Table 2.** Frequency of chromosomal aberrations (CA) and micronuclei (MN) in the peripheral blood lymphocyte of the patients undergoing to arteriography

| | | Chromosomal aberrations, % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| № Case | Sampling time* | CA, № scored cells | Cells with CA, % | Chromosome Fragments | Dicentrics | Chromatide Fragments | Total № of CA, % | MN, ? scored cells | Cells with MN, ‰o | Total № of MN,% |
| 1. GI | 1. | 200 | 2 | 1 | 0 | 1 | 2 | 2000 | 16.00 | 19.5 |
| | 2. | 250 | 2,8 | 2,4 | 0 | 0,4 | 2,8 | 2000 | 24.00 | 27.00 |
| 2. KG | 1. | 200 | 1 | 1 | 0 | 0 | 1 | 2000 | 8.00 | 8.00 |
| | 2. | 200 | 1 | 1 | 0 | 0 | 1 | 2000 | 13.00 | 15.00 |
| 3. DG | 1. | 200 | 1 | 0,5 | 0 | 0,5 | 1 | 2000 | 14.50 | 17.00 |
| | 2. | 200 | 0,5 | 0,5 | 0 | 0 | 0,5 | 2000 | 14.00 | 15.50 |
| 4. RF | 1. | 200 | 0.5 | 0 | 0 | 0,5 | 0,5 | 2000 | 7.00 | 7.00 |
| | 2. | 200 | 1 | 1 | 0 | 0 | 1 | 2000 | 9.00 | 9.50 |
| 5. DS | 1. | 200 | 1 | 0 | 0 | 1 | 1 | 2000 | 7.00 | 7.00 |
| | 2. | 200 | 2 | 1,5 | 0 | 0,5 | 2 | 2000 | 5.50 | 6.00 |
| 6. SM | 1. | 200 | 1,5 | 1 | 0 | 0,5 | 1,5 | 2000 | 7.00 | 7.00 |
| | 2. | 200 | 1,5 | 1 | 0 | 0,5 | 1,5 | 2000 | 11.50 | 11.50 |
| 7. DK | 1. | 200 | 1 | 0,5 | 0 | 0,5 | 1 | 2000 | 5.00 | 5.00 |
| | 2. | 200 | 1,5 | 0,5 | 0,5 | 0,5 | 1,5 | 2000 | 8.00 | 10.00 |
| 8. ED | 1. | 200 | 1 | 0 | 0 | 1 | 1 | | | |
| | 2. | 200 | 0,5 | 0 | 0 | 0,5 | 0,5 | | | |
| 9. MP | 1. | 200 | 0,5 | 0 | 0 | 0,5 | 0,5 | 2000 | 7.00 | 7.00 |
| | 2. | 200 | 0,5 | 0,5 | 0 | 0 | 0,5 | 2000 | 10.00 | 11.5 |
| 10. PD | 1. | 200 | 4.5 | 3 | 0.5 | 1 | 4.5 | | | |
| | 2. | 200 | 3 | 1.5 | 0 | 1.5 | 3 | | | |
| | 3. | 100 | 5 | 2 | 1 | 2 | 5 | | | |
| 11. II | 1. | 200 | 3 | 3 | 0 | 0.5 | 3.5 | | | |
| | 2. | 400 | 6 | 4.25 | 0.25 | 1.75 | 6.25 | | | |
| | 3. | 200 | 4.5 | 6 | 0.5 | 0 | 6.5 | | | |
| 12. EL | 1. | 200 | 2 | 1 | 0 | 1 | 2 | | | |
| | 2. | 200 | 3 | 1.5 | 0 | 1.5 | 3 | | | |
| | 3. | 100 | 3 | 2 | 0 | 1 | 3 | | | |
| 13. PX | 1. | 100 | 1 | 0 | 0 | 1 | 1 | | | |
| | 2. | 400 | 3.25 | 1.75 | 0 | 1.5 | 3.25 | | | |
| | 3. | 200 | 3.5 | 2.5 | 0 | 1 | 3.5 | | | |
| 14. HI | 1. | 200 | 2.5 | 2 | 0 | 0.5 | 2.5 | | | |
| | 2. | 200 | 3 | 2 | 0 | 1 | 3 | | | |
| | 3. | 200 | 5 | 3.5 | 0 | 1.5 | 5 | | | |
| 15. SV | 1. | 100 | 1 | 1 | 0 | 0 | 1 | | | |
| | 2. | 300 | 2.3 | 0.7 | 0 | 1.6 | 2.3 | | | |
| | 3. | 200 | 4 | 1 | 0 | 3 | 4 | | | |
| 16. HS | 1. | 200 | 1.5 | 1 | 0 | 0.5 | 1.5 | | | |
| | 2. | 400 | 4 | 1.5 | 0.5 | 2 | 4 | | | |
| | 3. | 200 | 3.5 | 3 | 0 | 0.5 | 3.5 | | | |
| 17. ML | 1. | 200 | 1 | 1 | 0 | 0 | 1 | | | |
| | 2. | 200 | 5.5 | 4.5 | 0 | 1 | 5.5 | | | |
| | 3. | 200 | 2 | 2 | 0 | 0 | 2 | | | |
| 18. VI | 1. | 200 | 1.5 | 0.5 | 0 | 1 | 1.5 | | | |
| | 2. | 200 | 2 | 1.5 | 0 | 0.5 | 2 | | | |
| | 3. | 200 | 3 | 1.5 | 0.5 | 1 | 3 | | | |
| 19. TG | 1. | 200 | 1.5 | 1 | 0 | 0.5 | 1.5 | | | |
| | 3. | 200 | 2 | 1 | 0 | 1 | 2 | | | |
| 20. PP | 1. | 200 | 1 | 0.5 | 0 | 0.5 | 1 | | | |
| | 2. | 200 | 1.5 | 1 | 0 | 0.5 | 1.5 | | | |
| | 3. | 200 | 3.5 | 2.5 | 0 | 1 | 3.5 | | | |

| Nº Case | Sampling time* | CA, Nº scored cells | Cells with CA, % | Chromosome Fragments | Dicentrics | Chromatide Fragments | Total Nº of CA, % | MN, ? scored cells | Cells with MN, ‰ | Total Nº of MN,% |
|---|---|---|---|---|---|---|---|---|---|---|
| 21. AD | 1. | 200 | 0.5 | 0.5 | 0 | 0 | 0.5 | | | |
| | 2. | 200 | 1 | 0.5 | 0 | 0.5 | 1 | | | |
| | 3. | 200 | 0.5 | 0.5 | 0 | 0 | 0.5 | | | |
| 22. VY | 1. | 200 | 1.5 | 1 | 0 | 0.5 | 1.5 | 2000 | 9.5 | 13.5 |
| | 2. | 400 | 3.75 | 3.25 | 0 | 2.5 | 5.75 | 2000 | 12.5 | 15.5 |
| 23. DZ | 1. | 100 | 0 | 0 | 0 | 0 | 0 | | | |
| | 2. | 200 | 3.5 | 1.5 | 0 | 2 | 3.5 | | | |
| | 3. | 100 | 3 | 2 | 0 | 1 | 3 | | | |
| 24. SD | 1. | 100 | 5 | 3 | 0 | 2 | 5 | | | |
| | 2. | 100 | 4 | 2 | 0 | 2 | 4 | | | |
| 25. ID | 2. | 200 | 3.5 | 2 | 0 | 1.5 | 3.5 | | | |
| | 3. | 200 | 6.5 | 3.5 | 1 | 2.5 | 7 | | | |
| 26. ME | 1. | 200 | 3 | 1.5 | 0.5 | 1 | 3 | | | |
| | 2. | 300 | 4.7 | 2.7 | 0.3 | 1.7 | 4.7 | | | |
| 27. GV | 1. | 200 | 2 | 1 | 0 | 1 | 2 | | | |
| | 2. | 200 | 2 | 1.5 | 0 | 0.5 | 2 | | | |
| 28. HP | 1. | 200 | 2 | 0.5 | 0 | 1.5 | 2 | | | |
| | 2. | 200 | 1.5 | 1 | 0 | 0.5 | 1.5 | | | |
| 29. TZ | 1. | | | | | | | 2000 | 14 | 15 |
| | 2. | | | | | | | 2000 | 17.5 | 17.5 |

*1 – before arteriography, 2 – after arteriography, 3 - 24 hours after arteriography

agnostic examination within the year before entering the study (Table 1).

The mean frequency of cells carrying chromosomal aberrations in the group of 28 investigated patients was 1.62% ± 0.18 before angiography, and 2.77% ± 0.21 immediately after diagnostic examination (Figure 1). The difference was statistically significant (t = 3.21; PZZZ0.01). The frequency of cells with aberrations was estimated 24 hours after the diagnostic exposure only in 14 subjects and was found to be 3.61 % ± 0.39. The frequency score for the same subjects immediately after angiography was 3.39 % ± 0.32 and did not differ significantly in the analysis after 24 hours (PVVV0.05). In the group of patients submitted to renal arteriography, the frequency of cells with chromosomal aberrations immediately before and after the exposure was 1.81% ± 0.22, and 3.22% ± 0.25, respectively (Table 2), (PZZZ0.01). No increase in the frequency of chromosomal aberrations was observed in the patients who has undergone cerebral arteriography (PVVV0.05).

The yield of micronuclei also increased significantly after angiography (Table 2). The frequency varied from 5‰ to 16‰ in subjects before, and from 5.5‰ to 24‰ in different subjects immediately after the examination. The mean values of micronuclei in peripheral lymphocytes of the investigated subjects was 9.5Č ± 0.69 before, and 12.5 ± 0.80 after the examination (Figure2). The difference was statistically significant ($\chi^2 = 7.85$; PZZZ0.01).

*Discussion*

In this study, we found a higher frequency of chromosomal aberrations and micronuclei in the group of patients exposed to the diagnostic x-ray with the application of contrast media during angiography compared to their control values before the exposure. The difference was statistically significant for both cytogenetic biomarkers used: chromosomal aberrations (PZZZ0.01) and micronuclei formation (PZZZ0.01). Micronuclei arose in the cytoplasm of binucleated cells as a result of CA induction[7] and they were proved to be a sensitive bioindicator of genotoxic exposure.

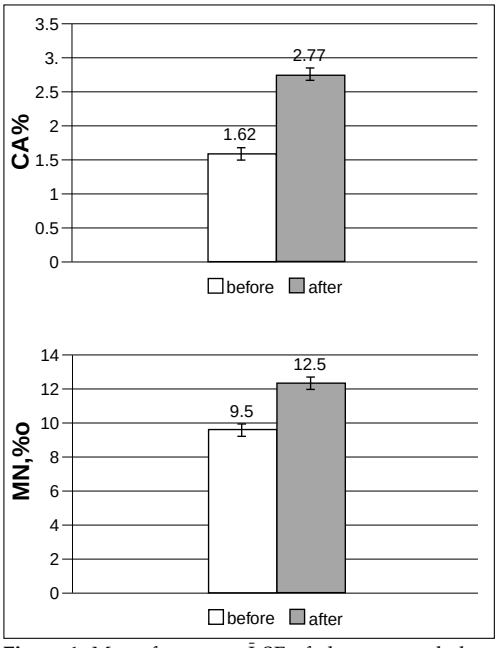


**Figure 1.** Mean frequency Ī SE of chromosomal aberrations (CA) and micronuclei (MN) in the patients immediately before and after arteriography.

The use of contrast agent in radiodiagnostic arteriography aimed to increase the absorption of X-rays in blood vessels. This was due to the iodine atom included and resulting effect of high photoelectric absorption. As a consequence, the cells in the vicinity of the contrast agent might have absorbed larger radiation dose and might have been exposed to greater cytotoxic effects.[4] This could explain the observed significant genotoxic damage in the peripheral blood lymphocytes of the investigated patients in our study.

Previous *in vitro* studies found that some contrast agents might possess genotoxic properties by themselves[1] and might have a potential to increase the genotoxicity of X-rays as well.[2,4] Previous studies also proved that certain contrast media could also penetrate the epithelial cells through a transcellular mechanism.[8,9]

In conclusion, there is a significant increase in the frequency of chromosome damage in the peripheral blood lymphocytes of the subjects undergoing diagnostic arteriography. These results suggest the need for studying the radiosensitizing property of the contrast media to reduce the patient dose without compromising the image quality. Further *in vitro* studies are needed to elucidate the mechanism of the combined genotoxic effects of iodinated contrast agents and radiation.

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## Kronično neishemično uvihanje tankega črevesa samega vase in v debelo črevo

**Roić G, Vrtar Z, Posarić V, Borić I, Cigit I**

**Izhodišča.** Kronično uvihanje (intususcepcija) dela črevesa samega vase ali v sosednjo črevesno vijugo traja 14 ali več dni. V članku prikazujemo takšen redek primer pri bolnici z neakutno bolečino v trebuhu.
**Prikaz primera.** Opisujemo 14-letno bolnico, ki je imela en mesec krčevite bolečine v presledkih v spodnjem delu trebuha in so bile odvisne od hranjenja. Naredili smo rentgensko slikanje trebuha, nato pa še ultrazvočno in CT preiskavo trebuha, ki sta nam omogočili diagnozo. Bolnico smo operirali. Ob laparatomiji smo ugotovili uvihanje tankega črevesa samega vase in v debelo črevo. Uvihanje je bilo dolgo 70 cm, prevladovalo je uvihanje Meckelovega divertikla.
**Zaključki.** Neznačilna klinična slika kroničnega uvihanja črevesa večkrat onemogoča takojšnjo točno diagnozo in zato tudi zakasnelo ali neustrezno ukrepanje. Ultrazvok in CT trebuha sta se ponovno pokazali kot najučinkovitejši in najkoristnejši predoperativni preiskavi. Ker je lahko ob uvihanju črevesa prisotna tudi druga lezija, je pri odraslih in pri mladostnikih vedno potrebna operacija.

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## Osteosarkom maksile

**Sayin B, Yildirim N, Vural M, Dede D**

**Izhodišča.** Maksilofacialni sarkomi so redki tumorji, še redkejši pa so osteosarkomi čeljusti. V nasprotju z osteosarkomi dolgih kosti se maksilofacialni pojavljajo predvsem v 3. in 4. desetletju življenja.
**Prikaz primera.** Opisujemo 18-letno bolnico, ki smo ji histološko potrdili osteoblastični osteosarkom maksile po predhodni preiskavi z računalniško tomografijo (CT). Čeprav smo bolnico radikalno operirali in nato adjuvantno zdravili s kemoradioterapijo, smo čez dve leti na obrazu ugotovili obsežno lokalno ponovitev bolezni.
**Zaključki.** Radiografska ocena osteosarkoma maksile je pomembna preiskava – zlasti CT – saj omogoča ob diagnozi načrtovanje radikalne operacije.

Radiol Oncol 2005; 39(2): 101-14.

# Večrezna računalniška tomografija pljučne embolije

**Bešlić Š, Dalagija F, Đurović V**

**Izhodišča.** Namen raziskave je bil ugotoviti, kakšen je prispevek večlistne računalniške tomografije (MSCT) pri diagnosticiranju pljučne embolije (PE) in kakšne spremembe smo našli pri naših bolnikih.

**Metode.** V obdobju enega in pol leta smo PE ugotovili pri 25 bolnikih (15 moških in 10 žensk). Povprečna starost bolnikov je bila 54,4 let (25 - 74). Preiskave smo naredili s »Somatom Volume Zoom« Siemensovo CT napravo, ki je imela 4 detektorje, kolimator 4 x 2,5 mm in s katero smo naredili retrospektivni EKG ter rekonstruirali reze na razdaljo 0,8 mm. Aplicirali smo 130 ml kontrastnega sredstva v raztopini s hitrostjo 3,5 ml/s in z zakasnitvenim časom 22 sekund.

**Rezultati.** Med preiskavo smo ugotovili embolizme v glavnih vejah pulmonarne arterije pri 14 (56%) bolnikih, v desni veji pri 10 (40%) in v levi veji pri 4 (16%), bilateralne pulmonarne embolisme pa smo videli pri 11 (44%) bolnikih. Subsegmentalne pljučne embolizme smo diagnosticirali pri pri 8 (32%). Pljučni infarkt smo ugotovili pri 12 (48%) bolnikih in je v 11 (44%) primerih povzročil razširitev istostranske pljučne arterije, redistribucijo cirkulacije in razširitev vej pulmonarne arterije pa smo v infarktnem področju pa smo opazili pri 9 (36%) bolnikih. Ojačanje pljučnega parenhima s kontrastom smo opazili pri 10 (40%), bolnikih, področja oslabljenja pa pri 15 (60%). Krvavitve smo opazili pri 21 (84%) bolnikih, mrežasto pljučno risbo pri 11 (44%), mozaično pa pri 3 (12%). Trombe v levem in desnem atriju smo videli samo pri 2 (8%) primerih, perikardialno krvavitev pri 1 (4%), mediastinalne bezgavke pri 1(4%), nenadno prekinitev periferne veje z infarktom apeksa pri pri 1 (4%) ter hemoptize pri 1 (4%) primeru. Ob globoki venski trombozi smo ugotavljali kot vzrok embolizmov še okvaro delovanja srca pri 7 (28%) bolnikih in maligno obolenje pri 3 (12%).

**Zaključki.** MSCT je odlična neinvazivna metoda za prikazovanje trombov v pulmonalni arteriji. Pri naših bolnikih smo najpogosteje našli embolizme v desni veji pulmonalne arterije. Različne spremembe ob pljučnih embolizmih lahko vidimo samo z MSCT, tako to preiskavo vedno pogosteje izvajamo ob sumu na pljučno embolijo.

Radiol Oncol 2005; 39(2): 115-21.

# Slovenske izkušnje pri obravnavi bolnikov s pljučnim rakom, njihove značilnosti in preživetje

**Debevec L, Debeljak A, Eržen J , Kovač V, Kern I**

**Izhodišča.** Namen raziskave je bil ugotoviti značilnosti bolnikov s pljučnim rakom, ki so bili diagnosticirani na Kliničnem oddelku za pljučne bolezni in alergijo Golnik v letu 1996. Prav tako smo želeli ugotoviti, kolikšna je bila razlika med izbranim in dejanskim zdravljenjem ter kakšno je bilo preživetje bolnikov.

**Metode.** Retrospektivno smo analizirali dokumentacijo 345 bolnikov, starih od 37 do 90 let (mediana 65), 285 moških in 60 žensk. Telesna zmogljivost (Karnofsky): VVV 80 pri 171 bolnikih, 60-80 pri 130 in ZZZ60 pri 44 bolnikih. Tumor smo mikroskopsko potrdili pri 97% bolnikov, z bronhoskopijo pri 281, s transtorakalno igelno biopsijo pri 23, z biopsijo perifernih bezgavk pri 12, s citološko preiskavo sputuma pri 7, s citološko preiskavo plevralnega izliva pri 4, z biopsijo oddaljenih zasevkov pri 2, z mediastinoskopijo pri 1 in z obdukcijo pri 4 bolnikih. Histološko in/ali citološko smo dokazali: pri 131 bolnikih epidermoidni, pri 86 žlezni, pri 63 velikocelični, pri 51 drobnocelični, pri 1 nedrobnocelični in pri 2 bolnikih neopredeljeni karcinom. Klinični stadij pri nedrobnoceličnem raku je bil v 63 primerih stadij I, v 32 stadij II, v 48 stadij IIIA, v 59 stadij IIIB, v 77 stadij IV, v 2 primerih pa stadija ni bilo mogoče določiti. Pri bolnikih z drobnoceličnim rakom smo ugotovili v 24 primerih omejeno obliko bolezni, v 27 pa razširjeno bolezen.

**Rezultati.** Dejansko onkološko zdravljenje je bilo drugačno kot izbrano zdravljenje pri 11% bolnikov. Primarno smo z obsevanjem zdravili 102 (30%) bolnika, z operacijo 77 (23%), s kemoterapijo 47 (14%) ter s podpornim zdravljenjem 111 (33%) bolnikov. Pri operiranih bolnikih je bil klinični stadij pravilno določen pri 46% bolnikov, prenizko ocenjen pri 44% ter previsoko ocenjen pri 10% bolnikov. Petletno preživetje vseh bolnikov je bilo 7,8% (mediana 6,2 meseca), petletno preživetje operativno zdravljenih bolnikov pa 41,9% (mediana 33 mesecev). Srednje preživetje obsevanih bolnikov je bilo 5,7 meseca, bolnikov zdravljenih samo podporno pa 2,5 mesecev. Preživetje je bilo statistično značilno odvisno od telesne zmogljivosti in stadija bolezni.

**Sklep.** Izbrano onkološko zdravljenje smo dejansko izvedli pri 89% bolnikov. S kemoterapijo smo zdravili majhen odstotek bolnikov z nedrobnoceličnim rakom. Pet let je preživelo samo 26 bolnikov zdravljenih z operacijo in eden, ki je bil zdravljen le podporno, kar potrjuje, da je kirurška odstranitev najuspešnejši način zdravljenja pljučnega raka.

Radiol Oncol 2005; 39(2): 123-31.

# Kirurško zdravljenje malignega plevralnega mezotelioma. Izkušnje interdisciplinarne obravnave v Sloveniji

**Eržen J, Vidmar S, Sok M, Debeljak A, Kecelj P, Kovač V, Stanovnik M, Rott T, Kern I**

**Izhodišča.** Namen raziskave je bil ugotoviti operacijske zaplete, pooperacijsko smrtnost, vrsto in načine dopolnilnega zdravljenja, potek bolezni in preživetje pri bolnikih, pri katerih je bila narejena ekstraplevralna pnevmonektomija (EPP) ali plevrektomija zaradi malignega plevralnega mezotelioma (MPM).

**Metode.** V letih od 2000 do 2003 je bilo 18 bolnikov z MPM napotenih na Klinčni oddelek za torakalno kirurgijo Kliničnega centra v Ljubljani. Operirali smo 17 bolnikov in pri pri dveh naredili samo eksplorativno torakotomijo, preostalih 15 pa smo operirali z namenom ozdravitve. Pri 5 ženskah in 9 moških (starih od 52 do 68 let) smo naredili EPP, pri enem pa plevrektomijo. Osem bolnikov je po operaciji dobivalo cisplatin 100 mg/m$^2$ + mitomicin C 6-10 mg/m$^2$ (5 bolnikov) ali gemcitabin 1000 mg/m2(3 bolniki) in imelo obsevanje hemitoraksa od 24 Gy do 58 Gy (KT+RT); 3 niso bili dodatno zdravljeni; 3 so prejeli le citostatike brez obsevanja (KT) od tega sta 2 bolnika dobila cisplatin 100 mg/m$^2$ + mitomicin C 6-10 mg/m$^2$, eden pa cisplatin 100 mg/m$^2$ in gemcitabin v podaljšani infuziji (250 mg/m$^2$ 1. in 8. dan); en bolnik je bil le obsevan (54 Gy).

**Rezultati.** V zgodnjem pooperacijskem obdobju ni nihče umrl, popoperativnih zapletov pa je bilo 42%. V srednjem opazovalnem obdobju 40 mesecev (28-64) smo pri 9 od 15 (60%) bolnikih ugotovili ponovitev bolezni, 8 od 15 (53,3%) bolnikov je umrlo, vsi zaradi lokalne ponovitve tumorja. Med tremi bolniki, ki niso bili dodatno onkološko zdravljeni, je eden (s stadijem T1bN0M0) živ brez znakov bolezni 46 mesecev po operaciji, pri drugi bolnici (stadij T2N0M0) se je bolezen ponovila v abdomnu ter je bila zdravljena s KT in operacijo in je živa 31 mesecev po prvi operaciji, tretji bolnik (stadij T1bN0M0) pa je umrl 2 meseca po operaciji zaradi lokalnega napredovanja bolezni. Iz skupine KT+RT je umrlo 6 od 8 bolnikov; bolnika s stadijem T1aN0M0 in T1bN0M0 9 mesecev po operaciji, 2 bolnika s stadijem T2N0M0 4 in 23 mesecev po operaciji, bolnik s stadijem T3N0M0 11 mesecev in bolnik s stadijem T3N2M0 7 mesecev po operaciji. Dva bolnika sta še živa (s stadijem T1bN0M0 in T2N0M0) 43 in 28 mesecev po operaciji. V KT skupini je eden od treh bolnikov (stadij T2N0M0) umrl 6 mesecev po operaciji, dva (s stadijem T2N0M0 in T3N0M0) pa sta še živa 43 in 20 mesecev po operaciji. Bolnica, ki je bila samo obsevana, je živa 50 mesecev po operaciji. Srednje preživetje vseh operiranih bolnikov je bilo 20 mesecev, enoletno preživetje je bilo 53,3% in dvoletno 46,7%.

**Zaključki.** Radikalna kirurška odstranitev tumorske mase pri MPM je indicirana pri izbranih bolnikih. Operacijo je mogoče narediti varno z majhno pooperacijsko smrtnostjo in brez hudih zapletov. Število naših bolnikov je bilo premajhno in dopolnilno zdravljenje je bilo zelo različno, da bi lahko sklepali o prednosti določenega načina zdravljenja. Potrebne bodo nadaljnje randomizirane študije in uvedba smernic za izbiro optimalnega zdravljenja pri posameznem bolniku.

Radiol Oncol 2005; 39(2): 133-40.

# Zdravljenje anemije z epoetinom alfa pri bolnikih z rakom danke

**Velenik V, Oblak I, Kodre V**

**Izhodišča.** Anemija, ki povzroča zmanjšanje funkcionalne zmogljivosti in kakovosti bolnikovega življenja, je pogosto spremljevalka raka. V klinični raziskavi smo želeli ugotoviti, ali lahko z epoetinom alfa preprečimo padec in vzdržujemo zadovoljive vrednosti hemoglobina (Hb) pri bolnikih s karcinomom danke, ki jih po operaciji zdravimo z radiokemoterapijo (RT-KT). Sledili smo tudi bolnikove potrebe po transfuziji in varnost epoetina alfa.

**Metode.** V raziskavo smo vključili 60 bolnikov po radikalni operaciji raka danke. V skupini A je bilo 39 bolnikov s koncentracijo Hb AAA 13 g/dl ob pričetku pooperativne RT-KT, v skupini B pa 17 bolnikov s koncentracijo Hb VVV 13 g/dl ob pričetku pooperativnega zdravljenja in pri katerih je koncentracija Hb padla pod 12 g/dl v času KT-RT. Bolniki so prejemali epoetin alfa v odmerku 10.000 IE subkutano trikrat na teden. Ocenjevali smo naslednje parametre: (1) značilnost gibanja Hb med terapijo z epoetinom alfa in KT-RT, (2) delež bolnikov, ki so potrebovali transfuzijo in (3) delež bolnikov, pri katerih smo opazili neželene učinke zdravljenja z epoetinom alfa.

**Rezultati.** Statistično smo obdelali 56/60 (93%) protokolov. Pri vseh bolnikih v skupini A je bilo opaziti statistično pomemben porast (pZZZ0.001) Hb že po štirih tednih zdravljenja z epoetinom alfa (povprečen dvig Hb 1,97 Ī 0,91 g/dl). Kljub nihanju koncentracije Hb je bila ta ves čas statistično pomembno višja kot ob začetku raziskave (p=0,0017). V skupini B je bilo opaziti v prvih tednih spremljanja postopen padec koncentracije Hb, ki je dosegla v tretjem tednu statistično pomembno nižjo vrednost kot ob vključitvi v raziskavo (p=0,006). Po uvedbi epoetina alfa je bilo tudi v tej skupini bolnikov opaziti normalizacijo vrednosti Hb in ustalitev med 12-13 g/dl. Nihče od bolnikov v raziskavi ni prejel transfuzije. Nobeden od devetih opisanih neželenih učinkov pri 6 bolnikih ni bil povezan z epoetinom alfa.

**Zaključki:** Epoetin alfa je učinkovit v preprečevanju padca in vzdrževanju normalne vrednosti Hb pri bolnikih z rakom danke, ki so bili pooperativno zdravljeni s KT-RT. Hkrati je učinkovit pri zmanjševanju bolnikovih potreb po transfuziji. Naša raziskava je pokazala, da je epoetin alfa varno zdravilo, saj nismo zabeležili z njim povezanih neželenih učinkov.

Radiol Oncol 2005; 39(2): 141-6.

# Prikaz bolnice z metastatskim timomom: solitarna metastaza je povzročala asimptomatsko utesnitev hrbtenjače

**Gold DG, Miller RC**

**Izhodišča.** Čeprav so timomi histološko benigni tumorji, je lokalno njihova rašča lahko zelo agresivna, redko pa tudi metastazirajo.

**Prikaz primera.** Opisujemo primer 47-letne bolnice, ki je bila pred 21 leti radikalno operirana zaradi timoma in nato postoperativno obsevana. K nam je bila napotena zaradi solitarne intraabdomimalne metastaze, ki je povzročala asimptomatsko utesnitev hrbtenjače. Bolnico smo zdravili s preoperirativnim radikalnim obsevanjem, ki smo ga načrtovali s pomočjo magnetne resonance in računalniške tomografije, nato pa operirali. Operacija je bila narejena prav tako radikalno, brez zajetih robov. Po zdravljenju nismo opazili nevroloških motenj.

**Zaključki.** Za lokalno zdravljenje z obsevanjem in operacijo smo se odločili, ker je poteklo kar 21 let od zdravljenja prvotnega tumorja in ker smo dopuščali možnost, da se je počasi rastoči tumor širil limfogeno preko plevralnega prostora v retroperitonealni, podobno kot mezoteliom.

Radiol Oncol 2005; 39(2): 159-66.

*Radiol Oncol 2005; 39(2): 147-52.*

# PCR in analiza talitvene krivulje kot metoda za odkrivanje najpogostejših dednih mutacij v BRCA1 genu pri slovenskih bolnikih

**Novaković S in Stegel V**

Odkrivanje dednih mutacij v genih, ki so povezani z nastankom raka, napove verjetnost nastanka raka pri nosilcih mutacij in pri njihovih potomcih. Najpogostejše oblike raka, ki so povezane s podedovanimi mutacijami, so črevesni rak (mutacije v APC genu pri bolnikih s familiarno adenomatozno polipozo – FAP, mutacije genov za popravljanje neujemanja pri bolnikih z dednim nepolipoznim črevesnim rakom – HNPCC), maligni melanom (mutacije v CDKN2A in CDK4 genih) in rak dojke (mutacije v BRCA1 in BRCA2 genih). V članku podajamo osnovne metodološke podatke za odkrivanje petih različnih mutacij v BRCA1 genu pri bolnikih s karcinomom dojke in njihovih sorodnikih. Mutacije 1806C>T, 300T>G, 300T>A, 310G>A, 5382insC smo določali s pomočjo polimerazne verižne reakcije v realnem času in analizo talitvene krivulje. Primerjava z direktnim sekveniranjem je pokazala, da je uporabljena metoda dovolj občutljiva in hitra za dnevno rutinsko določanje mutacij v DNA izolirani iz periferne krvi.

Radiol Oncol 2005; 39(2): 153-8.

# Citogenetska analiza limfocitov v periferni krvi po kontrastni arteriografiji

**Popova L, Hadjidekova V, Karadjov G, Agova S, Traskov D, Hadjidekov V**

**Izhodišča.** Namen citogenetske raziskave je bil ugotoviti učinek diagnostične arteriografije na limfocite periferne krvi pri 29 bolnikih.

**Metode.** Periferne vzorce krvi smo odvzeli 22 bolnikom, ki so bili napoteni na ledvično arteriografijo in 7 bolnikom napotenim na možgansko arteriografijo (17 moškim in 12 ženskam, starim 13 – 68 let). Citogenetska analiza limfocitov periferne krvi je bila narejena pred preiskavo, neposredno po preiskavi in 24 ur kasneje. Vstopno kožno dozo sevanja med celotno rentgensko preiskavo smo merili s termoluminescentnim dozimetrom in je bila 0,03-0,30 Gy. Uporabili smo kontrastno sredstva z nizko in visoko osmolarnostjo. Genotoksičnost smo ocenjevali s pogostnostjo kromosomskih aberacij in mikronukleusov.

**Rezultati.** Pogostnost kromosomskih aberacij in mikronukleusov v limfocitih periferne krvi je bila značilno višja po arteriografiji, kot pa jih je bilo pred njo. Število kromosomskih aberacij se je skoraj podvojilo in je po 24 urah ostalo nespremenjeno.

**Zaključki.** Rentgenske preiskave z jodnim kontrastnim sredstvom, kot je arteriografija, lahko statistično značilno zvišajo število citogenetskih poškodb v limfocitih periferne krvi.

# 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.*

### 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

### Radiotherapy

*July 3-7, 2005*

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

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

### Lung cancer

*August 15-17, 2005*

The »4th IASLC Chinese International Conference on Lung Cncer« will take place in Harbin, China.

**Contact:** Professor Li Houwen, MD China Medical Unviersity; Fax : +86 24 23251962.

### Gynaecological malignancies

*August 25-27, 2005*

The ESTRO course »Brachytherapy in Gynaecological Malignancies« will take place in Paris, France.

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

### Radiotherapy

*August 28 – September 1, 2005*

The ESTRO course »Physics for Clinical Radiotherapy« will take place in Como, Italy.

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

### Oncology

*September 5-9, 2005*

The EORTC (European Organisation for Research and Treatment of Cancer) annual course »Cancer Clinical Trials: Methods and Practice« will take place in Brussels, Belgium.

**Contact** Danielle Zimmermann, EORTC Education Office, Avenue E. Mounier 83, bte 11, B-1200 Brussels, Belgium; or call +32 2 774 16 02; or fax +32 2 772 62 33; or e-mail dzi@eortc.be; or see http://www.eortco.be/Seminar/Educationpgm/Programs/prog2005.htm

### Radiotherapy

*September 24-29, 2004*

The »8th Biennial ESTRO Meeting on Physics and Radiation Technology for Clinical Radiotherapy« and »Pre-Meeting Workshop on Image-Guided Radiotherapy« will take place in Lisbon, Portugal.

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

### Radiation oncology

*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

### Radiobiology

*October 2-6, 2005*

The ESTRO course »Basic Clinical Radiobiology« will take place in Izmir, Turkey.

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

### Oncology

*October 7, 2005*

The EORTC (European Organisation for Research and Treatment of Cancer) annual course »One-Day Introduction to EORTC Trials« will take place in Brussels, Belgium.

**Contact** Danielle Zimmermann, EORTC Education Office, Avenue E. Mounier 83, bte 11, B-1200 Brussels, Belgium; or call +32 2 774 16 02; or fax +32 2 772 62 33; or e-mail dzi@eortc.be; or see http://www.eortco.be/Seminar/Educationpgm/Programs/prog2005.htm

### Lung cancer

*October 16-20, 2005*

The IASLC workshop »Biology and Prevention of Lung Cancer« will be offered in Woodstock, Vermont, USA.

**Contact** Taryn Klocke at Envision Communications; call +1 770 763 5690; or see www.lungcancerprevention.net

### 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

### Radiation oncology

*November 13-18, 2005*

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

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

### Oncology

*November 21-25, 2005*

The EORTC (European Organisation for Research and Treatment of Cancer) course »Organization and Implementation of Cancer Clinical Trials« will take place in Leuven, Belgium.

**Contact** Danielle Zimmermann, EORTC Education Office, Avenue E. Mounier 83, bte 11, B-1200 Brussels, Belgium; or call +32 2 774 16 02; or fax +32 2 772 62 33; or e-mail dzi@eortc.be; or see http://www.eortco.be/Seminar/Educationpgm/Programs/prog2005.htm

### Mesothelioma

*November 2 2-27, 2005*

The »International Mesothelioma Symposium« will take place in Antalya, Turkey.

**Contact:** Taryn Klocke; call +1 770-984-5113; Fax: +90 232 278 33 73.

### Lung cancer

*June 18, 2006*

The »10th Central European Lung Cancer Conference« will be offered in Prague, Czech Republic.

**Contact:** +420-608-408-708; or e-mail info@conference.cz; or see http://www.conference.cz

### Lung cancer

*April 19-26, 2006*

The »2nd Latin American Conference on Lung Cancer« will be offered in Cancun, Mexico.

**E-mail:** LungCancerLA@meet-ics.com: or see http:// www.LCLA2006.com

### Lung cancer

*September 28-30, 2006*

The »2nd International Workshop Early Invasive Lung Cancer: New Diagnostic Tools & Treatment Strategies« will be held in Turin, Italy.

**E-mail:** a.crippa@congressiefiere.com or see http://www.congressifiere.com

**Lung and head & neck**

*October 26-28, 2006*

The »4th Lung & Head and Neck Conference« will be offered in Sheraton Hotel, Chicago, Illinois.

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**Lung cancer**

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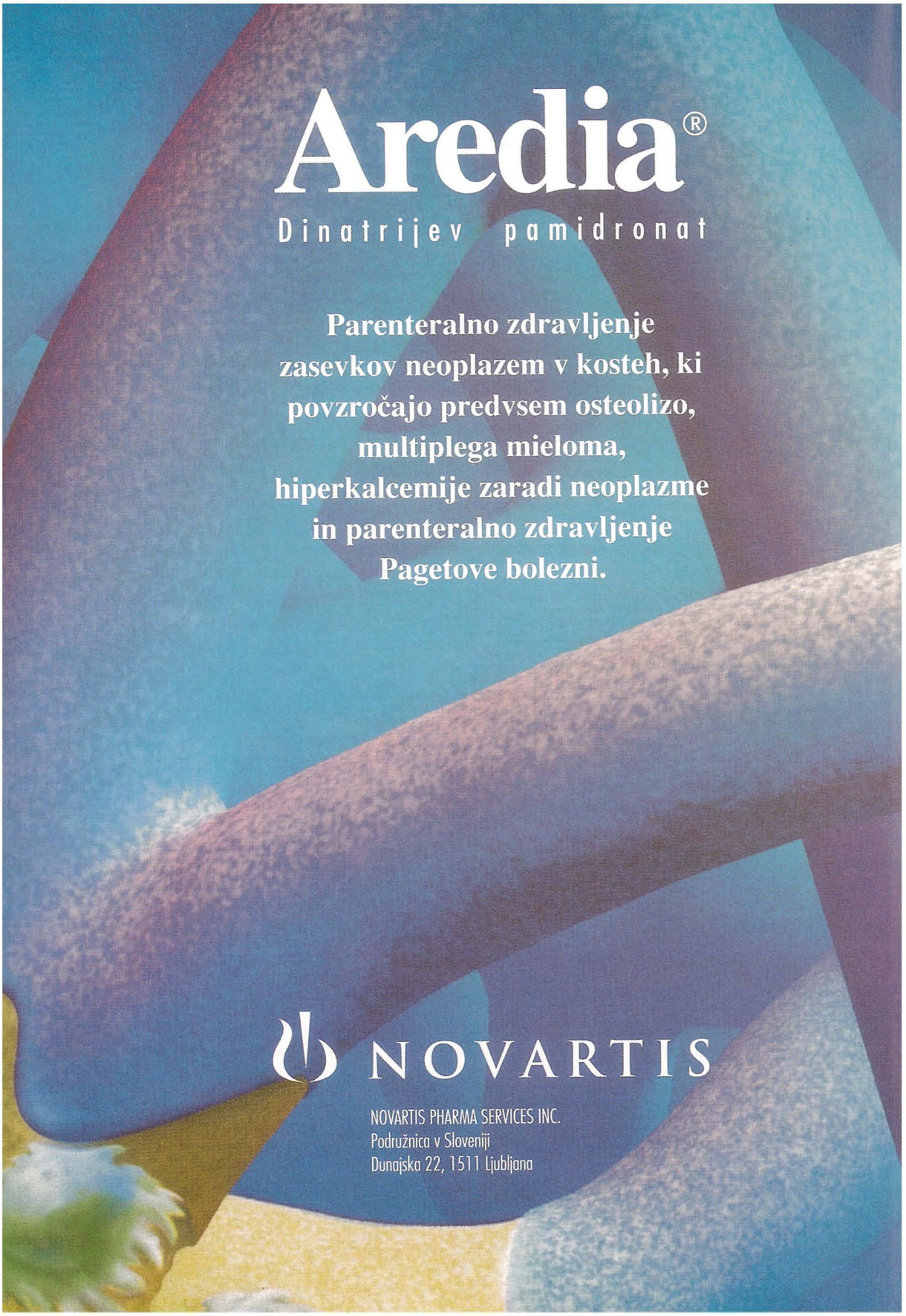
# Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education - A Report for the Second Quarter of 2005

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to support activities associated with cancer research and education in Slovenia with different initiatives, as suggested by the members of the Foundation and all other interested individuals in the country. Grant applications and other applications for various types of financial support are being dealt with immediately and thoroughly by the responsible bodies formed by Foundation members with clinical and cancer research experience and members with important experience in finance. The Foundation can claim several successful endeavours to its credit during the course of 2004 and already during the first quarter of 2005. The Dr. J. Cholewa Foundation for Cancer Research and Education continues to support the regular publication of "Radiology and Oncology" international scientific journal, which is edited, published and printed in Ljubljana, Slovenia, as it has done over the last couple of years and considering it one of its permanent commitments.

Unfortunately, it has to be acknowledged that various public and privately owned enterprises find it ever more difficult to contribute financially to the Foundation. Several new suggestions are being considered at the moment. The Foundation acknowledges the importance of the commitment of various public companies and private individuals to its cause.

Tomaž Benulič, MD
Andrej Plesničar, MD
Borut Štabuc, MD, PhD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**Datum priprave besedila** januar 2005

*Podrobnejše informacije so na voljo pri proizvajalcu.*

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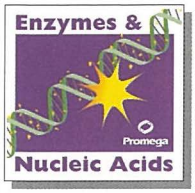



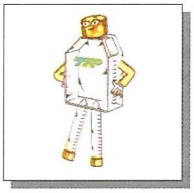


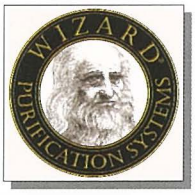



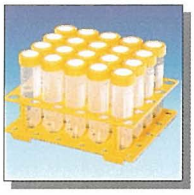

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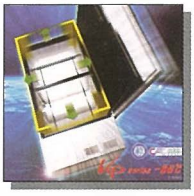

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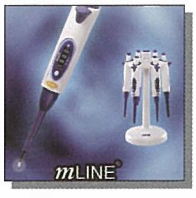


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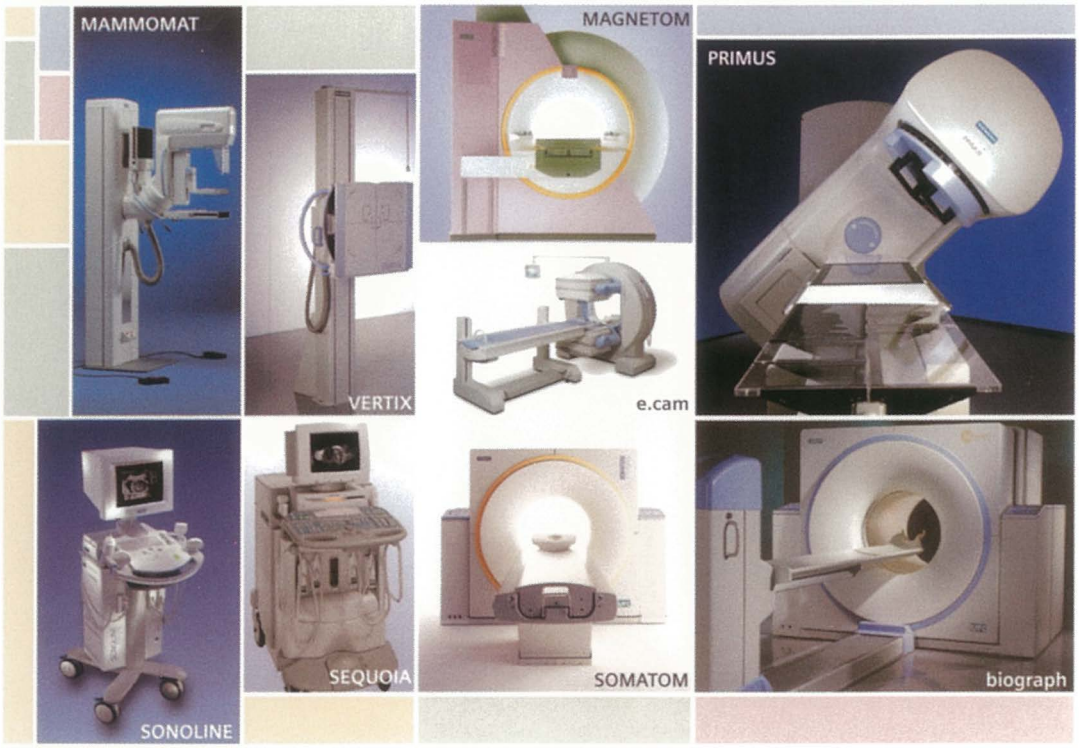




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