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CONTENTS

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Color duplex-Doppler ultrasonography of lower extremities veins - types of findings

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Background. *The types of ultrasonographic findings observed in patients referred for color duplex Doppler ultrasonography (CDD-US) of veins of lower extremities are presented in this paper.*

Patients and methods. *During 27 months, 934 patients were examined. Among these, 663 were women (71 %) and 271 men (29 %), with the age range 19-86 (mean 58.4) years. Color Doppler scanners Acuson 128 XP 10, ATL HDI 5000 and Siemens Sonoline Elegra were used, with the transducers in the frequency range from 2.5-12 MHz. The types of findings were classified as: (a) deep venous thrombosis (DVT), (b) pathology related to veins without DVT, (c) pathology of adjacent structures, (d) normal findings.*

Results. *DVT was observed in 210 patients (22.5 %) - acute or chronic in 129 patients, and 81 patients were examined in the follow-up of the DVT treatment. Postthrombotic syndrome, varicose veins, superficial thrombophlebitis and popliteal venous aneurysms were seen in 415 patients (44.4 %). The pathology unrelated to veins was observed in 117 patients (12.5 %). Muscular hematomas and popliteal cysts were most common in this group, but very rare pathology was noted, as well. In 192 patients (20.6 %) CDD-US was normal.*

Conclusions. *In patients referred for CDD-US examination of lower extremities veins, a high number of findings unrelated to veins, in addition to well-known findings of various venous pathologies, can be observed on CDD-US. The lesions that clinically mimic DVT should be recognized with US in order to avoid erroneous medical treatment.*

Key words: peripheral vascular diseases - ultrasonography, veins; ultrasonography, Doppler, duplex

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Introduction

In the last decade, ultrasonography (US) has become a primary and routine imaging method for the diagnosis of venous pathology of lower extremities.[1] It is most important and the most commonly used in diagnosing deep venous thrombosis (DVT).[1,2] Color duplex-Doppler ultrasonography (CDD US) has very high accuracy in the detection DVT in the illiac region and in the lower extremities and has almost completely replaced contrast venography in diagnostic algorithm of DVT.[1-3] The advantages of US over venography were well documented in several studies during the last decade.[4-6] CDD US is also routinely used for preoperative visualization of superficial veins, diagnosis and grading of saphenofemoral and saphenopopliteal insufficiency; it enables visualization of changes in postthrombotic syndrome, and it is useful for presurgical mapping of superficial veins used for bypasses.[1-3,7]

The purpose of this article is to present the types of findings observed in patients referred for CDD-US examination of lower extremities veins.

Patients and methods

Between October 20, 1997 and March 31, 2000, 934 patients were referred for CDD-US of lower extremities veins. Among these patients, 663 were women (71 %), and 271 men (29 %). The age range was 19-86 (mean 58.4 years). The two most common reasons for referral of patients were to rule out DVT in clinically suspected cases, or to evaluate deep, superficial and perforant veins prior to the surgery of superficial veins. Patients were also referred for CDD-US follow-up of anticoagulant treatment of the DVT. The most common clinical findings in the patients with suspected DVT were the following: unilateral swelling of the leg, direct trauma of the leg, postoperative state, postthrombotic syndrome with suspected rethrombosis, erysipelas Klippel-Trennaunay syndrome, hemangioma.

CDD-US was performed using state-of-the-art color Doppler scanners Acuson 128 XP 10, ATL-HDI 5000, and Siemens Sonoline Elegra, with the variety of transducers in the frequency range of 2.5-12 MHz. Mostly, transducers in the frequency range from 7,5 to 10 MHz were used.

Routine examination consisted of the compression of the deep veins with the transducer to evaluate venous compressibility, and to rule out DVT. Illiac veins, common femoral veins (CFV), superficial femoral veins (SFV), deep femoral veins, popliteal veins, and all three groups of crural deep veins were examined. Color duplex-Doppler evaluation was always performed. Normal spectra were obtained and tests of distal compression and flow augmentation were performed on the level of CFV, SFV and popliteal veins. Moreover, the superficial veins were examined also for saphenofemoral and saphenopopliteal insufficiency and for the presence of varices and superficial thrombophlebitis. The soft tissue of lower extremities was evaluated for the presence of edema, hematoma, or other pathology.

Contrast venography was not performed in these patients. The medical treatment of DVT was introduced on the basis of CDD-US findings, and was also used in follow-up.

The types of ultrasonographic findings were classified as: (a) deep venous thrombosis (DVT), (b) pathology related to the veins without DVT, (c) pathology of adjacent structures, (d) normal findings.

Results

The types of ultrasonographic findings classified into four groups are presented in Table 1.

Table 1. Types of ultrasonographic findings in all examined patients

Deep venous thrombosis	210	22.5 %
Venous pathology without DVT	415	44.4 %
Pathology of adjacent structures	117	12.5 %
Normal findings	192	20.6 %
Total number of findings	934	100.0 %

Among 934 examined patients, DVT was found in 210 (22.5 %). Acute complete DVT of the leg was found in 97 patients, and acute isolated DVT in 26 patients (crural DVT in 17, CFV DVT in one, popliteal vein DVT in four, illiac vein DVT in four patients). Chronic DVT was found in six patients. Eighty-one patients were referred for the follow-up of DVT during the medical treatment; partial recanalization of DVT was found in 45 patients, and complete recanalization was found in 36 patients. Types of findings in this group are presented in Table 2.

Table 2. Findings in patients with deep venous thrombosis (DVT)

Acute complete DVT	97
Acute isolated DVT	26
Chronic DVT	6
Partial recanalization	45
Complete recanalization	36
Total number of findings	210

Of 934 examined patients, 415 patients (44.4 %), who did not have acute or chronic DVT, were diagnosed with pathology related to veins. In 143 of these patients, the postthrombotic syndrome without signs of DVT was observed, with edema, swelling, insufficient perforate veins and varicose veins. Patients with crural ulcerations were included in this group. In 245 patients, we detected varicose veins, but no significant oedema or ulceration. Twenty-five patients had superficial thrombophlebitis. Popliteal venous aneurysm was observed in one male patient and the aneurysm of the gastrocnemic vein (part of the deep venous system) was observed in one female patient. Types of findings in this group are presented in Table 3.

Table 3. Findings in patients with pathology related to veins, who did not have acute or chronic DVT

Postthrombotic syndrome	143
Varicose veins	245
Superficial thrombophlebitis	25
Venous aneurysms	2
Total number of findings	415

The pathology unrelated to veins was observed in as many as 117 patients (12,5 % of all examined patients). In 27 patients, popliteal cyst was observed; ruptured cyst was seen in 11 cases, inflamed cyst in 2, and hemorrhagic cyst in two. In 34 patients, hematoma was observed in the musculature of lower extremities; the hematoma in the gastrocnemius muscle was seen in 24 patients, in the quadriceps muscle of the thigh in 5 patients, in the soleus muscle in three patients, and two hematomas were adjacent to ruptured Achilles tendons. Iliopsoas bursitis was observed in 10 patients with the enlarged bursa between the trochanter minor, common femoral artery and common femoral vein. Pronounced inguinal lymphadenopathy with swelling of the leg was observed in eight patients with normally patent deep veins. Diffuse phlegmonous inflammation of crural soft tissue was seen in three patients. Six patients had swelling with the clinical signs of erysipelas. Five patients had Klippel-Trennaunay syndrome, though with no evidence of venous thrombosis or A-V fistulas. Two patients had cavernous hemangiomas, one adjacent to the knee, and the other in the femoral region. In one patient with acute myeloic leukaemia, multiple abscesses in muscles of both legs were seen. One patient

had a large sarcoma of the gastrocnemius and soleus muscles, misdiagnosed clinically as DVT. One patient had iatrogenic pseudoaneurysm (PSAN) of the peroneal artery; it occurred after the orthopaedic surgery (patellar ventralization) with traumatic injury of the peroneal artery with a screw during the surgery. One patient had partially thrombosed aneurysm of the popliteal artery. In one patient with Von Recklingshausen's disease, multiple nodules were found in the soft tissue of lower extremities.

In a small group of patients without DVT, the anticoagulant therapy was erroneously introduced prior to the CDD-US examination, based only on clinical symptoms of leg swelling. The patients in whom DVT was misdiagnosed and mistreated with anticoagulant therapy had several underlying diseases: three patients had hematomas in the gastrocnemic muscle, and one in quadriceps muscle of the thigh; two patients had inflamed popliteal cysts; two patients had diffuse phlegmonous inflammation of the crural soft tissue; one patient had a large sarcoma of the gastrocnemius and soleus muscles. In one patient with iatrogenic PSAN of the peroneal artery, the anticoagulant medications were being administered for three months; actually, a large hematoma and swelling compromised arterial perfusion of the limb. The immunocompromized patient with acute myeloic leukaemia, who had multiple abscesses in the soft tissue of both legs, had a typical clinical manifestation of DVT. Luckily, unnecessary anticoagualant therapy was avoided with the CDD-US examination.

In addition to that, in seventeen patients, isolated edema of the superficial tissues was observed that could not be related to venous pathology. In seven of these patients, cardiac pulsatility was transmitted to the peripheral veins, with bilateral swelling, indicating that the edema was of cardiogenic origin.

Table 4. Findings in patients with pathology of adjacent structures unrelated to veins

muscular hematomas	34
popliteal cysts	27
isolated edema of soft tissues	17
illiopsoas bursitis	10
marked inguinal lymphadenopathy	8
erysipelas	6
Klippel-Trennaunay's syndrome	5
diffuse inflammation of the soft tissue	3
cavernous hemangiomas	2
very rare pathologies	5
Total number of findings	117

In 192 patients (20.6 %) CDD-US of lower extremities veins was completely normal, and no pathology was found in the soft tissue as well.

Discussion

In our practice, most common referrals for venous CDD-US are to rule out DVT, to follow-up the effects of anticoagulant therapy in established DVT, and to evaluate venous system prior to surgery of superficial veins. Groups of patients with the high risk of developing DVT are the patients after a major trauma, bone fractures, surgery, especially orthopedic surgery (e.g. hip replacement), patients with coagulopathies, pregnant and puerperal women, and all patients who are bed-ridden for longer period of time.[1-3,7,8] The risk increases with obesity and previous thromboembolic episodes. The risk of DVT is higher with aging; in old people, after long surgery, the risk of DVT is 40-70 %, whereas pulmonary embolia occurs in 1-5 % of patients.[1,2,8] The accuracy of CDD-US in the diagnosis of DVT above the knee is 99 %, and below the knee 81 %.[1-3,9-11] It is well-known that the clinical diagnosis of DVT is not very accurate. Classical clinical symptoms, like positive Homan's sign, local swelling and ten-

derness, are not reliable, and DVT is often overcalled, based on these findings. The same clinical symptoms can be caused by a variety of other conditions: abscesses, muscle hematoma, ruptured popliteal cyst, etc. Also, DVT is often clinically silent, with absent local symptoms.[1-7,11]

The results of the present study show that various pathology was found in almost 80 % of patients referred for CDD-US examination of lower extremities veins. The accuracy of CDD-US in diagnosis and follow-up of the therapy of DVT is well established, as well as in the diagnosis of the postthrombotic syndrome, varicose veins and superficial thrombophlebitis.[1-11] Contrast phlebography can be safely omitted in the diagnosis of these cases. In our study, US findings were normal only in 20.6 % of the referred patients. These data indicate the high clinical yield of US examination of lower-extremity veins. However, the referral of patients for US examination is not the responsibility of radiologist, but of the general practitioner and/or various clinicians (surgeons, specialists in internal medicine, oncologists, etc.).

A well-established capacity of US to visualize DVT, changes of postthrombotic syndrome, and changes of superficial veins was confirmed in the present study. Nevertheless, the reported results indicate that unexpected pathology, or pathology unrelated to veins was found in as many as 12.5 % of patients. This, we believe, may have important clinical consequences. Popliteal cysts, especially in cases of rupture, hemorrhage or inflammation, are known to be the causes of the leg swelling. The same applies to iliopsoas bursitis, traumatic muscular hematomas, and inguinal lymphadenopathy.[1-3] Such changes cannot be seen with contrast venography, while ultrasonography enables their visualization with very high accuracy.

We believe that, for an effective management of patients, it is important to emphasize relatively rare, and unexpected changes as observed by CDD-US in our patients. This refers especially to those patients who were misdiagnosed to have DVT on the basis of clinical symptoms, and who were consequently mistreated with anticoagulant therapy. These patients were not initially referred to CDD-US examination, and received therapy without US confirmation of the diagnosis of DVT. Among these patients, we found muscular hematomas, inflamed popliteal cysts, diffuse phlegmonous inflammation of the soft tissue, rare tumors, and even more rare iatrogenic pseudoanerysm of the peroneal artery. It should also be kept in mind that abscesses in the soft tissue can be seen in immunocompromized patients.

Ultrasonography is nowadays the main diagnostic modality in cases of venous pathology and ultrasonologists should be familiar with all the presented types of findings. There is no doubt that the erroneous diagnosis of DVT has serious clinical implications, as unnecessary administration of anticoagulant medications can result in life-threatening complications. All physicians included in diagnosis and treatment of the diseases related to the peripheral veins have to be aware of the high diagnostic accuracy of US in visualization of both, venous pathology and the pathology of adjacent structures that is unrelated to veins, but that can mimic venous diseases. Therefore, we believe that the anticoagulant therapy for DVT should not be introduced prior to US examination of lower extremities veins, even if all typical clinical symptoms of DVT are present.

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Sigmoid diverticulitis: A case report

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Background. *Diverticulitis could be a challenging diagnosis in a patient presenting with acute abdomen.*
Case report. *Our case presents a patient with acute abdomen in whom an abdominal ultrasound examination showed a mass with internal reflexes continued to the sigmoid colon and a diagnosis of diverticulitis was suspected. Later abdominal helical CT proved it to be diverticulitis.*
Conclusions. *The case emphasises the importance of ultrasound as a first line imaging modality for detecting bowel pathology.*

Key words: sigmoid diseases; diverticulitis, diverticulosis, colonic; acute-ultrasonography, abdominal ultrasound

Case report

A 56 year old woman who complained of fever, left lower quadrant pain which worsened, frequent urination without dysuria, onset of mild non bloody diarrhoea. On physical examination a mass was palpable under the umbilicus, which was mobile and very tender. WBC count was elevated (18000).

Gynaecologic examination: Just beside the uterus a very painful mass was palpable. Douglas pouch was empty of fluid. Uterus, ovaries were intact. So a gynaecological cause was ruled out.

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Abdominal ultrasound (US) examination: beside the uterus, above the bladder a big homogenous, hypoechogenic mass was seen. On suspicion of an abscess formation, an US-guided fine needle aspiration was attempted, but no fluid was aspirated.

Next day on admission fillowing control ultrasound examination the mass was seen as a continuation of the sigmoid colon with internal reflex representing the lumen and symmetrically thickened bowel wall (Figure 1). A diagnosis of sigmoid diverticulitis was highly suspected.

Abdominal and pelvic CT scan: thick walled sigmoid colon with diverticula outpouching from its surface, surrounded by an area of paracolic inflammation (Figure 2). Diagnosis: Sigmoid diverticulitis, diverticulosis.

Colonoscopy: The mucosa of the sigmoid colon was oedematous and rigid. On the oedematous mucosa an almost closed diverticular opening was seen, in addition to two

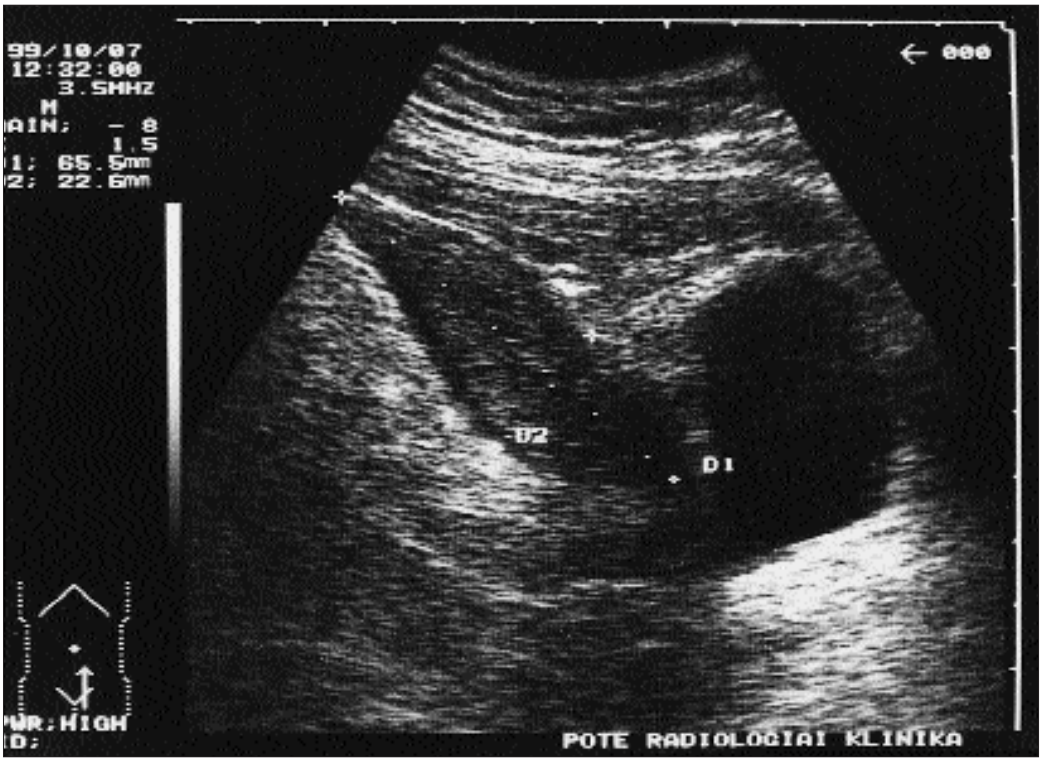

Figure 1. Abdominal ultrasound showing a mass in left lower quadrant in the continuation of sigmoid colon with central reflex representing bowel lumen and symmetrically thickened bowel wall.

other diverticulas. Diagnosis: Sigmoid divericulitis, diverticulosis.

The patient was treated with broad-spectrum antibiotics (cefriakson) along with appropriate diet and fluids. The patient did not need any surgery or drainage. Ten days later a control abdominal ultrasound was negative and a double contrast barium enema study showed free bowel lumen with small filling surpluses representing diverticulosis (Figure 3). The patient was discharged.

Introduction

Diverticulitis is among the first line in the list of differential diagnosis of acute abdomen, most frequently presenting as left lower quadrant pain and tenderness, leukocytosis, fever. Ultrasound is nowadays becoming the cheapest and easiest way in the diagnosis of the cause of acute abdomen, especially in places where access to CT is limited.

The purpose of our case report was to show the possible difficulties that can arise in the diagnosis of diverticulitis, and to show the use of ultrasound as a cheap and available method in reaching the diagnosis.

Discussion

The interesting point in this case is the misleading appearance of diverticulitis in the first ultrasound examination. The reasons could be: absence of the midline reflex representing the bowel gas and inability to follow the mass to the intestine.

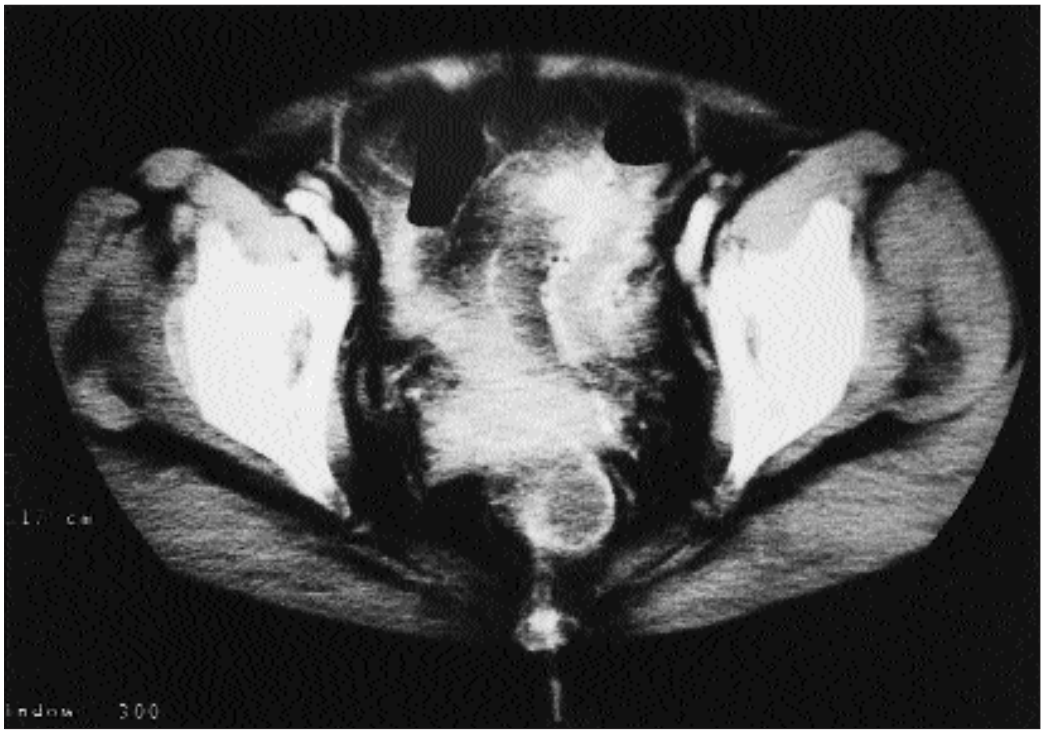

Figure 2. Abdominal CT showing a thick walled sigmoid surrounded by an area of paracolic inflammation and outpouchings representing diverticuli.

The approach to diverticulitis starts from a plain abdominal x-ray, which is normally used for ruling in or out perforation, obstruction. Traditionally barium enema examination had been the mainstay in the evaluation of patients suspected of having acute diverticulitis, but its sensitivity did not exceed 77 %-86 %. The signs could be localised extravasation of contrast material, colonic fold thickening and distortion, localised mass effect.[1] Many believe that this procedure is contraindicated in acute cases; if done, water-soluble contrast material should be employed.[2]

Ultrasound has gained a lot of popularity due to its high degree of accuracy; its widespread availability, relatively low cost, and no need for patient preparation and contrast agents. It can have a sensitivity of 84 %-100 % especially with graded compression technique.[1] The use of intravaginal ultrasound gives a higher sensitivity for evaluation of gut pathology and ruling out gynaecological causes of acute abdomen.[3]

CT has made a significant impact on the diagnosis of gastrointestinal disorders associated with perienteric inflammatory extension.[4] CT is becoming the primary imaging modality for evaluation of patients with clinical symptoms of acute abdomen and a confusing clinical picture.[1]

According to a study, a very accurate method for ruling in or out acute diverticulitis is spiral CT after contrast material administered only through colon (99% accuracy).[5]

Two sets of criteria should be used for a diagnosis of diverticulitis to be established:

1. Mural changes:
   1a- bowel wall thickening
   1b- presence of diverticula

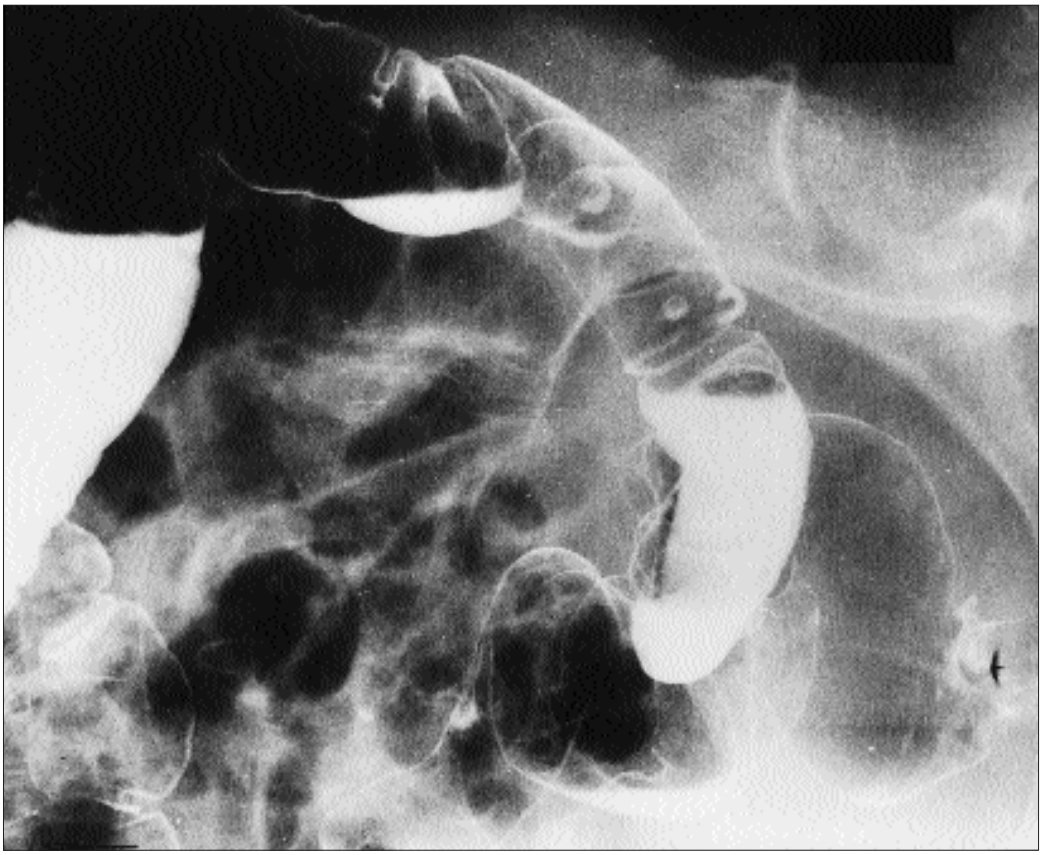

Figure 3. Double contrast barium enema study showing a free lumen and diverticulosis. The examination was done after receiving treatment and regression of symptoms.

2. Extramural changes:

2a- paracolic fat inflammation

2b- paracolic abscess formation

For a definite diagnosis of diverticulitis one from each group should be present.

Several studies show that the sensitivity and specificity of ultrasound and CT in detecting the above mentioned signs is almost the same, except that CT is more sensitive for detecting the extramural changes and divertivula. A problem, which exists, is that none of these signs are specific for diverticulitis, but could also be seen in other tumoral, inflammatory, ischemic conditions and further research should be done for finding specific signs.

According to some authors, the "arrowhead sign" in CT could be specific for diverticulitis (contrast material or gas seen pointing towards the opening of a diverticulum). Another helpful sign, but not specific, is the increasing width of right anterior extrarenal space, which is seen in inflammatory and tumoral conditions of the abdomen.

There are other conditions mimicking acute divericulitis e.g. appendicitis, pelvic inflammatory disease, ectopic pregnancy, oophoritis, renal colic, ischemic colitis, bowel obstruction, colon cancer.[1] Cancer of the sigmoid colon appears as the main differential diagnosis[6], so it is wise to rule out carcinoma after resolution of the acute event with the

follow-up colonoscopy-barium enema study. Appearance of lymph nodes along with thickened bowel wall also speaks in favor of cancer rather than of a chronic inflammatory process.[8]

Conclusions

Ultrasound is the first line imaging modality in ruling in or out acute diverticulitis or other similar conditions mimicking acute diverticulitis clinically.

In cases of critically ill patients presenting with an acute abdomen, CT should be considered as the first line modality.

Patients should be followed up by barium enema study for ruling out cancer after resolution of the acute event.

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Conventional staging and ^{18}F-FDG-PET staging of malignant melanoma

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Background. *Preliminary reports suggest that PET using ^{18}F-FDG may be a valuable diagnostic tool in patients with advanced malignant melanoma. Therefore, the aim of this study was to compare the findings of ^{18}F-FDG-PET and those of conventional imaging including physical examination for both primary and follow-up staging of patients with malignant melanoma.*

Patients and methods. *Thirty-five patients with histologically proven malignant melanoma underwent 61 PET examinations. After an intravenous injection of 370 MBq ^{18}F-FDG, whole-body images were acquired on an ECAT EXACT 47 (921) with an axial field-of-view of 16.2 cm. Moreover, all patients underwent physical examination and conventional imaging, i.e. ultrasound, CT, and MRI within a two-week interval after ^{18}F-FDG-PET. Based on the findings of both staging procedures, the patients were classified according to UICC.*

Results. *In primary staging or follow-up, 5 out of 35 patients were classified as stage I by conventional staging. Seven out of 35 patients were classified as stage II. The remaining 23 patients were initially classified as stage III. In the follow-up, two out of the latter 23 patients were upstaged to stage IV. However, none of these patients was classified as stage IV in primary staging by conventional diagnostic procedures.*

According to the results of ^{18}F-FDG-PET, 9 out of 35 patients revealed neither evidence for distant metastases nor presence of lymph node metastases in primary staging (stage I/II). However, initially 21 out of 35 patients were suspected for lymph node metastases but no distant metastases (stage III). Moreover, ^{18}F-FDG-PET suspected 5 patients, initially classified as stage IV, for distant metastases. However, in the follow-up, ^{18}F-FDG-PET turned out to be false-positive for distant metastases in one out of the latter 5 patients; therefore, this patient was staged down to stage III.

As compared to conventional diagnostic work-up, ^{18}F-FDG-PET revealed the corresponding tumor stage in 17 out of 35 patients (49 %). However, 14 patients (40 %) were staged up by ^{18}F-FDG-PET and 4 patients (11 %) were staged down by ^{18}F-FDG-PET in primary staging or follow-up investigations. With respect to anatomical localization, the majority of false-negative PET lesions were lymph node metastases close to the skin area.

Conclusions. *Our results underline the added value of ^{18}F-FDG-PET in staging of malignant melanoma. Since further treatment mainly depends on the clinical stage, ^{18}F-FDG-PET might help to select the appropriate treatment protocol for each individual patient.*

Key words: melanoma; neoplasms staging; tomography, emission-computed, ^{18}F-FDG-PET; morphological imaging; treatment strategy

Introduction

Cutaneous malignant melanoma is one of the most common malignancies with a twofold to threefold increasing incidence over the last 40 years.[1] The most important prognostic factor is tumor staging at the time of diagnosis.[2] According to the recommendations of the American Joint Commission on Cancer (AJCC), the clinical stage is divided into four groups. Clinical stages I and II are defined for primary malignant melanomas limited to the site of the origin without any evidence of a tumor spread elsewhere. In case of palpable local lymph node involvement or a disseminated disease, patients are classified as clinical stage III and IV, respectively. At the time of the first presentation, nearly 80 % of all patients are noted in clinical stage I or II with a mean 5-year survival rate of 85 %.[2] However, one third of the latter patients will have clinically undetectable lymph node metastases which, if left untreated, will significantly worsen the survival rate.[3,4] Thus, an accurate tumor staging is a prerequisite for selecting the adequate treatment protocol.

Conventional imaging, i.e. computed tomography, magnet resonance imaging, and ultrasound are valuable and well-established diagnostic tools in pretherapeutic staging.[5-8] However, these imaging modalities allow an identification of morphologic changes only, whereas the tumor tissue in normal-sized lymph nodes cannot be detected by definition.[9] Moreover, the morphologically orientated imaging permits a screening of a pre-selected body area only. Since malignant melanomas are known for their aggressive lymphatic and hematogenic spread potency [3,7], one single non-invasive imaging modality with simultaneous imaging of the whole-body would significantly facilitates pretherapeutic management of these patients. Thus, a number of radiotracers have been suggested for this purpose, i.e. ^{67}Ga-citrate [1], ^{123}I-benzamide, ^{123}I-α-methyltyrosine [9], and ^{99m}Tc-labelled antimelanoma-antibodies.[11] A great number of false-negative findings were reported for all of these radiotracers.[9,12] In contrast, initial experiences demonstrated the clinical potency of positron emission tomography (PET) using ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) for the detection of both local and systemic spread of metastatic malignant melanoma.[1,13-22] Within its geometric resolution of about 4-6 mm (FWHM), PET is able to detect tumor tissue independent of morphological changes due to an increased rate of glycolysis in malignant transformed cells. Since the early detection of malignant melanoma metastases increases the patients' survival rate, ^{18}F-FDG-PET might be a valuable diagnostic tool in detecting melanoma metastases.[23,24]

The aim of this study was to compare the findings of ^{18}F-FDG-PET and those of conventional imaging including physical examination for both, the primary and follow-up staging of patients with malignant melanoma.

Patients and methods

Patients

Thirty-five patients (13 female, 22 male) aged from 31 to 81 years with histologically proven malignant melanoma were investigated. The primary tumors were located in the skin area of the head and neck region in 5 patients, of the upper extremities in 4, of the lower extremities in 6, on the chest wall in 3, on the back in 15, and on the abdominal wall in 1 pa-

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tients. The anatomic site of the primary tumor was unknown in one patient.

Clark levels (CL)[25] and classification of the thickness of the primary lesions according to Breslow scheme [26] are listed in Table 1. In short, the following distribution was observed: CL I, no patient; CL II, 1 patient; CL III, 8 patients; CL IV, 18 patients; CL V, 1 pa-

Table 1. Staging of all melanoma patients, according to the findings of conventional imaging and ^{18}F-FDG-PET, respectively. Demographic data, Clark level (CL) and Breslow scheme (BS) are shown in detail as well as a comparison of both staging procedures, respectively. ↑: up-staging by PET; ↓: down-staging by PET; =: staging unchanged, Δ Staging: staging changed by PET with respect to conventional staging, NA: data not available

	Suspicious depth		Conventional staging		PET-staging		
Patient	CL	BS	Primary	Follow-up	Primary	Follow-up	Δ Staging
M/74	IV	0.7	I		III		↑
M/64	NA	3.7	III	III	III	III	=
M/41	III	0.4	III	III	I/II	I/II	↓
F/71	IV	3.3	II		I/II		=
M/48	II	0.5	III		III		=
F/61	IV	>6	III		III		=
F/66	IV/V	8.3	III		III		=
M/81	IV	>4	III		III		=
M/74	IV	1.0	III	III	III	III	=
M/71	NA	>8	III	III	III	IV	↓
M/61	IV	1.2	III		III		=
F/69	III	0.8	I	I	I/II	IV	↑
F/44	III	1.2	I	I	III	III	↑
M/56	IV	4.5	III		I/II		↓
M/59	IV	1.3	II	II	I/II	I/II	=
M/49	IV	2.1	II		IV		↑
M/43	IV	1.9	III		III		=
F/53	III	1.7	III	III	IV	IV	↑
M/63	NA	NA	II		I/II		=
F/79	IV	1.6	III	III, III	III	III, III	=
M/53	IV	3.0	III	III	I/II	I/II	↓
M/45	IV	3.5	III	III	III	IV	↑
M/62	IV	2.6	III	III	III	III	=
M/58	IV	1.1	II	II	III	IV	↑
M/81	NA	NA	II		I/II		=
F/55	III	NA	III	III	I/II	I/II	↓
F/46	IV	1.9	III	III, III	III	III, III	=
F/66	II/III	0.6	I		III		↑
F/60	IV	1.4	III	III, IV, IV	IV	III, IV, IV	↑
F/47	III	1.0	I		III		↑
M/31	IV	2.1	III	IV	III	IV	=
M/66	II/IV	1.9	II	IV	IV	IV	↑
M/43	III	1.6	III	III, III	III	III, III	=
F/52	V	7.0	III		IV		↑
M/57	III	0.4	III	III	III	IV	↑

tient, and 1 patient in each of the following levels: CL II/III, CL III/IV, and CL IV/V. Five patients presented with thin lesions (0.75 mm or less), 21 intermediate lesions (0.76-3.99 mm), and 6 patients thick lesion (4 mm or more). Clark levels and Breslow scheme were not available in four and three patients, respectively, due to the localization of the primary tumor and initial resection.

For the primary staging (n = 35) or follow-up study (n = 26), all patients underwent conventional staging consisting of physical examination as well as of morphological imaging, i.e. chest x-ray, CT scans of the chest, brain and abdomen or MRI. A total of 61 ^{18}F-FDG-PET examinations were performed on these patients. According to the criteria of the UICC [27], (Table 2), the patients were staged both conventionally and by the findings of ^{18}F-FDG-PET, and both results were compared. All tumor-suspicious findings were evaluated by histopathology as a golden standard.

PET scanning

The patients fastened for at least 12 hours prior to PET-scanning in order to minimize blood insulin levels and glucose utilization of normal tissue.[28] Whole-body emission images were acquired without attenuation correction 60 min after i.v. injection of 370 MBq ^{18}F-FDG using an ECAT EXACT 47 (921) scanner (Siemens/CTI, Knoxville, TN, USA) with an axial field-of-view of 16.2 cm.

Table 2. Staging of the cutaneous malignant melanoma according to the criteria of the UICC from 1997

Tumour stage	T	N	M
Stage I	PT1, pT2	N0	M0
Stage II	PT3	N0	M0
Stage III	PT4	N0	M0
	Any pT	N1, N2	M0
Stage IV	Any pT	Any N	M1

Patients were laid in the PET gantry feet first with both arms folded over the abdomen. Images were acquired for 4 min per bed position covering the feet up to the middle of the femurs. Then, the patients were repositioned in the gantry head first, and the second set of images was acquired from the brain down to the waist. Prior to the third acquisition set from the waist down to the lower extremities, the patients were asked to empty the bladder in order to decrease urine activity. Emission data were reconstructed by filtered back projection using a Hanning filter with a cut-off frequency of 0.4 of the Nyquist frequency. PET images were printed on transparency film (Helios 810, Sterling) using a linear gray scale with the highest activity displayed in black. Images were displayed with an upper threshold of five times of the mean activity in the lung. Standardized documentation included both 20 transversal and 20 coronal slices, and maximum-intensity-projections (MIPs) in the anterior, left lateral, right-anterior-oblique, and left-anterior-oblique view as published previously.[29]

Two independent nuclear medicine physicians, blinded to the results of conventional staging, interpreted PET images visually.

Results

Conventional staging

The results of conventional diagnostic procedures are listed in detail in Table 1. According to the results of conventional imaging and clinical examination, 5 out of 35 patients were classified as stage I in primary staging or follow-up, and 7 out of 35 patients as stage II in primary staging. One out of these 7 patients was initially classified as stage II but was then staged up to stage IV at the first follow-up. The remaining 23 patients were initially classified as stage III. In the follow-up investigations, 13 out of these 23 patients remained stage III, whereas two patients were

upstaged to stage IV. However, none of the patients was classified as stage IV in primary staging by conventional diagnostic procedures.

^{18}F-FDG-PET staging

Results of ^{18}F-FDG-PET are listed in detail in Table 1 as well. According to the results of ^{18}F-FDG-PET, nine out of 35 patients had neither evidence of distant metastases nor presence of lymph node metastases at primary staging. These patients were initially classified as stage I to II since ^{18}F-FDG-PET allows in principle no differentiation between pT1, pT2 or pT3. In further follow-up staging, this initial tumor stage was changed in one patient to stage IV malignant melanoma. In primary staging, 21 out of 35 patients were suspected for lymph node metastases, but not for distant metastases; therefore, these patients were classified as stage III by ^{18}F-FDG-PET. In the follow-up investigations, this initial stage was changed in five patients due to distant metastases seen by ^{18}F-FDG-PET. These patients were classified as stage IV. As far as primary staging is concerned, ^{18}F-FDG-PET suspected five patients for distant metastases, classifying these patients as initial stage IV. However, in the follow-up, ^{18}F-FDG-PET turned out to be false-positive for distant metastases in one out of the latter patients; therefore, this patient was staged down to stage III.

Comparison of conventional diagnostic work-up and ^{18}F-FDG-PET

As compared to the conventional diagnostic work-up, ^{18}F-FDG-PET revealed the corresponding tumor stage in 17 out of 35 patients (49 %), whereas 14 patients (40 %) were staged up by ^{18}F-FDG-PET and 4 patients (11 %) were staged down by ^{18}F-FDG-PET at primary staging or follow-up investigations.

Discussion

Initial studies assessed the clinical utility of ^{18}F-FDG-PET for the detection of metastatic malignant melanoma. Gritters and coworkers[3] studied 12 patients with a total of 52 biopsy- or CT-diagnosed melanoma lesions. All patients underwent additional ^{18}F-FDG-PET. Their initial data demonstrated the potential role of ^{18}F-FDG-PET for the detection of metastatic malignant melanoma, especially in untreated extrathoracic lesions. Steinert and coworkers[21] examined 33 patients with the primary diagnosis or known relapse of malignant melanoma. In their patients, ^{18}F-FDG-PET showed a sensitivity of 92 % for the detection of malignant melanoma lesions. Moreover, the specificity was 77 % without further clinical information and 100 % with clinical information. Corresponding findings were demonstrated by Holder and coworkers[16] who recommended ^{18}F-FDG-PET as a primary strategy imaging modality in the staging of melanoma patients.

In this study, a total of 35 patients with malignant melanoma underwent 61 ^{18}F-FDG-PET examinations. In nine of these patients, initial tumor staging revealed a stage I/II disease with no evidence of lymph node metastases or distant metastatic spread. However, in four of these nine patients, morphological imaging and physical examination revealed lymph node metastases and, due to the findings of conventional imaging, these patients were classified as stage III. Thus, ^{18}F-FDG-PET initially led to down-stage these patients. However, in the great majority of the patients, a stage III malignant melanoma was detected both by conventional diagnostic procedures and by ^{18}F-FDG-PET. Thus, 23 and 21 patients were initially classified as stage III melanoma by conventional diagnostic procedures and by ^{18}F-FDG-PET, respectively. However, a detailed comparison of primary staging by ^{18}F-FDG-PET and by conventional imaging showed that only 13 out of 21 pa-

tients, classified as stage III by ^{18}F-FDG-PET, were staged equivalently also by conventional imaging. Yet, in 8 of these patients, conventional imaging and physical examination were false-negative concerning the detection of lymph node metastases. In these 8 patients, ^{18}F-FDG-PET required an up staging. Moreover, ^{18}F-FDG-PET was not able to detect the presence of lymph node metastases only in 4 of 23 patients initially classified as a stage III malignant melanoma by conventional diagnostics. In six of these 23 patients, ^{18}F-FDG-PET not only detected lymph node metastases, but was also suspicious of distant metastatic spread. These patients were therefore classified by ^{18}F-FDG-PET as stage IV. In all patients but one mentioned before, ^{18}F-FDG-PET was true-positive concerning the presence of distant metastases at primary staging.

Comparing the results of both staging methods, it is remarkable that none of the patients was initially classified as stage IV by conventional staging at primary staging. In contrast, ^{18}F-FDG-PET showed suspicious-suspicious tracer accumulations, which aroused suspicion of stage IV. The histological evaluation of the detected lesions confirmed the stage IV in all these patients but one. Thus, concerning the detection of distant metastases at primary staging, ^{18}F-FDG-PET was true-positive in a total of 4 out of 35 patients.

With regard to the findings of conventional diagnostic work-up and those of ^{18}F-FDG-PET, corresponding results were seen in about half of the patients investigated. In 11 % of all patients, conventional diagnostic work-up staged-up the patients comparably to ^{18}F-FDG-PET.

Surprisingly, in the patients in whom ^{18}F-FDG-PET was not able to detect the presence of lymph node metastases, it is remarkable that most of these lesions were found in the inguinal area close to the skin. Thus, the skin might be problematic for the detection of malignant melanoma metastases by ^{18}F-FDG-PET. One potential cause of false-negative results is the fact that ^{18}F-FDG is excreted via the urine. Thus, suspicious lesions of the skin, predominantly on the lower extremities and in the inguinal area, might be interpreted as contaminations. Moreover, it is also known that the patients treated with interferon alpha and interleukin-2 exhibit cutaneous inflammatory infiltrations at the injection site[24] which may be difficult to be differentiated from a metastastic spread. The limited impact of ^{18}F-FDG-PET for the detection of metastases close to the skin might be explained for physiological and technological reasons. First, suspicious lesions located within the regions of high physiological ^{18}F-FDG uptake, i.e. the brain or the kidneys, might not be identified by ^{18}F-FDG-PET imaging. Second, the detection of small lesions with diameters of less than 5 mm might be limited by geometrical resolution of ^{18}F-FDG-PET. Moreover, PET-images in this study were reconstructed by filtered back-projection. As a consequence, melanoma metastases in borderline areas, i.e. the skin, can hardly be differentiated from non-malignant tissue. This problem might be overcome by time-consuming iterative reconstruction algorithms. With these limitations in mind, whole-body ^{18}F-FDG-PET is a suitable imaging modality in order to prove suspicious lesions in malignant melanoma. However, for the exclusion of skin metastases, an accurate and careful physical examination by a dermatologist is still indispensable in daily clinical patient management.

Any diagnostic test should, in principle, not only be judged with respect to its statistic data, but rather in the light of its effect on a treatment strategy. The therapeutic approach in malignant melanoma mainly depends on the extent of the disease. In clinical stages I and II, the excision of the primary malignancy has always been the golden standard. In the last few years, elective lymphadenectomy

was abandoned because its additional value in improving the patients' survival rate was demonstrated only in retrospective[30,31] but not in randomized prospective studies of patients.[31] If patients present with regional lymph node metastases (stage III), the therapeutic approach includes therapeutic lymphadenectomy. However, 10-year-survival-rate decreases from 97 % in patients staged pT1N0M0 to 19 % in patients staged N1 or N2 and M0 melanoma.[32] The primary treatment goal in patients with M1 malignant melanoma (stage IV) is the reduction of tumoral masses in order to prolong the patients' life expectancy as well as to improve the quality of life.[33] In principle, there are three therapeutic options: surgery, external radiotherapy, and chemotherapy. In case of isolated metastases, surgical operative treatment has appeared to be helpful in the prolongation of patients life expectancy. In most studies, life prolongation was demonstrated only in cases of total resection of all tumoral masses.[34] Thus, a 10-year-survival-rate was expected to be as low as 3 % in the patients with advanced malignant melanoma.[32] Unfortunately, there is no well-established, standardized systemic treatment protocol for managing the patients with distant metastases. The treatment strategy itself is still under clinical investigation and the subject of several patients studies. It is now evident that the patients with stage IV malignant melanoma benefit from an aggressive chemotherapy consisting of the application of interleukin-2 and interferon alpha. These authors report 5-year-survival-rate of up to 10 %.[24,35]

In addition to sensitivity and specificity of high-resolution ultrasonography of 70 % and 90 %,[36] respectively, even the patients with advanced malignant melanoma may benefit from the detection of metastases by ^{18}F-FDG-PET due to several reasons. First, patients' survival rate decreases with an increasing number of involved lymph node regions.[37] Second, the prognosis of patients is better with an early detection of metastases and with less suspicious masses at the time of detection.[37] Third, in the detection of lung metastases ^{18}F-FDG-PET has been proven superior as compared to conventional, well-established computed tomography.[38,39] And last, ^{18}F-FDG-PET offers the advantage to image the whole body in one single procedure which is especially important since in malignant melanoma often unexpected, aberrant metastatic spread is found. Thus, ^{18}F-FDG-PET has already been suggested as a tool for staging malignant melanomas.[21]

Conclusion

Our results underline the added value of ^{18}F-FDG-PET in the staging of malignant melanomas. Since further treatment mainly depends on the clinical stage, ^{18}F-FDG-PET might help to select the appropriate treatment protocol for each individual patient. However, for the exclusion of metastases, physical examination by a dermatologist and conventional imaging are indispensable.

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Comparison of CT analyses of primary renal cell carcinoma and of metastatic neoplasms of the kidney

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Background and purpose. *We compared the computed tomography (CT) findings in 25 patients, in 10 with pathologically proven metastases in the kidney and in 15 with renal cell carcinoma to establish the difference on CT scan.*

Patients and methods. *All 25 patients with kidney neoplasm were analysed by the conventional contrast-enhanced CT criteria. Imaging initiated 2 min after intravenous contrast injection.*

Results. *The sensitivity of CT to discriminate renal cell carcinoma from renal metastases and to discriminate renal metastases from renal cell carcinoma were 98 % and 70 %, respectively.*

Conclusions. *This study indicates that CT could be useful in clinical practice for distinguishing renal cell carcinoma and metastatic neoplasms of the kidney.*

Key words: tomography, x-ray computer; carcinoma, renal cell; kidney neoplasm-secondary

Introduction

In order to decide on the type of therapy it is necessary to differentiate between renal carcinoma and renal metastases.

If the renal cell carcinoma is diagnosed, nephrectomy is indicated (in more than 95 %), but in the case of renal metastases, nephrectomy is not the best possible therapy.

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The most common origin of kidney metastases is the carcinoma of the lung.[1] Other primary malignancies are the carcinomas of the colon, breast, stomach, ovaria, uterus and prostate.[2-5]

Although CT is more sensitive than ultrasound and urography in the differentiation of the renal metastases from the renal cell carcinoma, there is only one report comparing CT findings of renal cell carcinoma and of renal metastases.[3]

We report here on CT findings of renal metastases and renal cell carcinoma in order to establish the criteria for the differentiation of these two forms of kidney malignancies.

Patients and methods

CT examination was performed in 25 patients with kidney neoplasms, using a Shimatzu 4500 T with scan times of 2 to 3 seconds. Conventional contrast-enhanced computed tomography studies were perfomed by using intravenous 60 % iodinated contrast medium administered by bolus injection or drip infusion technique. In 15 out of 25 patients (mean age 58 years, range 21-89 years) renal metastases were found. The most common origin of the metastases was the carcinoma of the lung (n = 4), followed by the carcinomas of the colon (n = 3), ovaria, pancreas and a lymphoma, each in one patient. The interval between the initial diagnosis of the primary malignancy and the occurrence of renal metastases was 1 to 5 years (mean 1.9 years).

The diagnoses were pathologically confirmed by surgery in 19 patients (renal cell carcinoma 18, renal metastases 1), by biopsy in 4 patients (renal metastases 4), and by autopsy in 2 patients (renal metastases 2). When multiple tumours existed in one or both kidneys, the largest tumours were chosen for evaluation because they were the most frequently biopsied.

Renal function was normal except in one patient with lymphoma and acute renal failure, successfully treated by haemodialysis.

There were no patients with acquired renal cystic disease or patients with Von Hippel-Lindau disease.

Results

We retrospectively reviewed 25 cases of kidney neoplasms diagnosed during the past 5 years. Fourteen CT criteria were chosen to characterise the tumours: bilateralism, number, location, size, shape, margin, calcification, involvement of the renal vein, involvement of collecting system, hydronephrosis, perirenal extension, attenuation, thickening of Gerota's fascia and lymphadenopathy. Table 1 presents the result concerning individual predictors of renal cell carcinoma and renal metastasis.

Criterion location included 2 categories: type I - tumour located entirely within the renal parenchyma and capsule, less than 50 % of the tumour has an exophytic pattern; type II - more than 50 % of the tumour demonstrated an exophytic pattern. The largest axis was used as an expression of the tumour size. The lesion's shapes were divided into round or wedge-shaped. The tumour margin was characterised as well or poorly demarcated, and the attenuation (density) as homogenous or inhomogeneous. The lymph nodes were measured by the length of their longest axis and those that were more than 10 mm long were diagnosed as positive. The calcification, renal vein involvement, collecting system involvement, hydronephrosis, perirenal extension and Gerota involvement were descirbed as yes or no. All patients with renal cell carcinoma had solitary tumours (100 %). Five patients (50 %) with renal metastasis had solitary tumours, 3 patients (30 %) 2 unilateral tumours, and 2 (20 %) patients had more than 2 bilateral tumours.

Renal metastases were smaller (mean 3.1 cm) than renal cell carcinoma (mean 8 cm). A round shape was found in 80 % of patients with renal cell carcinoma, and in 70 % of patients with metastases.

Renal cell carcinoma were of exophytic pattern in 60 % of patients, with the size of 6-9 cm in 53 % of patients, well demarcated tumour margin in 66 % of patients, calcification in 33 % of patients, renal vein involvement in 20 % of patients, collecting system involvement in 73 % of patients, with hydronephrosis in 36 % of patients, perirenal extension in 60 % of patients, and lymph node metastasis in 53 % of patients.

Renal metastases were located within the kidney parenchyma in 80 % of patients; their size ranged 0-3 cm in 60 % of patients. The metastases had smooth margins and were without calcification in 80 % of patients; in 10 %

Table1. Individual predictors between renal cell carcinoma and renal metastasis in our patients (I part)

Predictors		Renal cell carconoma	Renal metastases
Laterally	Unilateral	15	8
	Bilateral	0	2
Number	One	15	6
	Two	0	3
	>=3	0	1
Location	a) within parenchyma and capsule, less than 50 % of tumour is exophytic	6	8
	b) more than 50 % of tumour is exophytic	9	2
Size	0-3 cm	2	6
	3.1-6 cm	5	3
	6.1-9 cm8	1	
	> 9.1 cm	0	0

Table 2. Individual predictors between renal cell carcinoma and renal metastasis in our patients (II part)

Predictors		Renal cell carcinoma	Renal metastases
Shape	round	12	7
	irregular	3	3
Margin	smooth	10	3
	irregular	5	8
Attenuation	inhomogeneous	6	8
	homogenous	4	6
Calcification	no	10	10
	yes	5	0
Renal vein involvement	no	12	0
	yes	3	9
Collecting system involvement	no	4	7
	yes	11	3

Table 3. Individual predictors between renal cell carcinoma and renal metastasis in our patients (III part)

Predictors		Renal cell carcinoma	Renal metastses
Hydronephrosis	no	10	9
	yes	5	1
Perirenal extension	no	6	7
	yes	9	3
Gerota involvement	no	8	8
	yes	7	7
Lymph node metastases	no	7	7
	yes	8	8

of patients, renal vein involvement and in 30 % of patients collecting system involvement were observed; 80 % patients had lymph node metastasis.

The stepwise discriminant analysis showed that number (N), laterality (L), location (LO), perirenal involvement (P) and calcifications were the strongest predictors. The primary and secondary scores were calculated according to Honda et al. as follows:

Primary score = (L x 3.63) + (N x 0.85) + + (P x 0.83) + (LO x 4.29) - - 9.65.

Secondary score = (L x 5.01) + (N x 2.67) - (P x 1.27) + (LO x 3.33) - - 11.60.

The radiologic variables were defined as follows:

L = laterality; 0 = unilateral, 1 = bilateral
N = number; actual number of the tumours
P = perirenal involvement; 0 = yes, 1 = no
LO = location: 0 = a, 1 = b.

Using these primary and secondary scores the posterior probabilities (PP) of primary versus secondary tumour were computed as follows:

Posterior probability (primary) =
= exp(primary score) / exp(primary score) + exp(secondary score)

Posterior probability (secondary)=
= exp(secondary score) / exp(primary score) + exp(secondary score)

The PP (primary) + PP (secondary) = 1.
When PP (primary) > PP (secondary) the number can be diagnosed as primary tumour. When PP (primary) < PP (secondary) it can be diagnosed as secondary tumour.

The classification functions detected 98 % of primary renal cell carcinoma and 70 % of metastases.

Discussion

The kidney is a common site of metastases, with reported incidence of 2 to 20 % at autopsy.[6-9] The tumour that most commonly metastasises to the kidney is the lung carcinoma[1], followed by the tumours of the breast and stomach, melanoma and contralateral renal cell carcinoma.[5]

Most renal metastases are less than 3 cm in diameter, whereas more than 50 % of renal cell carcinomas are more than 6 cm long.[6]

Bilateral, multiple, small lesions without an exophytic appearance may be seen in multiple areas of renal inflammation, renal infarction and multiple renal cysts.[10]

It is well known that renal cell carcinoma can also occur bilaterally or multifocally, especially in the patients with predisposing conditions (i.e. in the patients with acquired renal cystic disease or patients with Von Hippel-Lindau disease).[11,12] This study did not include any patients with acquired renal cystic disease or patients with Von Hippel-Lindau disease.

In recent years, more and more small renal masses have been reported (usually incidentally) due to the widespread use of cross-sectional imaging modalities (especially ultrasound and computed tomography) as well as other reasons.[13,14] Most of these masses are low stage renal cell carcinomas. The problem is that the growth rate of small renal tumours is variable; the tumours that are destined to grow and possibly metastasise do so early. So, bilateral or multifocal involvement doesn't exclude renal cell carcinoma as the diagnosis.[14]

The size "per se" cannot be a strong predictor for the metastases.[15,16] The indication for surgery in renal cell carcinoma is under discussion in the urologic literature.[12] The main problem of nephron-sparing surgery is the multifocality of renal cell carcinoma. Modern double-phase helical CT can distinguish among the subtypes of renal cell carcinoma

(clear, chromophobe, papillary), and correlates with microvessel density or the existence of intratumoral necrosis or haemorrhage. However, it does not differentiate between renal cell carcinoma and other solid tumors.[17]

In the preparation for nephron-sparing surgery of renal cell carcinoma, preoperative routine imaging cannot safely predict multifocal lesions of renal cell carcinoma.[12]

In this study, tumour calcification was a diagnostically strong predictor for the renal cell carcinoma. Calcifications were present in five cases of renal cell carcinoma and in none of the cases of renal metastases. Metastases were more frequently bilateral or multifocal, and smaller than renal cell carcinoma.

Stepwise, discriminant analysis showed that the useful radiologic predictors were the number, laterality, location and perirenal extension. The sensitivity of CT to discriminate renal cell carcinoma from renal metastasis was 98 %, and to discriminate renal metastases from renal cell carcinoma was 70 %. In contrast to the investigation of Honda et al., the margin of the lesion, the involvement of the renal vein and collecting system, existence of hydronephrosis, thickening of Gerota's fascia and lymphadenopathy were not diagnostically strong predictors, like in.[3]

Conclusions

Using the stepwise discriminant analysis and posterior probabilities of primary versus secondary tumour, computed tomography could be useful to differentiate between non-multifocal renal cell carcinoma and renal metastasis.

In patients with a single, exophytic, large and perirenally extending lesions with calcifications, renal cell carcinoma is more likely than renal metastasis.

In patients with multiple, less exophytic, small renal lesions with or without wedge shaped appearance, the renal metastasis is more likely than the renal cell carcinoma.

The biopsy of tumour lesions is restricted to cases with discrepancy between clinical manifestation and computed tomography findings.

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Review

Opportunities for up to date treatment of the colorectal cancer

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Background. *Up to now the basic methods in the treatment of colorectal cancer are surgery, chemo- and radiotherapy. Throughout current years new methods were developed and successfully used in oncology; they consist of application of specific antibodies, the antibody driven enzyme pro-drug treatment, the application of radioimmunoconjugates and the radioimmunoguided surgery.*
Conclusions. *With the applied methods for the treatment of colorectal cancer we prolong a disease-free surviving period, reduce subjective complaints and decrease mortality.*

Key words: colorectal neoplasms-therapy

Introduction

The colorectal cancer (CRC) provides great opportunities for challenging the surgeon's skills, as well as for the application of the modern molecular biological and radioimmune methods for its diagnosis and treatment.

The presented review aims to introduce the contemporary state of the problem and the possibilities for the application of some new methods for treatment into the surgical society.

Despite the achievements of the modern clinical oncology the colorectal cancer is diagnosed relatively late, i.e. in the advanced clinical stage. The treatment is unsatisfactory. The mortality is high.

The annual mortality in the United Kingdom in 1995 was about 20 000; Italy 7000; in Bulgaria 1400.

The most frequent localisation of the colorectal cancer is the rectal cancer. Its incidence in the Western European countries is 70 / 100 000 population. Many people could be protected from the colorectal cancer by introducing accessible screening methods. Many of the complications of the traditional surgery can be avoided by improving the technical abilities for the operative treatment.

In about 50 % of the patients suffered from the rectal cancer the definitive colostomy is unavoidable. In 2/3 of them it could be avoided by applying the so-called total mesenteric excision (TME) with a modern stapling technology. The early diagnosis, the accurate preoperative staging, the radical surgical inter-

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vention and the subsequent postoperative chemo- and radiotherapy are of great importance for the complex treatment of the colorectal cancer.

Up to now the literature does not comment the issues about the functional disorders of the reservoir functions and the disturbances of the sexual function and the socialisation of the person.[1]

At present the main methods for the treatment of the colorectal cancer are:
— Surgery
— Chemotherapy
— Radiotherapy

In the recent years the following new technologies and methods are applied for the treatment of the colorectal cancer:
— Application of specific antibodies;
— Creation and application of radioimmunoconjugates;
— Radioimmunoguided surgery (RIGS);
— Antibody driven enzyme pro-drug treatment (ADEPT).[2]

Application of specific antibodies

The development of immunology and immunotherapy as a branch of the oncology originates from the works of Cooley who established that in patients with the advanced sarcoma the same has a regressive course after a severe infection.

There were hopes due to some medicines, like BCG vaccine, levamisol (Lev), interferon, interlevkin -2 (IL-2). There are several randomised studies for the effect of BCG-vaccine application in patients with CRC but none of them has proved some advantage regarding the total or the disease-free surviving period.

Levamisol increases the immune response by stimulating the T-lymphocytes, the macrophages and the neutrophils. The simultaneous application of Lev+5 Fluorouracil (5-FU) to the patients in stage C, according to Dukes, decreased mortality in 1/3 of the cases. The single use of Levamisol does not cause changes in the percentage of the survival rate compared with the other group of patients who do not receive the medicine.

Another study of the application of IL-2 has found higher percentage of the survival of patients who have received this medicine before the operation, followed by the postoperative application of 5-Fu and Folic acid. There was found that this medicine increased the ability of patients to tolerate easier the postoperatively developed lymphocytopenia.[2,3] The works of Leonard P.C. (1999) and Brivio et al. (1996) claim that the medicines stimulating the humoral immunity do not meet the hopes reposed on them. That is why in the clinical practice the antitumor antibodies (Ab2) were established and introduced. The works in this field are directed to:
— Manipulation of antigen presenting cells;
— Use of co-stimulating molecules for facilitating the specific cell activation;
— Use of double specific antibodies by T-cell targeting to the tumour.

Monoclonal antibodies

The designing and introducing first in the experiment and later in the clinical practice of monoclonal antibodies is related with the invention of CEA. Its relation with the cancer of the colon has encouraged studies using radiolabelled anti-CEA monoclonal antibodies. Other two classes with even higher specificity are TAG-72 and 17-1A. In a randomised study on 189 patients with CRC, stage C according to Dukes, who have been treated by the resection received either 500 mg 17-1A antibody, followed by 4 x 100mg infusions every month or have been just followed up for 5 years. In the treated group it was found 27 % decrease of the relapses and 30 % of the mortality.[2,4]

High affinity single-chain Fv antibodies loaded with radioisotope and CEA were cre-

ated in the last 2 - 3 years. They, with high tumour affinity and their sensitivity, significantly exceed this of the up to now used computer tomography (CT).[5]

Radioimmunoconjugates

The radioimmunotherapy was developed as a type of treatment due to the ability for the successful targeting of radiolabeled antibodies to the tumour antigens (e.g. radioactive CEA antibodies for the treatment of CRC).[2] They are high - energy beta-particles, emitted from Radionuclide, such as ^{131}I, ^{90}Yt, ^{111}In, accumulating in the tumour, characterised with high efficiency in experimental models and for ^{131}I and ^{111}In in patients.

Radioimmunoguided surgery

The implementation of the above-mentioned radioimmunoconjugates in the medical practice contributed to the development and application in the surgical diagnosis of the so-called radioimmunoguided surgery. The postoperatively applied radioimmuno-antibodies are targeted against the tumour tissue. By the aid of a gamma-detector in the particular time interval and even intraoperatively the tumour process can be exactly located and staged. The implementation of the method will facilitate:

- Finding metastases in hepatogastric ligament
- More comprehensive and exact staging of the tumour process.

A problem for the intraoperative staging is whether there are metastatic lymph nodes in hepatogastric ligament or not. The application of anti -TAG - MoAbs changed the decision making for the surgical treatment and staging of patients with primary or relapsing colorectal tumour. There can be concluded that TAG - MoAbs can be used for the intraoperative detection of the tumour even when there are no significant levels of the serum TAG- 72 and /or CEA.[6]

In the study of Filez L. (1999), carried out on 26 patients with CRC, the application of RIGS has led to the change of the operative technique in 16 patients.[6]

At present in USA and Europe a multicenter clinical trial for the evaluation of the possible benefits of RIGS is going on in patients with the primary colorectal tumour as well as with its relapses.[7]

Chemotherapy of CRC

Already for several decades 5-Fu the main stream of the treatment of advanced colorectal cancer and of some other solid tissue malignancies is obvious, despite that its success in patients with the advanced colorectal cancer is low (incidence of effectiveness 10-15 % when using bolus injections).

The application of 5-Fu by the infusion has a better effect than the bolus injection due to the route of administration or to the dose intensity achieved or as a combination of both factors.[8-10]

The presence of some new drugs including biochemical modulators of 5-Fu, increasing its cytotoxicity, has renewed the interest to these agents in the recent years.

Some of them are other fluoro-pyrimidins, new modulators of 5-FU or new ingredients, activated in a different way.

5-Etinoluracil. At present a clinical trial of this agent in combination with 5-Fu is carried out.

Trimetrexat. It is considered as a more potent modulator of 5-Fu than metotrexate. One recently completed phase III clinical trial has found good results in the treatment of patients with CRC.[11-12]

Thymidilat - syntetase (TS) inhibitors

The TS inhibitors catalyse the uridin monophosphate (UMP) methilation to the timidilatmonophosphate (TMP), which is after that metabolised to the timidilatmonophosphate (TTP). At present 6 TS inhibitors are included in the clinical practice as pre-clinical or early clinical trials.

Tomudex (ZD 1694 or raltritrexed) is a specific TS inhibitor in the advanced stage of a clinical trial. In a large phase II study 187 patients with the untreated colorectal cancer were included. An objective effect is found in 26 %. In a completed randomised phase III clinical trial comparing Tomudex with 5-Fu+Lev. (bolus injections) the identical survival and degree of effectiveness has been found. Tomudex was been applied in a dose of 3 mg/m^2 as an infusion in every three weeks.

Other drugs

Irinotecan is a topoisomerase I inhibitor and it is created for the treatment of the advanced CRC. The DNA-synthetase inhibition leads to a retention of S-phase of the cell cycle. In a trial with the agent on 455 patients with the advanced CRC there was found the stabilisation of the disease in 42 %, benefit incidence of 13 % and symptoms suppression in 62 %.[13,14]

Oxaliplatin. This is a diamonohexan platinum complex with an alkylating agent. There was found the benefit incidence of 10 % and in combination with 5-Fu+Lev.of 20-40 %.

Prevention of the relapsing CRC

The incidence of relapse after the radical resection in patients with CRC varies from 2,6 up to 32 %. The time for the local relapse is various but in 55 to 80 % it occurs in the first 2 years following to the operation.[15]

The incomplete tumour resection is one of the causes, as according to different authors it varies from 4 to 27 % as 85 % of the patients have tumour invasion of the lateral resection lines and develop a relapse in a term of 23 months.[15]

According to the data of Burkhardt et al., cited from other authors too[15] by the aid of the conventional histology bone marrow metastases in 17 % of patients with the intestinal cancer without any evidence of the systemic problems were diagnosed.

Except these two widely accepted methods in the recent years there were accepted methods for:

- Intralumen tumour sterilisation by Povidone iodine 10 % or 5 % solution, iertimide, chlorhexidine and Dakin's solution which were assessed as more cytotoxic and cancericide than some other agents.[15]
- Systemic chemotherapy
- Intraportal chemotherapy

Their implementation immediately after the operation causes the destruction of the tumour cells, which could disseminate in the portal circulation at the time of the surgical intervention. The analysis based on the data upon 3824 patients and consistent with the aim of the treatment showed a reduction of the risk for relapse with 14 ± 5 % (p = 0,007) and for death with 13 ± 6 % (p = 0,007) after median 5 year follow up.[16]

- Intraperitoneal chemotherapy. There is no available data about performed controlled trials.

Conclusions

Reaching high incidence of surgical healing is the most important aim in the present time.

Instead of being considered as "harmless" the abdomino-perineal extirpation should be applied only for the highest situated cancers.

The high specificity of imunotherapy will lead to the effective treatment but will create an immune memory providing a defence against relapses.

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Radical irradiation of the prostate. Combination of percutaneous irradiation and irradiation with LDR Ir-192 implants

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Background. *The irradiation of the carcinomas of the prostate with the doses above the tolerable ones of standard radiotherapy improves the local control of the disease. The aim of this study is to determine the acute toxicity and tolerability of the high-dose prostate irradiation combining external beam radiotherapy (EBRT) and interstitial low dose rate (LDR) brachyradiotherapy (BRT) with Ir-192 of the prostate.*

Material and methods. *We examined medical records of 8 patients with localized carcinoma of the prostate (T2-T3 No-x Mo) treated from August 1999 until February 2000. The initial PSA was 2.7-37.5 ng/ml (median 13.7) and Gleason score 4-9 (median 7). Radiotherapy consisted of 48.6 - 50.4 Gy of EBRT to the prostate and seminal vesicles (4 patients) or the whole pelvis (4 patients) and 20.0-28.0 Gy of interstitial LDR Ir-192 BRT given as a single fraction, fluoroscopic guided transperineal implantation of the prostate. The cumulative doses of percutaneous and interstitial irraditations to the prostate were 68.6 - 79.1 Gy.*

Results. *Acute toxic effects of irradiation though observed in all patients were of only mild intensity. According to the RTOG criteria, 20/30 toxicities were assessed as grade 1, 9/30 as grade 2, and 1/30 as grade 3. In none of the patients, toxic effects required any specific modification of the treatment regimen.*

Conclusions. *The very first experiences indicate moderate toxicity and optimal tolerance of the treatment by patients. An improvement of implantation techniques may be expected with regular CT controls of the implants and extra attentive care of the implants in the urethra region.*

Key words: prostatic neoplasms - radiotherapy; radiotherapy dosage; brachytherapy; radiotherapy - adverse effects

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Introduction

The aim of any local therapy has always been to obtain local control of the disease. A better local control over the localized carcinomas of the prostate and the locally advanced tumors invading to the seminal vesicles, periprostatic tissue or urinary bladder can improve also the systemic control of the disease - better local control is associated with better biochemical, distant metastasis-free and cancer specific survival rates.[1-3]

The probability of local recurrence after standard irradiation with the doses not exceeding 70 Gy is 20-60 % in locally advanced tumors (T3,T4),[4] and 8-27 % in T1 and T2 tumors.[2,5-7] However, the effectiveness of standard radiation in terms of local disease control might be even lower. As suggested by the PSA-based follow-up, the rate of local disease control assumed from the digitorectal and imaging examinations of the prostate is perhaps overestimated.[6]

One of the factors that influence local disease control is the radiation dose. Even within the range of conventional external beam radiotherapy (EBRT), the dose increase improves the local control of disease. In conformal radiotherapy; a better biochemical control of disease, at least temporarily, within five-year projection, is obtained with a dose increase up to 81 Gy. In view of the treatment modality, this is due to a better local control. The effectiveness of conformal radiotherapy may be observed in particular in the group of patients with the initial PSA between 10 and 20 ng/ml or with high tumor grade (Gleason score 8-10) in whom standard radiation is often unsuccessful.[8,9]

Tumor dose depends upon the tolerance of surrounding organs to radiation. In conformal radiotherapy, higher tolerance may be obtained with a more precise adjustment of radiation fields to target volume, thereby reducing the involvement of the surrounding organs that are not affected with tumor mass.[9-11] Similarly, the increase of a tumor dose not exceeding the level of admissible impairment of the surrounding organs can be obtained with the combination of percutaneous radiation and brachyradiotherapy (BRT) using J-131, Pd-103[12,13] seeds or Ir-192 wires[14-17] as permanent or temporary implants, respectively. The article describes our experiences with the combination of percutaneous irradiation and interstitial low dose rate (LDR) BRT with Ir-192.

Material and methods

From August 1999 to February 2000, 8 patients with localized carcinoma of the prostate received combined therapy of percutaneous irradiation and interstitial brachyradiotherapy with Ir-192.

In all patients, transrectal ultrasonography was carried out before treatment. In seven patients, the US guided biopsy from six typical sites was performed, whereas in 1 patient only the biopsy of tumor mass was made. In all patients, the PSA concentration in the serum was measured. In all of them, the carcinoma of the prostate was histologically confirmed and its grade assessed according to Gleason score. They also underwent the CT scan of the pelvis, bone scintigraphy, X-ray of the thorax and renography.

The treatment indications were given with the histological confirmation of the adenocarcinoma of the prostate, stage T1-T3 No Mo, while the contraindication was earlier transurethral resection of the prostate. Some restrictions were imposed by the expected survival rate - 5 years in patents with high tumor grades (Gleason over 7), and 10 years in the rest of the patients, all with PSA concentration in the serum not exceeding 30 ng/ml.

The recruitment of the patients was based on negative selection, i.e. unsuitability of the patients for a radical surgery due to the risk factors, such as high tumor grade, tumor

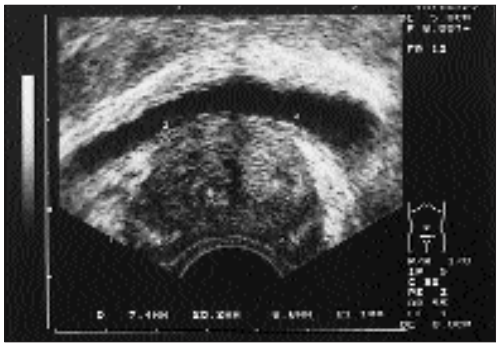

Figure 1. US-guided implantation of metal implants. The implants are marked with arrows.

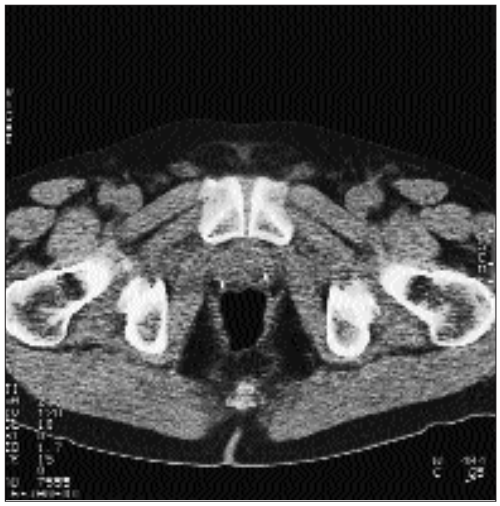

Figure 2. Metal implants viewed by CT scan. The implants are marked with arrows. The distance between the implants and the prostate margins on CT and US images is used in assessing the target volume and implantation planning.

spread into seminal vesicles, tumor overlapping the capsule, PSA over 10 ng/ml, or accompanying diseases that may add on doubts to the fitness of the patients for surgical treatment.

The patients' characteristics are presented in Table 1.

The preparations for brachytherapy started with the US-guided insertion of 3 to 4 permanent metal implants into the prostate (Figure 1). CT scans were used for the planning of radiation delivery and metal implants served as markers. The location of markers in the prostate, especially with respect to the prostate margins, was determined from the CT scans (Figure 2). The planned target volume encompassed at least 0.5 cm margin around the outer border of prostate or any extracapsular tumor extension. The needles were implanted under digital and fluoroscopic control using metal implants as orienters. A proper needle positioning was achieved by a template with 1 to 1.5 cm spacing between the needles. The contrast in the urinary bladder served for a proper positioning of needles' points into the bladder wall in order to assure a satisfactory radiation of the base of the prostate. In planning the implantation as well as carrying it out, we were careful to avoid the urethra. During the implantation, the

Table 1. A survey of patients with regard to their age, tumor stage, initial PSA concentration and tumor grade (Gleason score)

No. of patients	Age (years)	T stage	PSA (ng/ml)	Grade
1	68	T2c	24.4	7
2	68	T3	7,2	4
3	71	T2a	18,9	7
4	68	T3	37,5	7
5	72	T2b	12,5	5
6	72	T3	14,3	9
7	73	T3	2,7	5
8	68	T3	13,2	7

position of the urethra was marked by the contrast contained in the urinary catheter. With regard to the size of the prostate and activity of Ir wires, the number of implanted needles varied from 11 to 16. Following the tradition of the house, we applied, in 7 patients, metal needles, which were later replaced by plastic ones, to provide higher comfort to patients and also to facilitate the subsequent determination of the location of the needles with CT scan. We used 20 cm long needles with a diameter of 1.9 mm.

A single implantation was planned before starting with of EBRT. The prescribed dose was defined as the dose applied to the peripheral isodose area involving the planned target volume and, at the same time, assuring a minimal exposure of the rectal wall and urethra (the so-called *100 % isodose*) (Figure 3). The dose calculation was made according to the Paris dosimetry system. The reference dose was 15 % lower than the minimum dose within the implant. The calculations of the prescribed dose also took account of biological correction factor with respect to the dose rate. The so-calculated radiation dose ranged from 2000 cGy to 2800 cGy.

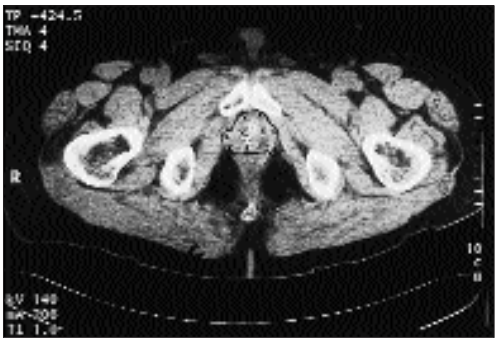

Figure 3. CT image of the implant with reference isodose.

Brachyradiotherapy was followed by EBRT. The patients were irradiated with the linear accelerator of the energy of 10 MV using the technique of four fields and individual shieldings. The standard fractionation was applied. The prescribed target dose was 50.4 Gy given in daily doses of 1.8 Gy. With regard to the probability of lymphogenic spread that was calculated from Roach's equation, the radiation was targeted exclusively to the prostate and seminal vesicles if the estimated risk was lower than 15 %; otherwise the regional lymph nodes were also involved.[17] In these cases, standard, pelvic fields were applied. In EBRT, limited to the prostate and seminal vesicles, target volume included also a 2.5 cm wide surrounding margin.

The details of radiation therapy are presented in Table 2.

All patients received complete androgen

Table 2. A survey of patients with regard to the external beam radiotherapy (EBRT) field and dose, dose delivered by brachiradiotherapy, total dose delivered to the prostate and treatment time

No. of patients	EBRT field	EBRT dose (Gy)	EBRT dose (cGy) dose (cGy)	Dose to (Gy) the prostate	Treatment) time (days
1	pelvis	48,6	2000	68,6-78,6	54
2	P+SV	48,6	2000	68,6-72,3	48
3	P+SV	48,6	2000	68,6-69,5	42
4	pelvis	48,6	2500	73,6-78,9	47
5	P+SV	50,4	2500	75,4-80,6	53
6	pelvis	50,4	2000	70,4-74,4	48
7	P+ SV	50,4	2400	74,4-79,6	45
8	pelvis	50,4	2800	79,1-84,1	56

P+SV: prostate and seminal vesicles; Dose to the prostate: total dose including the mean minimal dose within the implant.

blockade for a period of at least three months before irradiation.

Toxic effects of irradiation were evaluated according to the RTOG criteria.

Results

In all patients, the treatment was completed within the expected period. The treatment time ranged from 42 to 56 days (median 48 days). The differences in treatment time are due to different time intervals between brachy- and teleradiotherapy, which could not be avoided because the treatment facilities are overcrowded. In no one of the patients, the toxic effects of radiation were so severe that they would require discontinuation of the therapy.

In most patients (7/8 patients) the treatment was completed without major complications. In one patient, the position of the implant changed. The implant was therefore prematurely removed and reimplanted after the completed percutaneous irradiation.

The toxic side effects of the irradiation of the urinary bladder, urethra and rectum occurred in all patients. They were generally mild and did not radically affect the quality of life. According to the RTOG criteria, 20/30 side effects were categorized as morbidity grade 1, 9/30 as grade 2, and 1/30 as morbidity grade 3.

The side effects arising from the radiation toxic effects on the urinary organs were evaluated in 6 patients. In one patient, this evaluation could not be made because the urinary catheter had been inserted permanently before treatment. The most often side effects were more frequent urinations, urge to urinate (7/7 patients), stranguria (6/7 patients), dysuria (4/7 patients), and hematuria (1/7 patient). This single case of hematuria, which occurred immediately after the removal of the implant and required the whole day rinsing of the bladder, was the only morbidity grade 3.

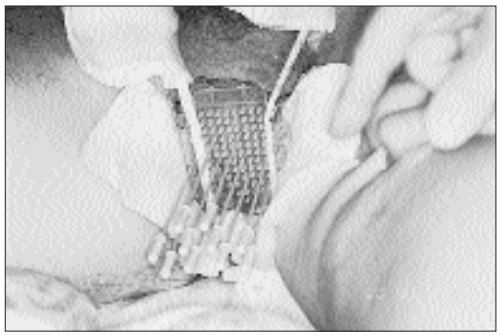

Figure 4. A patient with the inserted implant: a clear view of plastic guides and perineal template.

Table 3. Acute toxic effects of percutaneous irradiation combined with low dose rate brachyradiotherapy (LDR BRT) Ir-192: urinary toxicity with regard to the pain, frequency of mictions, decreased stream, and hematuria. The grade of these complications is evaluated according to RTOG criteria

No of patients	Pain (grade)	Frequency (grade)	Decreased stream (grade)	Hematuria (grade)
1	2	1	+	0
2	2	1	0	0
3	1	1	+	0
4	0	1	+	3
5	0	1	+	0
6				
7	1	1	+	0
8	0	1	+	0

Table 4. Acute toxic effects of percutaneous irradiation combined with LDR BRT Ir-192: intestinal toxicity with regard to stool frequency, painful defecation, tenesmuses and bleeding. The grade of these complications is evaluted according to RTOG criteria

No. of patients	Stool frequency (grade)	Pain (grade)	Tenesmuses (grade)	Bleeding (grade)
1 2	1	0	0	
2 0	0	0	0	
3 0	1	0	0	
4 1	1		2(*)	0
5 0	0		2(*)	0
6 2	2	0	0	
7 1	0		2(*)	0
8 0	2	0	0	

(*) concurrent miction, evacuation of winds and mucinous rectal discharge

Painful defecation was the most often toxic effect of the rectal irradiation (5/8 patients), followed by more frequent defecation (4/8 patients), and tenesmuses (3/8 patients). No hemorrhage from the colon was observed.

The complications in the urinary organs occurred in all patients immediately after the completion of BRT. During percutaneous irradiation, these complications were intensified in 3/7 patients: in 2 patients, the urge of frequent urination further increased, whereas in one patient, stuttering urination became more disturbing. Radiation proctitis was noted in 3/8 patients after the removal of the implant: in one patient, it was manifested as more frequent tenesmuses, in the second as tenesmuses and more frequent defecations, and in the third as painful defecations.

The occurrence of side effects was higher with higher BRT doses. They were mostly related to more intensive proctitic complications. All patients who had proctitic complications after brachyradiotherapy received a dose exceeding 2000 cGy. In all these patients, the complications persisted also during the percutaneous irradiation. The cystitic symptoms were also more pronounced and long lasting in the treatment with higher doses, while with lower doses, this complications disappeared in the first two or three weeks of percutaneous irradiation.

Within the short follow up, no biochemical recurrence was observed in the patients with the PSA concentration that was at the beginning of radiotherapy lower than 1 ng/ml.

Discussion

The technique of transperineal biopsy of the prostate with the US-guided needle was introduced by Holm in the 1980s. The technique was then used primarily for diagnostic purposes, and after unsuccessful retropubic implantations of J-125 seeds into the prostate, also for therapeutic purposes in the treatment of the carcinoma of the prostate. The findings of some radiobiological facts on the unsuitability of the treatment with J-125 and the development of high dose rate (HDR) BRT urged the application of permanent Pd-103 implants and temporary HDR Ir-192 implants in the treatment of the carcinoma of the prostate. At the same time, new data and knowledge on the value of particular tumor characteristics in prognosticating the natural progression of very different tumor types were being gathered.

The prognostic factors, such as PSA concentration, local spread of the disease, and histological tumor grade, allow the categorization of the patients with localized disease into the groups with respect to the assumed disease progress. This also facilitates a better analogy of different treatment modalities and, consequently, also the selection of the most suitable one. In view of radical radiotherapy, the patients may be classified into three groups; the first group, termed as 'prognostically favorable', includes the patients with the tumor stages T1 and T2, PSA level below 10 ng/ml and Gleason score grade lower than 8. In this group, the conventional teleradiotherapy, implantation of J-125 or Pd-103 seeds [8,18-20] and radical prostatectomy18 are all considered as effective treatment modalities. The second group comprises the patients in whom high dose radiation therapy,[8,9] eventually with the irradiation of the regional lymph nodes,[13,20] seemed to be more effective than standard radiotherapy. The patients falling into this group have the serum PSA levels ranging between 10 and 20 ng/ml,[8,9,13,21] tumor stage T3,[8,14] and Gleason score grade above 7[8] or 8.[22] The patients with more of the above mentioned unfavorable prognostic factors[8,23,24] or PSA level exceeding 20 ng/m[l8,9,13,22] may be defined as 'high risk group', at least in view of the curability with only local or locoregional treatment - however, in these patients the local control, relapse-free and overall survivals[25,26] can be improved by an adjuvant hormonal therapy. With regard to the above prognostic factors, our patients were consistent with the mean and the high-risk group. The decision on treatment modality was therefore focused on three main issues: the use of high dose irradiation of the prostate,[8,9,14-17] elective irradiation of the seminal vesicles[27] or regional lymph nodes[24] and instantaneous medicamentous androgen blockade.[25,26] These issues were resolved by applying the combination of EBRT to the prostate and seminal vesicles or to the pelvic region and the LDR Ir-192 BRT to the prostate, together with an instantaneous application of LH-RH agonists and blockers of androgen receptors.

Our brachyradiotherapy technique was based on the CT and transrectal ultrasound (TRUS) determinations of the target volume, the introduction of the needles with respect to the position of implanted metal markers, fluoroscopic control of the position of the needles, and choice of LDR Ir-192 as the radiation source. The main reasons for this specific technique were the in-house experiences with LDR BRT Ir-192 method, limited possibilities of US-guided implantation of the needles and unavailability of technical devices for HDR. These are also the basic differences between our technique and more advanced ones.

The advantage of the HDR BRT Ir-192 technique is the possibility of more accurate adjustment of irradiated field to the prostate, thereby reducing the exposure of the surrounding tissue to irradiation; it is also possible to avoid hot spots that may occur because of the improper geometry of the implant. This may be obtained by planning the treatment after the needles have been in place, and by precise placing of a single movable high intensity Ir-192 source anywhere in a after loading needle, and by varying the time spent at a particular location to control the dose deposition. By choosing different lengths of active Ir-192 wires and by varying the time of insertion of a particular active wire into the after loading needle it is possible to adjust to a certain point also the dose in LDR BRT; but this is only a rough approximation to the possibilities of HDR BRT.

An important advantage of the US-guided implantation is higher accuracy in positioning the needles. Besides, in the determination of target volume, our technique can hardly assure the same accuracy as that achieved in TRUS-guided implantation.[15] However, the accuracy of TRUS has certain limitations: the accuracy of the TRUS measurements of the

tumor volume is 62-92 %.[28] Moreover, in the determination of the prostate volume, there is a discrepancy between CT scan and TRUS - the target volume determined by CT scan may exceed the volume determined by TRUS by 25-40 %.[17] TRUS is also unreliable in predicting the invasion into the capsule and periprostatic tissue. This is particularly important in bilateral tumors in which as high as 72 % probability of the invasion into the capsule has been recorded. In view of the possibility of underestimation of the tumor volume by TRUS, especially in T2B, T3 tumors, a larger treatment volume determined by CT scan from the target volume and wider safety margin, due to a lesser accuracy of needle placement, may contribute to a more reliable implantation.

The limited follow-up of our patients has not allowed any comparison of the late sequels of the LDR and HDR BRT Ir-192 treatment modalities. The only components of the two modalities that could be compared were acute toxicity of the treatment and tolerance of the patients to the treatment. Both treatment modalities are comparable as regards the non-occurrence of serious toxicity and 100 % tolerance of the patients to the planned therapy. Perhaps, an exception was a patient with hematuria. It was classified as RTOG toxicity grade 3, but it was short and transitory and did not affect the physical condition of the patient. Similar complications were observed also in US-guided implantations and were classified as low degree toxic effects (15). A higher toxicity, due in particular to proctitic complications, was observed with the doses escalating up to 2500 cGy. Nevertheless, even in these dose ranges, the toxicity remained within low to median limits.

The factors that may influence the toxicity, such as the accuracy of irradiated volume to fit the prostate, and the quality of treatment planning are not in favor of our technique - the main advantages of more accurate adjustment of irradiated to the target volume by US-guided HDR BRT Ir-192 are lower exposure of the surrounding organs to radiation and lesser possibilities of hot spots inducing acute and late sequels of treatment. The dose, another factor influencing the occurrence of toxic effects is, at least nominally, comparable or even higher than 36-50 Gy of EBRT and 12- 30 Gy of BRT in HDR 192-Ir treatments (14,15,22). Hence, one can speculate that the comparability of the least acute toxicity may be due to better biologic tolerance of LDR BRT.

The possibilities to improve our technique lie in the use of TRUS during the implantation without the help of a fixed template, and in the routine use of CT scan after the implantation. The determination of the actual position of needles allows more adequate calculation of the dose. Another advantage is the possibility to irradiate different areas of the implant with different doses, i.e. increasing the dose in the tumor area and decreasing it in the area of the urethra and of the wall of the rectum - i.e. the organs most at risk for the development of late irradiation injury.[21] With further technical improvements, we expect to decrease toxicity or, at least, preserve the existing tolerance with increasing the tumor dose.

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Dividing patients with brain metastases into classes derived from the RTOG recursive partitioning analysis (RPA) with emphasis on prognostic poorer patient groups

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Background. *The aim of our study was to investigate whether selecting the patients with brain metastases by classifying them into three classes according to the results of the recursive partitioning analysis (RPA) of the Radiation Therapy Oncology Group (RTOG) is useful or not for further decision concerning altered treatment schedules in patients.*

Patients and methods. *The investigated group included 57 male and 48 female patients having received whole brain radiotherapy in a total dose of 30 Gy / 3 Gy daily / 5 days a week. Patients who had surgical excision of brain metastases or had radiosurgical intervention were excluded. All patients were stratified according to the findings of RPA (Class I: Karnofsky Performance Status (KPS) =70, age <65, controlled primary tumour, no other metastases; Class II: not Class I or III; Class III KPS <70).*

Results. *The six/twelve months survival probability for classes I to III was 80 %/44 %, 43 %/17 % and 6 %/0 %, respectively. KPS and extracerebral tumour activity, but not age (<>65) had an impact on survival according to multivariate analysis.*

Conclusions. *Selecting the patients by dividing them into the three RPA classes seems to be useful. Considering the short survival time in RPA Class III, those patients might be well treated with a shorter treatment course.*

Keywords: brain neoplasms-secondary-radiotherapy, brain metastases; survival analysis; Karnofsky performance status; recursive-partitioning analysis, prognostic groups

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Introduction

The Radiation Therapy Oncology Group (RTOG) performed a recursive partitioning analysis on 1200 patients from three consecutive RTOG trials which tested different dose fractionation schemes and radiation sensitizers.[1] The goals of this analysis were a) to analyse the relative contributions of pre-treatment variables to the survival of patients with brain metastases using an interactive, non-parametric statistical technique known as recursive partitioning analysis; b) to define the influence of treatment variations on survival among patients enrolled on three consecutive RTOG randomised trials and c) to identify patient subgroups or stages.[1]

Based on this analysis, a classification in three classes was suggested to test new treatment techniques on homogeneous patient groups.

To learn more about the survival characteristics, we retrospectively analysed a homogenous group of 105 patients with brain metastases treated by whole brain radiotherapy. The highest emphasis was placed on the prognostically poorer groups to find out if it might be reasonable to enter these patients into shorter treatment courses with higher single doses and a higher probability of late toxicity reactions.

Methods and materials

To gain a homogenous patient group, only patients without previous treatment, like surgical resection or radiosurgical intervention, were accepted. The investigated group included 57 (54.2 %) male and 48 (45.8 %) female patients, who were irradiated at our Department between 1987 and 1997. All patients had received whole brain radiotherapy of 30 Gy in ten fractions within two weeks. Following CT-assisted treatment planning, irradiation was administered using a linear accelerator with 18 MV photon beams. Reproducible patient positioning was achieved by using a thermoplastic mask system. During irradiation, all patients received corticosteroids as prophylaxis of cerebral oedema. All patients were stratified into three classes according to the findings of Gaspar et al.: Class 1: Karnofsky Performance Status (KPS) = 70, age < 65 years with controlled primary and no evidence of extracranial metastases (16 pts, 15.2 %), class 3: KPS < 70 (37 pts, 35.2 %) and class 2: all remaining patients (52 pts, 49.5%).

Patients' characteristics and class characteristics are provided in Table 1.

Statistics

The survival curves were calculated using the Kaplan Meier method and the log rank test was used for univariate comparison. Prognostic factors were analysed using Cox's regression model.

Results

The mean follow up time of the whole group was 6.9 months (0.4-53.3). The median survival of all 105 patients was 3.2 (95 % confidence interval (CI), ±0.98) months. The median survival of the classes one to three was 10.7 (95 % CI, ±1.6), 4.7 (95 % CI, ±1.2) and 2 (95 % CI, ±0.79) months, respectively. The six/twelve months survival probability of classes one to three was 80 %/44 %, 43 %/17 % and 6 %/0 %, respectively. Comparing the survival times of the three classes, a distinct difference was seen ($p < 0.0001$)

Univariate analysis of the whole group showed significant differences in the survival of patients with a Karnofsky Performance Status = 70 or < 70 ($p < 0.001$), of the patients with or without extracerebral tumour activity ($p < 0.001$) and of the patients with or without

Table 1. Patient characteristics according to classes resulting from recursive partitioning analysis (RPA)

	Class 1		Class 2		Class 3		Total	
	n	%	n	%	n	%	n	%
Gender								
Female	8	50	20	39	20	54	48	46
Male	8	50	32	61	17	46	57	54
Age								
< 65	16	100	35	67	17	46	67	64
> 65	0	0	17	33	20	54	38	36
Performance Status								
< 70	0	0	0	0	37	100	37	35
> 70	16	100	52	100	0	0	68	65
Neurological symptoms								
No	13	81	34	65	12	32	59	56
Yes	3	19	18	35	25	68	46	44
Number of brain lesions								
< 3	8	50	24	46	18	49	50	48
> 3	8	50	28	54	19	51	55	52
Primary tumour								
Lung cancer	6	38	28	54	15	40	49	47
Breast cancer	5	31	14	27	12	32	31	30
Melanoma	3	19	3	6	4	11	10	9
Renal cancer	0	6	1	2	1	3	3	3
Gynaecological cancer	1	0	0	0	1	3	1	1
Unknown primary	0	0	0	0	1	3	1	1
Others	1	6	6	11	3	8	10	9
Active primary tumour								
Yes	16	100	35	67	23	62	74	71
No	0	0	17	33	14	38	31	29
Extracerebral metastases								
No	16	100	24	46	15	40	54	51
Yes	0	0	28	54	22	60	51	49

neurological symptoms stage 3 and 4 ($p = 0.01$). Details of neurological function status are given in Table 2. Age did not seem to have an effect on survival with a p-value of 0.8. A multivariate Cox regression model revealed the Karnofsky Performance Status ($p < 0.001$, relative risk (RR), 3.2) and extracerebral tumour activity ($p = 0.004$; RR, 2.4) as significant prognostic factors.

Discussion

According to the findings of the RTOG[1] and validating studies [2,3], we saw a distinct and significant ($p < 0.0001$) difference in the survival of the three prognostic classes. Age, however, did not show statistically significant impact on survival. Selecting patients according to the parameters derived from the RPA analysis might be a good way of predicting

Table 2. Neurological function status[1]

Stage	Symptoms
0	No neurological symptoms; fully active at home/work without assistance
1	Minor neurological symptoms; fully active at home/ work without assistance
3	Moderate neurological symptoms; less than fully active at home/work and requires assistance
4	Severe neurological symptoms; totally inactive requiring complete assistance at home or in institution. Unable to work

the survival time not only for the patients with favourable prognosis but also for those with poor prognosis. Identifying this group of patients gives the possibility to adept the treatment to their needs. In Table 3, the survival times of four studies on the RPA findings are shown. The six/twelve months survival ranged between 6-20 % and 0-6 %, respectively for patients of the RPA class III. The median survival ranged between 2 to 2.3 months. Considering these short survival times we should apply the shortest and least demanding scheme of therapy possible.

Haie-Meder et al.[4] performed a randomised trial on two radiation schedules comparing 18 Gy in 3 fractions versus the same fractionation followed by a second course of radiotherapy with a one-month time interval. The second course was identical to the first one or delivered 25 Gy/10 fractions/14 days. The neurological improvement was similar in both treatment arms; no neurological complications were observed. Concerning the survival, the two treatment arms were equivalent with 4 to 5 months of median survival. The authors conclude, that a radiation schedule as short as 18 Gy in 3 fractions can provide good palliation with the advantage of saving time spent by the patient in the hospital and smaller cost and the maintenance of the same level of palliation. It has also been indicated that the patients might not have lived long enough to experience serious complications.

Short fractionation programs have also been tested by the RTOG.[5-7] The investigation on 10 Gy in one fraction or 12 Gy in two fractions showed comparable results with those of the patients receiving 20 to 40 Gy, single fraction 2-4 Gy, concerning response rates, promptness of neurological improvement,

Table 3. Survival in different studies on RPA classification

		RPA Classes		
		I	II	III
Gaspar et al. 19961	6 mo (%)	59	36	~16
	12 mo (%)	32	16	~6
	median (mo)	7.1	4.2	2.3
Nieder et al. 19993	6 mo (%)	~70	~30	~20
	12 mo (%)	~38	~16	~5
	median (mo)	10.5	3.5	2
Gaspar et al. 20002	6 mo (%)	51	33	-
	12 mo (%)	29	12	-
	median (mo)	6.2	3.8	-
Present study	6 mo (%)	80	43	6
	12 mo (%)	44	17	0
	median (mo)	10.7	4.7	2

treatment morbidity and median survival. However, the duration of improvement, time to progression of neurological status and rate of complete disappearance of neurological symptoms were generally less for those patients who received 10 or 12 Gy, suggesting that ultra rapid high dose irradiation schedules might not be as effective as higher-dose schedules in the palliation of patients with brain metastases.[5]

Conclusion

It still has to be considered, that there are long time survivors among the patients with brain metastases and longer schedules still should be routine. But considering the short survival times of patients in the RPA class III, the use of a short schedule might give precious time at home to the patient with the same palliation and reasonable small risk of more complications than from longer schemes.

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Predictors of recurrence in stage I invasive breast carcinoma

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Background. *The aim of the retrospective study was to determine whether 6 classical prognostic factors might predict a disease-free survival (DSF) in stage I breast carcinoma.*
Patients and methods. *We analysed 181 patients who were operated on from 1991 through 1995. Measurements were made to find the association between the incidence of recurrence and prognostic features (size; histological subtype; lymphatic/vascular invasion (LVI); histological grade; hormone receptor status; age).*
Results. *There were 4 cases with locoregional recurrences (2.2 %), 6 with locoregional and distant metastases (3.3 %) and 13 women with distant metastases (7.2 %). In univariate analysis, the following prognostic factors were significantly related to DSF: tumour size, age and LVI. In the multivariate analysis age ($p = 0.007$) and LVI ($p = 0.00001$) remained firmly associated with DSF, although the tumour size ($p = 0.067$) lost its significance.*
Conclusions. *Our experience indicates that the combined use of the tumour size, LVI and age may be a better predictor of recurrence in T1N0M0 breast cancer.*

Key words: breast neoplasms, stage I breast carcinoma; prognosis, prognostic factors; recurrence

Introduction

The last decade has witnessed changing trends in the presentation and primary treatment of, and adjuvant therapy for women with early breast carcinoma. Patient awareness and mammographic screening have resulted in earlier detection of the disease.[1,2]

Women with breast cancer-lacking evidence of regional lymph node metastases and systemic disease (stage I) fare significantly better than those in whom nodal but not systemic involvement (stage II) occurs. Disease-free survival (DFS) of the former has been estimated to be approximately 93.8 % for 5 years and 79.3-81 % for 18-20 years following surgical treatment.[3-5]

The literature discussed various prognostic factors of T1 (≤ 2 cm) tumours for their association with the likelihood of locoregional and distant recurrences. This study for stage

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I breast cancer was performed to determine whether 6 classical clinical and histological features might predict DSF and also be used to identify patients who have increased or decreased risk of relapse.

Patients and methods

A total of 181 patients with T1 lesions were initially examined at the University Centre of Oncology in Pleven from 1991 through 1995. They all underwent axillary node dissection (complete or levels I and II) as part of their treatment for breast carcinoma and those who had an adequate follow-up were included into the study. The women's age range was 24-75 years (median 58.8 years).

None of them had any known regional or distant metastases at the time of initial diagnosis and, according to the International Union Against Cancer (UICC) classification, they were presented as patients with pT1N0M0 deasise.[6] Invasive carcinomas were classified using the largest dimension of the invasive component to determine the size: 5 mm or less, T1a; 6-10 mm, T1b; 11-20 mm, T1c. The axillary contents were dissected fresh; all identified lymph nodes (10-24, median 12.9) were sectioned through the hilum and examined histologically.

Pathologic characteristics of the primary tumour (size, histological type and grade, lymphatic/vascular channel invasion (LVI) by tumour emboli) were evaluated on the routine haematoxylin and eosin slides. Oestrogen receptor (ER) and progesterone receptor (PR) status were determined by radioimmunoassay.

The patients were treated with a modified radical mastectomy (81 %) or breast-conserving surgery and radiation therapy (19 %). Of 181 patients with ER or PR positive cases, 121 women received adjuvant hormonal treatment with Tamoxifen for 5 years. Seven node-negative T1c patients with high risk of recurrence (age < 40 years, ER/PR negative) received six courses of cyclophosphamide, methotrexate and 5-fluorouracil (classical adjuvant CMF), repeated every 4 weeks.

The cases of recurrence were defined separately as locoregional (after mastectomy) and distant metastases. The median follow-up duration of patients was 7 years (range 5-9 years).

The log rank test was used to perform the univariate analyses. Multivariate analysis was based on the Cox proportional hazards regression model and included any variable found to be significant in the univariate analysis.

Results

Table 1 illustrates the distribution of various clinical and pathologic features studied. The median tumour size was 14.8 mm. Ten patients (5.5 %) were with T1a tumours, 38 (21 %) were with T1b, and 133 (73.5 %) were with T1c. The majority of tumours (80.7 %) were infiltrating ductal carcinoma, 16 (8.8 %) were of infiltrating lobular type, and 19 (10.5 %) were of "favourable" (mucinous, tubular or papillary) histology. One hundred and forty-four patients (79.6 %) had positive steroid hormone receptor status - oestrogen and/or progesterone receptor positive (> 10 fmol). The majority of cases (86.8 %) had LVI (-) tumours. Within the period of 1991-1995, the histological grading was studied on 80 cases out of 181 patients. In 31 patients (38.7 %), the tumour was well differentiated, and in the remaining 49 women, the tumour was moderately or partly differentiated.

Twenty-three cases (12.7 %) developed the disease recurrence; ten were with locoregional recurrences (5.5 %), and 19 were with distant metastases (10.5 %), four women developed only locoregional, and the other 6 had locoregional and distant recurrence. Thirteen patients with distant metastases (7.2 %) died of the disease.

Table 1. Patients with T1N0M0 breast cancer

Variable	N	(%)
Tumour size (mm)	181	
< 10	48	26.5 %
11-20	133	73.5 %
Histologic type	181	
"Favourable"	19	10.5 %
ductal/lobular	162	89.5 %
Histologic grade	80	
G1	31	38.7 %
GII/GIII	49	61.3 %
Lymphatic/vascular invasion	166	
Absent	143	86.8 %
Present	23	13.2 %
Hormone receptor status	181	
(+) or (+/-)	144	79.6 %
(-)	37	20.4 %
Age (yr)	181	
≥ 60	99	51.9 %
< 60	82	48.1 %

On univariate analysis, variables significantly associated with the disease recurrence were: tumour larger than 1 cm (p = 0.03), presence of LVI (p = 0.00001) and patient's age under 60 years (p = 0.018).

The variables statistically significant at the univariate level entered into a multivariate logistic regression model with backward elimination. Only two variables remained statistically significant as independent predictors in the final model. They were LVI (odds ratio 13.41; p = 0.00001) and age (odds ratio 5.21; p = 0.007) (Table 2).

Among 77 older patients (≥ 60 years) without LVI, the incidence of disease recurrence was observed only in 2 cases (2.6 %). However, 4 patients out of 6 with the two risk factors (LVI positive; age < 60 years) had an incidence of relapse that accounted for 66.7 %.

Table 3 present the relationship of various clinical and pathologic markers to the clinical

Table 2. Statistical associations between recurrences and prognostic variables

Factor	% Recurrences	Univariate p value	Multivariate p value (Odds ratio)
Tumour size (mm)			
≤ 10	4.3 %		0.067 (4.57)
11-20	15.8 %	0.03	NS*
Histological type			
"Favourable"	5.3 %		
Ductal/lobular	13.7 %	0.3	
Histological grade			
G1	6.5 %		
GII/GIII	12.2 %	0.35	
Lymphatic/vascular invasion			
Absent	7.3 %		
Present	43.5 %	0.00001	0.00001 (13.41)
Hormone receptor status			
(+) or (+/-)	11.2 %		
(-)	18.9 %	0.15	
Age (yr)			
≥ 60	7.2 %		
< 60	17.1 %	0.018	0.007 (5.21)

*NS: not significant

Table 3. Pathologic parameters and recurrence at 7 years

Factor	Disease free survival	p value	Distant disease free survival	p value
Tumour size (mm)				
≤ 10	95.8 %		97.9 %	
11-20	84.2 %	0.38	86.5 %	0.026
Histological type				
"Favourable"	94.7 %		94.7 %	
Ductal/lobular	86.4 %	0.45	88.9 %	0.62
Histological grade				
G1	93.5 %		96.8 %	
GII/GIII	87.8 %	0.61	89.8 %	0.44
Lymphatic/vascular invasion				
Absent	92.4 %		93.8 %	
Present	54.5 %	0.000002	63.6 %	0.000048
Hormone receptor status				
(+) or (+/-)	88.9 %		91.0 %	
(-)	81.1 %	0.27	83.8 %	0.28
Age (yr)				
≥ 60	92.6 %		93.6 %	
< 60	81.6 %	0.027	85.1 %	0.06

outcome. By univariate analysis, the tumour size, LVI and age were significant prognostic factors for disease free survival. These factors also showed a trend toward better outcome for distant relapse-free survival, although only LVI and age reached statistical significance.

Discussion

Absence of metastases in the axillary lymph nodes has traditionally been considered as favourable biologic condition for patients with invasive breast cancer. However, all the cases with node-negative breast cancer are at risk for disease recurrence. Intensive efforts to define an individual patient's risk of relapse have produced a plethora of potential prognostic factors, from patient features to histological, biochemical and molecular characteristics of the tumour. The importance of these various prognostic factors has been the subject of controversies.

The frequency of the reported DFS period (83.3 % for 7 years) in 181 patients with the stage I disease is close to that reported by other authors.[3,4]

The most important predictors of DFS, out of the studied 6 ones, are LVI and the patient's age followed by the size of the primary tumour. These results, excluding the histological grading, concur with a number of preceding analyses, demonstrating their extreme prognostic importance. As to the histological grading, the lack of statistic authenticity in our study ($p = 0.35$) can be explained by a limited number of cases with a histological grading defined.[5,7-11]

For the patients with node-negative disease, International Consensus Panel (St. Gallen, 1998) recommends that the tumour size, histological and nuclear grade, steroid hormone receptor status, LVI and age are the

factors considered by the Panel to define groups with differential prognosis for use in treatment selection. For women assumed to be at high risk of recurrence (T > 2 cm; hormone receptor status negative; Grade II-III; age < 35 years) the treatment choice follows an algorithm similar to that for node-positive disease, which has a similar prognosis.[12]

The current multivariate analyses aiming to define the role of the growth rate of the tumour, measuring in terms of S-phase fraction, DNA ploidy, the occurrence of oncogene amplification of the epidermal growth-factor receptor or the c-erb B-2 gene, are going to determine the scope of the routine clinical implementation of these new prognostic factors to estimate the risk of the disease recurrence with the cases of early breast cancer.

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MRI macromolecular contrast agents as indicators of changed tumor blood flow

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Background. *A rapid mapping technique derived from dynamic contrast enhanced MRI data was used to identify and characterize reduction of blood flow in fibrosarcoma SA-1 tumors treated either by application of electric pulses or vinblastine.*

Materials and methods. *Tissue permeability surface area product (PS) and fractional blood volume (BV) were calculated on a pixel-by-pixel basis using dynamic MRI intensity data after administration of gadomer-17 or polylysine-Gd-DTPA; prototypic macromolecular contrast agents designed for blood pool enhancement. PS and BV values of untreated tumors were compared to those of tumors treated by local application of 8 electric pulses (amplitude/distance ratio, 1300 V/cm; duration, 100 μs, frequency, 1 Hz) percutaneously to the tumor or by systemic administration of vinblastine (2.5 mg/kg).*

Results. *Both treatments transiently, but significantly reduced tumor blood flow, application of electric pulses to the tumors being by 40% more effective in reducing tumor blood flow than systemic administration of vinblastine. PS and BV values derived with polylysine-Gd-DTPA-enhanced MRI were lower compared to those with gadomer-17, due to larger molecular size. Interestingly, Gd-DTPA-enhanced MRI did not show any significant changes of PS and BV between untreated and treated tumors.*

Conclusion. *This study demonstrates that dynamic contrast enhanced MRI can be effectively used to qualitatively monitor tumor blood flow, and quantitatively by means of BV and PS.*

Key words: sarcoma experimental - therapy - blood supply; vinblastine; electroporation; magnetic resonance imaging; contrast media; macromolecular systems

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Introduction

Tumors are physiologically different compared to normal tissues. Tumors are usually poorly perfused, have low oxygen tension and lower pH, due to chaotic vascularization. If the blood flow is chronically impaired, a cascade of tumor cell death occurs due to the lack of nutrients and accumulation of catabolic products. Therefore, the knowledge of tumor physiology is important for understanding of tumor growth.[1]

Knowledge about tumor perfusion and its consequences on tumor cells' oxygenation is also important for planning of different treatments.[2] Radiation therapy requires good tumor oxygenation; adequate tumor perfusion is also important for successful delivery of chemotherapeutic drugs to tumor cells. Many anticancer agents and therapies in current use have been shown to have tumor blood modifying effect, and exert their antitumor action also by compromising tumor vascular function.[3]

In order to measure tumor blood flow several techniques have been developed.[2] One of imaging techniques that have already significantly contributed to better tumor visualization is magnetic resonance imaging (MRI). The use of contrast-enhancing agents in conjunction with MRI provides an opportunity to non-invasively extract physiological information, in addition to anatomical data offered by unenhanced images.[2] Contrast agents that are being developed nowadays are designed to define the physiology and pathophysiology in various tissues. In general, they can be divided into two groups: low-molecular-weight contrast agents and macromolecular contrast agents. Low-molecular-weight contrast agents, represented in one study by Gd-DTPA, have proved to be clinically useful in detecting abnormalities in blood-brain barrier.[4] Unfortunately their performance is limited by rapid clearance from the blood into the extra-vascular compartment.[5] Macromolecular contrast agents are being developed to investigate blood pool, to specifically enhance the blood pool and evaluate capillary integrity.[6,7] Multiple applications of these contrast agents have been tested, including assessment of relative tissue blood volume and abnormal capillary permeability.[8,9]

The aim of this study was to demonstrate the potential of dynamic contrast tissue-enhanced MRI to evaluate changes in tumor perfusion by calculating permeability surface area product (PS) and fractional blood volume (BV) on a pixel-by-pixel basis.[10,11] We hypothesized that estimates of permeability and blood volume based on dynamic contrast tissue-enhanced MRI data should reliably describe the changes in tumor blood flow. For this purpose two tumor blood flow modifying approaches were used, a chemical agent given systemically, and a physical approach applied locally. Vinblastine is a chemotherapeutic agent, used in treatment of cancer. Besides direct effect on tumor cells, it also has tumor blood flow modifying effect, inducing profound, but transient reduction in tumor blood flow.[12,13] Local application of electric pulses to the tumors also induces transient, but even greater reduction in tumor blood flow compared to vinblastin.[14,15] Furthermore, macromolecular agents gadomer-17 and the new polylysine-Gd-DTPA were used to more accurately quantify the reduction of tumor blood flow due to their specific enhancement of tumor blood pool in contrast to Gd-DTPA, that readily diffuses across endothelium of normal and neoplastic microvessels.

Materials and methods

Animals and tumors

An inbred strain of A/J mice was used. They were maintained at a constant room temperature (22°C) with natural day and night light cycle in conventional animal colony. Before the experiment, the mice were subjected to

an adaptation period of at least 10 days. Mice in good condition, without fungal or other infections, and 10-20 weeks of age were included in experiment. Fibrosarcoma SA- 1 tumor (The Jackson Laboratory, Bar Harbor, ME) syngeneic to A/J mice was used as a tumor model. Tumor cells were obtained from the ascitic form of the tumors in mice serially transplanted every 7 days. Solid subcutaneous tumors located dorsolaterally were induced by an injection of 5×10^5 SA-1 cells in 0.1 ml of 0.9 % NaCl solution. The viability of the cells was over 95 % as determined by trypan blue dye exclusion test. Tumors were imaged 6-8 days after implantation (app. 7 mm diameter).

Treatment of tumors

Eight square-wave electric pulses, divided in two sets of 4 pulses in opposing directions, of 1040 V amplitude (amplitude/distance ratio 1300 V/cm), with pulse width of 100 μs and repetition frequency 1 Hz were delivered by two flat, parallel stainless-steel electrodes 8 mm apart (two stainless-steel strips: length 15 mm, width 7 mm with rounded corners), which were placed percutaneously at the opposite margins of the tumor. Good contact between the electrodes and the skin was assured by the means of a conductive gel. Electric pulses were generated by an electroporator Jouan GHT 1287 (Saint Herblaine, France). Treatment was performed without anesthesia and was well tolerated. Vinblastine (Lilly France S.A., Fagersheim, France) was administered intraperitoneally in a dose of 2.5 mg/kg. Thereafter, animals were anesthetized with a mixture of Domitor (1.0 mg/kg body weight) (Pfizer GmbH, Karlsruhe, Germany) and 10 % ketamine (75.0 mg/kg body weight) (Veyx-Pharma GmbH, Schwartzenborn, Germany) administered intraperitoneally. During anesthesia, body temperature was kept at physiological values. Both treatments were applied 5-10 min prior to imaging.

MRI

MRI was performed on a 2.35 T Bruker Biospec system with horizontal bore magnet. First, a pre-contrast image (complete k-space data set) was acquired using standard spin-echo technique with the following imaging parameters: T_R = 600 ms, T_E = 18 ms, matrix 256 × 256, slice 2 mm, field of view 7 cm and acquisition time 5 min. Subsequently, contrast agent was administered, and a small, central data subset of the k-domain (in the phase-encoding direction) with dimensions 32 × 256 k-space data points was acquired repetitively for 60-100 min (80-100 "key" images). Each "key" image was acquired with 32 phase encoding steps that took 38 s. Before the reconstruction, dynamically acquired data subset was first completed in remaining k-space points (which were not included in temporal acquisition) with the data from the first acquisition. This was followed by the dynamical image reconstruction with 2D inverse Fourier transformation.

MR contrast agent

Clinically available Gd-DTPA (Magnevist®, Schering AG, Berlin, Germany) was used as a small-molecular-size contrast agent, administered to a subgroup of 5 animals, in a dose of 0.1 mmol Gd/kg. Gadomer-17 (Schering AG, Berlin, Germany) was used as an intermediate molecular size contrast agent, but still macromolecular compared to Gd-DTPA. The size of the agent is approximately 30 kDa, allowing its complete renal elimination. Gadomer-17 was administered to a second sub-group of 5 animals. The new polylysine-Gd-DTPA (Schering AG, Berlin, Germany) was used as a representative macromolecular contrast agent (≈ 50 kDa). Similarly, polylysine-Gd-DTPA was administered to a third subgroup of 5 animals. Both macromolecular agents were administered in a dose of 0.025 mmol/kg and were well tolerated. Because of the increased relaxation potency

of gadolinium in the macromolecule compared to that in the small-molecular contrast agent, this lower dose gives approximately equal initial blood enhancement. All three contrast agents were administered in a bolus via 23-gauge intravenous cannula (Vygon 247 Venoflux infusion set, France) that was inserted into a tail vein.

Postprocessing

Magnetic resonance signal was measured in a region of interest (tumor) in precontrast images and at least 80 postcontrast images at each timepoint. Signal was corrected for signal variations against water phantom. From the measured signal, tissue contrast agent concentration (C_T) was calculated with a subtraction of precontrast signal from postcontrast signals on a pixel-by-pixel basis. Contrast agent concentration in a slowly flowing vessel (C_B), such as inferior vena cava was obtained in a similar way, only within the inferior vena cava. The linearity of the C_T / C_B fit was checked for the first 30-50 points. Statistical analysis using a paired t-test was applied to compare values and significance concluded if $P < 0.01$.

Data analysis

Fractional blood volume BV and permeability surface area product PS were calculated using the method described previously.[8,16-18] Briefly, BV is estimated as a ratio of tissue signal intensity C_T at time t divided by signal intensity for blood C_B in slowly flowing vessels such as the inferior vena cava. On a pixel-by-pixel basis, BV was calculated as:

$$BV \cong \frac{C_T(t)}{C_B(t)} - PS' \qquad [1]$$

where C_T is tissue contrast agent concentration, C_B blood contrast agent concentration and PS':

$$PS' \cong \frac{\left| \begin{matrix} C_T(t_2) & C_T(t_1) \\ C_B(t_2) & C_B(t_1) \end{matrix} \right|}{t_2 - t_1} \qquad [2]$$

For the vascular permeability, a two-compartment, one directional flow model was adopted for the movement of the macromolecular contrast agent from the blood to the interstitial space.[17] PS was calculated using equation:

$$PS = PS'(1\text{-}Hct) \qquad [3]$$

where Hct is the measured hematocrit of the blood (47 % for tumor in animals).

Results

Qualitative MRI data in Figure 1 showed that untreated tumors enhanced heterogeneously with contrast agents used; highly vascular rim enhancing more than the partly vascular, partly necrotic tumor center. Enhancement with Gd-DTPA was prompt and included the whole tumor, but tended to decline after the first minute, due to rapid transendothelial diffusion and rapid renal elimination (Fig. 1a; left column). Prompt and marked enhancement of the highly vascularized tumor rim was also observed with polylysine-Gd-DTPA and was less pronounced with gadomer-17 (Fig. 1 b, c; left column). The enhancement of subcutaneously implanted tumors increased gradually with both macromolecular agents, reflecting diffusion from blood into the interstitial space. Tumors treated with vinblastine or application of electric pulses showed little or no enhancement of the tumor within the first hour after the treatment, due to reduced blood flow (Fig. 1, middle and right column). Afterwards, enhancement started to increase since the reduction in tumor blood flow was transient. Enhancement with Gd-DTPA was not significantly affected by both treatments.

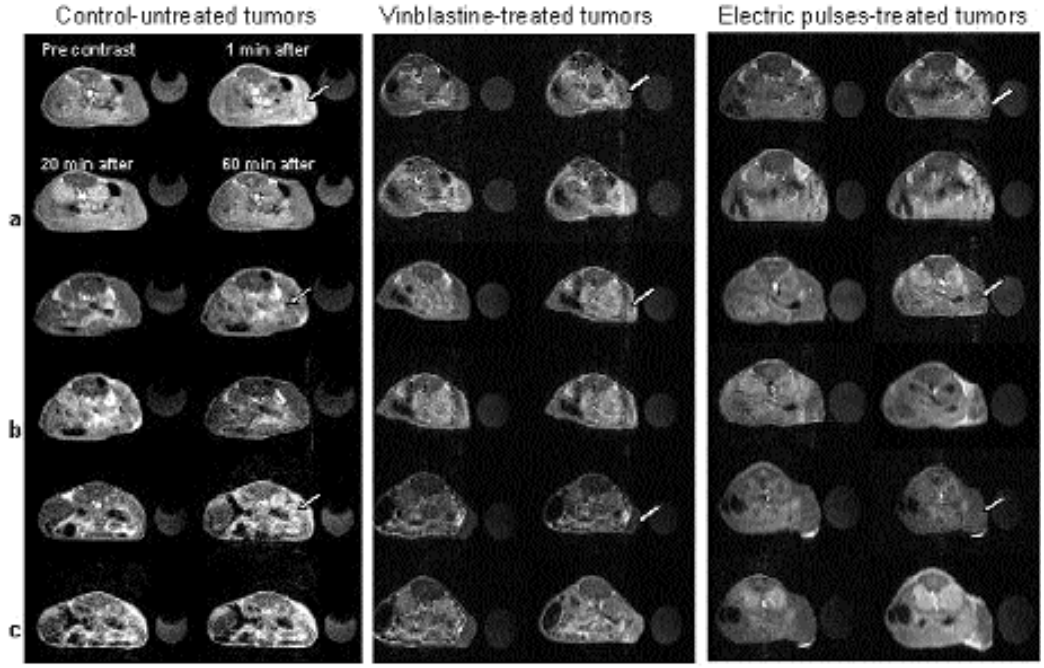

Figure 1. Representative dynamic images of tumors in untreated animals, and those treated with vinblastine or application of electric pulses. Clusters of four images depict each combination of tumor and contrast agent; images in each cluster are arranged as: pre-contrast, 1 min, 20 min and 60 min post-contrast. (A) Cluster was obtained with Gd-DTPA, (B) with gadomer-17 and (C) with polylysine-Gd-DTPA. Note the difference in contrast agent accumulation between untreated and treated tumors and between contrast agents themselves (arrows).

The time course of gadomer-17 and polylysine-Gd-DTPA accumulation (described as C_T) in the untreated tumors and tumors treated with vinblastine or application of electric pulses is shown in Figure 2. In untreated tumors, concentration of the gadomer-17 (C_T) increased gradually over the first 10 minutes indicating microvascular leak and accumulation of the agent in the interstitial space of the tumor and than started to decreased at 20 min due to the clearence (Fig. 2 a). The C_T data for polylysine-Gd-DTPA also increased substantially over the time, again indicating microvascular leak and longer accumulation of the agent in the interstitial space of the tumor, due to its large molecule (Fig. 2 b). After both treatments, vinblastine or application of electric pulses, tumor blood flow was reduced and consequently also contrast agents accumulation. The effect of vinblastine was less pronounced than that of application of electric pulses (Fig. 2)

High mean BV and PS values in untreated tumors, obtained with Gd-DTPA indicated rapid transendothelial equilibration (Table 1). Approximately equal mean BV and PS values that were obtained with gadomer-17 and polylysine-Gd-DTPA, but lower compared to Gd-DTPA, indicated slow diffusion of both agents from blood into the interstitial space due to larger molecular size. Large molecular size impairs passage through vascular endothelium compared to the small Gd-DTPA, inspite of the intercellular gaps. Within the first hour after the application of electric pulses, calculated BV and PS values from data obtai-

Table 1. Fractional blood volume BV and permeability surface area product PS values of untreated and tumors treated by vinblastine or application of electric pulses

	gadomer-17		polylysine-Gd-DTPA		Gd-DTPA	
	BV (%)	PS (μl/cc/h)	BV (%)	PS (μl/cc/h)	BV (%)	PS (μl/cc/h)
Untreated tumors	8.8 ± 1.3	680 ± 30.1	8.6 ± 1.1	510 ± 27.3	20 ± 2.3	4710 ± 45.8
Electric pulses	0.5 ± 0.03	72.3 ± 16.1	0.27 (0.06	58 (18.1	12.7*	4040*
Vinblastine	4.0 ± 1.13	359 ± 50.4	1.37 ± 0.22	231.4 ± 60.7	19.8*	4180*

* one data set only

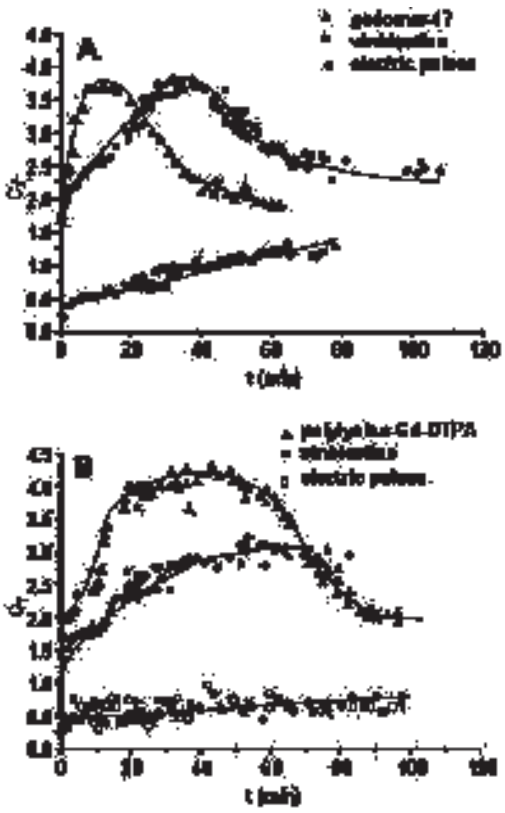

Figure 2. Time course of (A) gadomer-17 and (B) polylysine-Gd-DTPA accumulation in untreated and vinblastine or electric pulses treated tumors.

ned with both macromolecular contrast agents dropped on average to 10 % or less, compared to those of untreated tumors. After treatment with vinblastine, calculated BV and PS values of gadomer-17-enhanced MRI were higher for approximately 65 % and 35 %, respectively, compared to BV and PS values of polylysine-Gd-DTPA-enhanced MRI.

Discussion

Results of this study demonstrate that dynamic contrast enhanced MRI can be effectively used to qualitatively monitor tumor blood flow, and quantitatively by means of BV and PS from the gadomer-17 and polylysine-Gd-DTPA enhanced MRI. In order to determine the value of contrast enhanced MRI, two approaches were used to reduce tumor blood flow, treatment with vinblastine and application of electric pulses to the tumors. Tumor blood flow in both cases rapidly decreased with a slow recovery. Relatively high BV and PS values of untreated tumors were due to microvascular abnormalities - vascular leakage in the tumor region. Both treatments also resulted in reduced BV and PS values, treatment with vinblastine was less effective in reducing tumor blood flow than application of electric pulses. The data support the evidence on tumor blood flow modifying effect of these two treatments, provided with other methods.[12-15]

Changes in endothelial cells of microvessels manifest as contraction of these cells, forming intercellular gaps, allowing intravascular fluids and macromolecular solutes to leak into the interstitial space.[19] Gd-DTPA in general promptly enhances tumors.[20] Due to its

rapid equilibration between intra-and extravascular compartments, enhanced tumor vessels could not be distinguished. With macromolecular contrast agent such as gadomer-17 or polylysine-Gd-DTPA, transendothelial passages depend on the size of the molecule. Larger molecules stay within the vessel for a longer period of time, thus enabling differentiation of the tumor vessels from the extravascular compartments. This is shown on Figure 1, where highly vascularized tumor rim was enhanced for a longer period due to the large molecular size of polylysine-Gd-DTPA.

Tumor blood flow modifying effect of electric pulses has already been described. It was shown that application of electric pulses locally to the tumor reduces tumor blood flow transiently, returning to almost pretreatment value within 24 hours.[14,15] The reduction in tumor blood flow was very quick, reaching 30 % pretreatment value within 1 hour after application of the same set of pulses as used in this study. These data were obtained with rubidium extraction technique, a pharmacological technique measuring plasma flow through the tumor. Confirmed were the data by Patent blue staining technique, which also estimates tumor blood flow. Vinblastine also perturbs tumor blood flow.[12,13] Studies demonstrated that with the same dose of vinblastine as used in this study, the onset of reduced tumor perfusion after vinblastine was fast, maximal reduction was observed by 1 hour after the treatment, thereafter tumors gradually started to reperfuse. Reperfusion was not completed by 48 hours. The data obtained in the present study on tumor blood flow modifying effect of electric pulses and vinblastine are in accordance with the data in the literature.[12-15] After both treatments, blood flow was reduced and consequently also contrast agent accumulation. The effect of vinblastine was less pronounced than that of applied electric pulses; the degree and duration of tumor blood flow reduction was smaller. Since the reduction of blood flow with vinblastine was not as severe as with electric pulses, the difference in gadomer-17- and polylysine-Gd-DTPA-enhancement was not as pronounced.

Besides gadomer-17- and polylysine-Gd-DTPA-enhanced MRI, Gd-DTPA was also used to evaluate tumor BV and PS in untreated and tumors treated with vinblastine or application of electric pulses. In the treated tumors, BV and PS values failed to highlight the reduction of tumor blood flow. This is also in accordance with literature data.[20,21] The accuracy of the maps in tissues outside central nervous system is questionable because of the high and variable permeability of Gd-DTPA even in normal tissue.[20,21]

Earlier reports have described the value of pixel-by-pixel mapping of parameters derived from MRI signal intensity data.[8,20] Parameters mapped included T_1, T_2, proton density, diffusion coefficient[22], oxygenation[23], temperature[24], magnetization transfer[25], chemical shift[26], susceptibility[27], electric current[28], blood flow[29], and contrast media.[30,31] Our results are based on the use of macromolecular contrast agents, gadomer-17 and polylysine-Gd-DTPA respectively, that allow quantitative estimation of PS and BV. Small paramagnetic Gd-chelate distribution (Gd-DTPA) can only give qualitative impression.[21] It's difficult to speculate, which macromolecular contrast would give better estimate of tumor blood flow reduction, however due to the complete renal clearance gadomer-17 might provide better basis for use in clinical practice.

In conclusion, dynamic contrast enhanced MRI showed qualitatively that application of electric pulses to the tumors and systemic treatment of animals with vinblastine induced reduction of tumor blood flow, and quantitatively by means of BV and PS calculations. From the enhancement curves as well as from the BV and PS values, the decrease in tumor blood flow was approximately 40 % more pronounced with electric pulses compared to vinblastine. Dynamic contrast enhanced MRI

also showed that this reduction was transient, but did not completely return to the values of untreated tumors during the observation time. This approach could therefore be used for monitoring the time window and the extent of the tumor blood flow reduction in the tumor after tumor blood flow modifying therapies.

Acknowledgement

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Radiol Oncol 2001; 35(2): 83-8.

Preiskava ožilja spodnjih okončin z dvojnim barvnim Dopplerjem - tipska razvrstitev rezultatov preiskave

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Izhodišča. V študiji smo tipsko razvrstili rezultate ultrazvočne preiskave ožilja spodnjih okončin z dvojnim barvnim Dopplerjem.
Bolniki in metode. V 27 mesecih smo pregledali 934 bolnikov, 663 žensk (71 %) in 271 moških (29%), starih od 19 do 86 let (povprečna starost 58,4 let). Uporabili smo barvne Dopplerske čitalnike Acuson 128 XP 10, ATL HDI 500 in Siemensov Sonoline Elegra ter transduktorje s frekvenco od 2,5-12 MHz. Rezultate preiskav smo razvrstili: (a) globoka venska tromboza, (b) patološke spremembe na venah, na katerih nismo odkrili znakov globoke venske tromboze, (c) patološke spremembe na sosednjih strukturah in (d) normalni rezultati.
Rezultati. Globoko vensko trombozo smo odkrili pri 210 bolnikih (22,5 %). Pri 129 je bila venska tromboza akutna ali kronična, pri 81 bolnikih pa je bila prisotna tudi po zdravljenju, saj smo jo odkrili v času kontrolnih pregledov. Pri 415 bolnikih (44,4 %) smo opazili posttrombotični sindrom, varikozno razjedo, površinski tromboflebitis ter vensko anevrezmo pod kolenom. Patološke spremembe, ki niso nastale zaradi bolezni ožilja, smo odkrili pri 117 % bolnikih (12,5 %). Najpogostejše spremembe v tej skupini so bile mišični hematomi in podkolenske ciste, opazili pa smo tudi nekaj zelo redkih patoloških spremmeb. Pri 192 bolnikih (20,6 %) so bili rezultati normalni.
Zaključki. Poleg že znanih in zelo različnih patoloških sprememb na ožilju spodnjih okončin smo pri bolnikih, ki so prišli k nam na ultrazvočno preiskavo ožilja spodnjih okončin z dvojnim barvnim Dopplerjem, odkrili razmeroma veliko patoloških sprememb, ki niso bile povezane z boleznimi ožilja. Ultrazvočna preiskava ožilja je nujna za prepoznavanje poškodb ožilja, ki klinično spominjajo na globoko vensko trombozo, da ne bi po pomotoma napačno zdravili.

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Sigmoidni diverticulitis: prikaz primera

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Izhodišča. Eden od vzrokov akutnega abdomna je diverticulitis, ki ga je včasih težko prepoznati.
Prikaz primera. Predstavljamo primer bolnice z akutnim abdomnom. Ultrazvočna preiskava je pokazala mase z notranjimi odboji, ki so se širili k sigmoidnemu delu debelega črevesa. Sumili smo, da ima bolnica diverticulitis. Kasneje smo diagnozo potrdili s CT preiskavo.
Zaključki. Opisani primer poudarja pomembnost ultrazvočne preiskave, ki predstavlja začetno slikovno metodo pri ugotavljanju črevesne patologije.

Radiol Oncol 2001; 35(2): 95-103.

Določanje razširjenosti bolezni pri bolnikih z melanomom na konvencionalni način ali z ^{18}F-FDG-PET

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Izhodišča. Doslej opravljene predhodne raziskav potrjujejo, da je ^{18}F-FDG-PET (pozitronska emisijska tomografija z 18-deoksifluorglukozo) zelo koristna preiskava za določanje razširjnosti napredovalega malignega melanoma. Namen naše raziskave je bil primerjati rezultate slikanja s ^{18}F-FDG-PET ter rezultate konvencionalnega slikanja in kliničnega pregleda bolnikov z malignim melanomom tako pri primarnem ugotavljanju razširjenosti bolezni kot pri ugotavljanju njene razširjenosti na kontrolnih pregledih.

Bolniki in metode. Skupini 35 bolnikov s histološko potrjenim malignim melanomom smo opravili 61 PET preiskav. Ko smo jim vbrizgali 370 MBq +F-FDG, smo poslikali celotno telo z napravo ECAT EXACT 47 (921) z aksialnim vidnim poljem 16,2 cm. Vseh 35 bolnikov smo v štirinajstih dneh po slikanju s ^{18}F-FDG-PET tudi klinično pregledali in opravili konvencionalne slikovne preiskave, kot so ultrazvočna preiskava, CT in MRI. Na osnovi rezultatov obeh metod za določanje razširjenosti bolezni smo bolnike razvrstili v skupine v skladu s klasifikacijo UICC.

Rezultati. Pri primarnem določanju razširjenosti bolezni in pri ugotavljanju njene razširjenosti na kontrolnih pregledih s konvencionalnimi metodami smo pri 5 od 35 bolnikov ugotovili, da je bolezen v stadiju I in pri 7 od 35 bolnikov da je v stadiju II. Pri ostalih 23 bolnikih smo sprva določili melanom v stadiju III. Na kontrolnih pregledih smo pri 2 od 23 bolnikov ugotovili višji stadij melanoma, in sicer stadij IV. Vsekakor pri primarnem določanju razširjenosti bolezni s konvencionalnimi diagnostičnimi slikovnimi metodami pri nobenem od bolnikov nismo ugotovili stadija IV.

Pri primarnem določanju razširjenosti bolezni s preiskavo ^{18}F-FDG-PET pri 9 od 35 bolnikov nismo odkrili niti zasevkov v bezgavkah niti oddaljenih zasevkov (stadij I/II). Pri 21 od 35 bolnikov je obstajal sum na razširjenost zasevkov v bezgavkah, ni pa bilo suma oddaljenih zasevkov (stadij III). Maligni melanom preostalih 5 od 35 bolnikov je bilo opredeljenih kot stadij IV, ker je obstajal sum na oddaljene zasevke. Pri enem od teh bolnikov pa se je ob kontrolnih pregledih izkazalo, da je bila preiskava s ^{18}F-FDG-PET lažno pozitivna zato smo ga razvrstili v nižji stadij (stadij III).

V primerjavi s konvencionalnimi slikovnimi diagnostičnimi metodami smo s preiskavo 18F-FDG-PET pri primarnem določanju razširjenosti bolezni in pri ugotavljanju njene razširjenosti pri kontrolnih pregledih določili enak stadij melanoma pri 17 od 35 bolnikov (49 %), pri 14 (40 %) smo določili nižji stadij in pri 4 (11 %) višjega. Z ozirom na anatomsko mesto metastatskega razsoja smo s preiskavo PET največ lažno negativnih diagnoz postavili za zasevke v tistih bezgavkah, ki ležijo najbližje kožni površini.

Zaključki. Naši rezultati potrjujejo dodatno vrednost ^{18}F-FDG-PET pri določanju razširjenosti bolezni malignega melanoma. Ker je način zdravljenja predvsem odvisen od klinično ugotovjene razširjenosti bolezni, nam lahko ^{18}F-FDG-PET odlično pomaga pri izbiri vrste zdravljenja za posamičnega bolnika.

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CT primerjava primarnega ledvičnega karcinoma in metastaz v ledvicah

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Izhodišča. Primejali smo rezultate preiskav z računalniško tomografijo (CT) pri bolnikih s primarnim ledvičnim karcinomom z bolniki z metastazami v ledvicah, da bi ugotovili razlike, ki se kažejo na CT posnetkih.
Bolniki in metode. Preiskavo smo opravili na 25 bolnikih, od katerih jih je bilo 10 s patološko potrjenimi metastazami v ledvicah in 15 s primarnim ledvičnim karcinomom. Dve minuti po intravenoznem vbrizgu kontrasta smo začeli s slikanjem. Pri analizi rezultatov preiskav smo upoštevali standardna merila za oceno CT posnetkov s kontrasti.
Rezultati. Pri razločevanju primarnega ledvičnega karcinoma od ledvičnih metastaz je bila občutljivost CT preiskave 98-odstotna, pri razločevanju ledvičnih metastaz od ledvičnega karcinoma pa 70-odstotna.
Zaključki. V študiji smo ugotovili, da je CT preiskava v klinični praksi lahko koristno orodje za razlikovanje med primarnim ledvičnim karcinomom in metastazami v ledvicah.

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Možnosti sodobnega zdravljenja karcinoma debelega črevesa in danke

Yovtchev Y, Nikolov S

Izhodišča. Tudi danes zdravimo karcinom debelega črevesa in danke kirurško ter s kemo- in radioterapijo. V zadnjih letih pa so razvili nove metode, ki jih uspešno uporabljamo v onkologiji. Te metode so uporaba specifičnih protiteles, uporaba encimov in zdravil vezanih na protitelesa, uporaba radioimunokonjugatov in radioimuno vodena kirurgija.
Zaključki. Z novimi metodami lahko pri bolnikih s karcinomom debelega črevesa in danke podaljšamo preživetje brez znakov bolezni, zmanjšamo umrljivost in izboljšamo kvaliteto življenja.

Radiol Oncol 2001; 35(2): 117-26.

Radikalno obsevnje prostate v kombinaciji s perkutanim obsevanjem in implantacijo prostate z LDR Ir 192

Kragelj B, Guna F, Burger J

Izhodišča. Obsevanje prostatičnih karcinomov z dozami višjimi od še sprejemljivih doz ob klasični radioterapiji izboljša lokalno kontrolo bolezni. Namen študije je bil ugotoviti akutno toksičnost ter sprejemljivost visokodoznega obsevanja prostate s kombinacijo perkutanega obsevanja in intersticijske brahiradioterapije, kjer smo implantacijo prostate izvedli z Ir 192, ki je imel nizko hitrost doze (LDR).

Materijal in metode. Pregledali smo dokumentacijo 8 bolnikov z lokaliziranimi karcinomi prostate (T2-3 N0-X M0). Izhodna vrednost PSA je bila 2,7 - 37,5 (mediana 13,7) ng/ml., točkovanje po Gleasonu pa 4-9 (mediana 7). Zdravljeni so bili od avgusta 1999 do februarja 2000 s kombinacijo perkutanega obsevanja prostate in seminalnih vezikul (4 bolniki) oziroma medničnega področja (4 bolniki) s 48.6 - 50,4 Gy ter intersicijskega obsevanja prostate LDR IR-192 z 20,0 do 28,0 Gy.

Rezultati. Akutni stranski učinki obsevnja, ki so se pojavili pri vseh bolnikih, so bili neizraziti - glede na RTOG kriterije je pri 20 od 30 bolnikov ocenjeno kot 1. stopnje, pri 9 od 30 2. stopnje in pri 1 od 30 bolnikov 3. stopnje. Pri nobenem bolniku ni bilo potrebno prilagajati zdravljenja zaradi stranskih učinkov.

Zaključki. Začetne izkušnje kažejo na zmerno toksičnost ter optimalno sprejemljivost kombinacije perkutanega obsevanja in implantacije z LDR Ir 192. Tehniko implantacije bi lahko izboljšali z rednimi CT kontrolami implantata in z dodatno pozornostjo pri uvajanju igelj v področje ob uretri.

Radiol Oncol 2001; 35(2): 127-31.

Razvrstitev bolnikov z možganskimi metastazami v skupine, ki jih priporoča RTOG analiza, s poudarkom na prognostično slabe bolnike

Willfurth P, Mayer R, Stranzl H, Prettenhofer U, Genserc B, Hackl Arnulf B

Izhodišča. Namen naše raziskave je bilo ugotoviti, ali je razvrščanje bolnikov v skupine, ki jih priporoča RTOG analiza (RPA) koristno za nadaljnjo odločanje, kako zdraviti bolnike z možganskimi metastastazami.

Bolniki in metode. Retrospektivno smo analizirali 57 bolnikov in 48 bolnic, ki smo jim predhodno obsevali možgane s skupno tumorsko dozo 30 Gy / 3 Gy dnevno / 5 krat na teden. Bolnike, pri katerih smo možganske metatstaze zdravili tudi kirurško ali z radiokirurgijo, smo izključili iz študije. Obravnavane bolnike smo razvrstili v skupine glede na stanje splošne zmogljivosti po Karnofskem (KPS) in glede na starost (skupina I: KPS = 70, starost < 65, nadzorovan primarni tumor, brez drugih oddaljenih metastaz; skupina II: bolniki, ki niso razvrščeni v skupino I ali III; skupina III: KPS < 70).

Rezultati. Verjetnost šest in dvanajstmesečnega preživetja za skupine I, II in III je bila 80 %/44 %, 43 %/17 % in 6 %/0 %. Z multivariantno analizo smo ugotovili, da sta na preživetje vplivala predvsem KPS in rast primarnega tumorja, ne pa starost bolnikov.

Zaključki. Menimo, da je razvrščanje bolnikov v skupine, kot ga priporoča RTOG analiza (RPA), koristno. Bolnike, ki smo jih razvrstili v skupino III, lahko zaradi kratkega preživetja časa zdravimo s krajšim načinom obsevanja.

Radiol Oncol 2001; 35(2): 133-7.

Predvidevanje ponovitve bolezni pri bolnicah z rakom dojke, stadij I

Baitchev G, Gortchev G, Velkova A, Deliisky T

Izhodišča. V naši retrospektivni študiji smo želeli ugotoviti, ali lahko s šestimi klasičnimi napovednimi dejavniki predvidimo preživetje brez znakov bolezni pri bolnicah, ki smo jih zdravili zaradi raka dojke, stadij I.

Bolniki in metode. Proučevali smo 181 bolnic, ki smo jih kirurško zdravili v obdobju med 1991 in 1995.Opredelili smo velikost tumorja, histološki tip, invazijo v limfne in krvne žile, malignostno stopnjo tumorja, hormonske receptorje in starost bolnic. Želeli smo ugotoviti soodvisnost med temi napovednimi dejavniki in ponovitvijo bolezni.

Rezultati. Pri 4 bolnicah (2,2 %) se je bolezen ponovila lokoregionalno, pri 6 (3,3 %) pravtako lokoregionalno, vendar z oddaljenimi zasevki, pri 13 (7,2 %) pa z oddaljenimi zasevki. Rezulati univariatne analize so potrdili, da so statistično značilno povezani s preživetjem brez znakov bolezni naslednji napovedni dejavniki: velikost tumorja, starost bolnic ter tumorska invazija v limfne in krvne žile. Rezultati multivariatne analize pa so pokazali statistično zelo pomembno soodvisnost med preživetjem brez znakov bolezni ter starostjo ($p = 0,007$) in tumorsko invazija v limfne in krvne žile ($p = 0,00001$), medtem ko velikost tumorja ni bila več statistično značilno povezana s preživetjem ($p = 0,067$).

Zaključki. V razsikavi smo ugotovili, da naslednji trije hkrati uporabljeni napovedni dejavniki, kot so velikost tumorja, tumorska invazija v limfne in krvne žile in starost bolnic, lahko zanesljiveje predvidijo ponovitev bolezni po zdravljenju raka dojke v stadiju T1N0M0.

Radiol Oncol 2001; 35(2): 139-47.

Uporaba kontrastno povdarjenega dinamičnega MR slikanja za spremljanje pretoka krvi v tumorjih

Ivanuša T, Beravs K, Čemažar M, Jevtič V, Demšar F, and Serša G

Izhodišče. Dinamično slikanje z magnetno resonanco je diagnostična metoda, ki omogoča prikaz in vrednotenje prekrvavljenosti tumorjev. Namen naloge je bil z makromolekularnimi kontrastnimi sredstvi spremljati zmanjšanje pretoka krvi v mišjih fibrosarkomskih tumorjih po aplikaciji električnih pulzov ali zdravljenju z vinblastinom.

Materiali in metode. Permeabilnost tumorskega žilja (PS) in prekrvljenost tumorskega tkiva (BV) smo ocenjevali na nivoju točkovnih elementov MR signala po aplikaciji dveh prototipov makromolekularnih kontrastnih sredstev: gadomer-17 in polilizin-Gd-DTPA, ki za razliko od nizko molekularnega gadolinija (Gd-DTPA) omogočajo prikaz tumorskega žilja. PS in BV netretiranih tumorjev smo primerjali z PS in BV vrednostimi tumorjev, katerim smo aplicirali električne pulze ali jih zdravili z vinblastinom.

Rezultati. Oba načina zdravljenja sta značilno zmanjšala pretok krvi v tumorjih. Aplikacija električnih pulzov pa je bila za 40 % učinkovitejša v zmanjšanju pretoka krvi v tumorjih kot sistemska aplikacija vinblastina. PS in BV vrednosti za polilizin-Gd-DTPA so bile nižje kot vrednosti za gadomer-17 (30 kDa), kar pojasnjujemo z velikostjo molekul polilizina-Gd-DTPA(50 KDa). Zanimivo je, da PS in BV vrednosti kontrastno podarjenega dinamičnega MR slikanja z gadolinijem niso pokazale značilne razlike med netretiranimi in zdravljenimi tumorji.

Zaključek. Rezultati raziskave utemeljujejo uporabo kontrastno povdarjenega dinamičnega MR slikanja za spremljanje pretoka krvi v tumorjih in kvantitativno določanje PS in BV vrednosti.

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.*

Radiology

July 5-7, 2001

The course "Abdominal Imaging and Intervention 2001 - State of the Art and New Developments" organised by John Hopkins University School of Medicine will be held in Salzburg, Austria.

Contact Ms Edeltraut Treptow, Radiologische Universitaetsklinik, Department of Diagnostic Radiology, Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany; or call +49 7071 298 6676; or fax +49 7071 295 845; or e-mail edeltraut.treptow@med.uni-tuebingen.de

Radiophysics

September 17-22, 2001

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

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

Life sciences

September 22-26, 2001

The international conference "Life Science 2001" organised by Slovenian Biophisical Society will be held in Gozd Martuljek, Slovenia.

Contact Dr. Marjeta Šentjurc, Laboratorij za biofiziko - EPR center, Institut "Jožef Štefan", Jamova 39, SI-1000 Ljubljana, Slovenia; or call +386 1 477 36 89; or fax +386 1 436 32 69; or e-mail Is2001@ijs.si; or see Internet http://www.drustvo-biofizikov.si/Is2001/

Gastro-intestinal malignancies

October, 2001

The ESO training course will be offered in Cairo, Egypt.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Pediatric oncology

October, 2001

The ESO training course will be offered in Trabzon, Turkey.

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Breast cancer

October 4-6, 2001

The ESO training course will be offered in Sarajevo, Bosnia and Herzegovina.

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Radiotherapy

October 7-11, 2001

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

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Radiotherapy

October 7-11, 2001

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

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Renal carcinoma

October 9-11, 2001

The ESO training course "Renal Carcinoma" will be offered in Moscow, Russia.

Contact M. Vukelic, CSC Ltd., Heligenstadter Strasse 395b, 1190 Vienna, Austria; or call +43 1 369 0444; or fax +43 1 369 0444 20.

Malignant lymphoma

October 19-20, 2001

The ESO training course will be offered in Nicosia, Cyprus.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Radiation therapy

October 21-25, 2001

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

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Lymphoma

October 26-28, 2001

The ESO training course "Non Hodgkin's Lymphoma, Patho-Biology, Classification and Clinical Relevance" will be offered in Cairo, Egypt.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Clinical trials

November, 2001

The ESO training course will be offered in Ioannina, Greece.

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Psycho-oncology

November, 2001

The ESO training course will be offered in Nicosia, Cyprus.

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Radiation therapy

November 4-7, 2001

ASTRO Annual meeting will be held in San Francisco, California, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; web site: www.astro.org

Neck and thyroid surgery

November 5-7, 2001

The master course will be offered in Milan, Italy.

Call P. Lonati +39 (0)257 489 490; or fax +39 (0)257 489 589 491; or e-mail head&neck@ieo.it

Cancer risk

November 12-13, 2001

The ESO conference "Reducing Cancer Risk. Focus on the four big killers" will take place in New York, USA.

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

Lung cancer

December 6-8, 2001

The International Forum for Lung Cancer will be offered in Athens, Greece.

Contact Congress Secretariat - Organising Bureau, "MOEL" Ltd, 36, Eleon str. - GR 14564, Nea Kifissia, Greece; or call +301 6203 614; or fax +301 8078 342; or e-mail liagramo@internet.gr

Lung cancer

March 14-15, 2002

The IASLC international workshop "Early Invasive Lung Cancer. New Diagnostic Tools & Treatment Strategies will be offered in Turin, Italy.

Contact Organising Secretariat, CCI Centro Congressi Internazionale srl, Via Cervino 60, 10155 Turin, Italy; or call +39 011 244 69 16; or fax +39 011 244 69 00; or -mail info@congressiefiere.com

Radiotherapy

May 9-11, 2002

The Annual Brachytherapy Meeting GEC/ESTRO will take place in Antalya, Turkey.

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Radiation therapy

May 15-19, 2002

The 7th International Meeting on Progress in Radio-Oncology ICRO/EGRO 7 will take place in Salzburg, Austria.

Contact Prof. D.H. Kogelnik, Salzburg, Austria; call +43 662 44823900; or fax +43 662 4482887; or e-mail d.kogelnik@lkasbg.gv.at

Radiation therapy

September 15-19, 2002

The 21st Annual ESTRO Meeting will take place in Prague, Czech Republic.

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

Radiation therapy

October 6-9, 2002

ASTRO Annual meeting will be held in New Orleans, Louisiana, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; web site: www.astro.org

Radiation therapy

September 21-25, 2003

The ESTRO 22 / ECCO 12 Meeting will take place in Copenhagen, Denmark.

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

Radiation therapy

October 19-23, 2003

ASTRO Annual meeting will be held in Salt Lake City, Utah, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; web site: www.astro.org

Radiation therapy

September 12-16, 2004

The 23rd Annual ESTRO Meeting will be held.

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Radiation therapy

October 3-7, 2004

ASTRO Annual meeting will be held in Atlanta, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; web site: www.astro.org

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Activity of "Dr. J. Cholewa" foundation for Cancer Research and Education - A Report for the First quarter of 2001

The activity of the Executive and Advisory Boards of the "Dr. J Cholewa" Foundation for cancer research and education in the year 2000 and to the time of the present report continued to focus on the solution of financial problems connected with the financial inflow and the use of the funds available. It was noted that the attention of possible donors had been directed elsewhere, especially to sponsoring various sports activities, an understandable shift in the year 2000, since many of the would-be sponsors decided to help the participants of the Olympic games in Sydney that year. However, the Foundation continued to receive support from many of its long-time supporters in Slovenia, especially from Krka pharmaceutical company from Novo Mesto, Pivovarna Laško brewery from Laško, NLB bank from Ljubljana, SKB bank from Ljubljana, NKBM bank from Maribor, Sanolabor company from Ljubljana, Droga food processing company from Portorož, and many others.

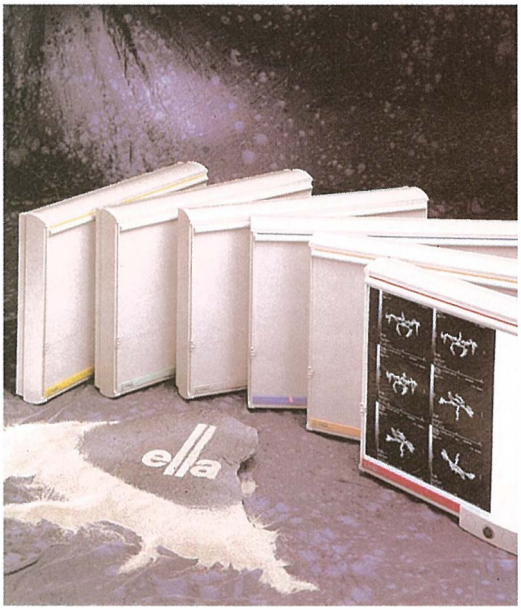
The Foundation continues to support the regular publication of "Radiology and Oncology" international scientific journal, that is edited, published and printed in Ljubljana, Slovenia. The support for the publication of the "Challenge Newsletter" will be re-evaluated shortly. In the year 2000 the Foundation also contributed support to the organisation of the traditional "Oncology Weekend" meetings, the annual "Plečnik Memorial Meeting", dedicated to honour the anniversary of Professor Vinko Kambič, one of the Founding members of the Foundation and who among many other honours also received the Honorary Award of the Foundation at the special ceremony held at the Medical Faculty of the University of Ljubljana. The Foundation also supported the organisation of the congress of "Slovenian Association of Genetics" held in Bled, Slovenia.

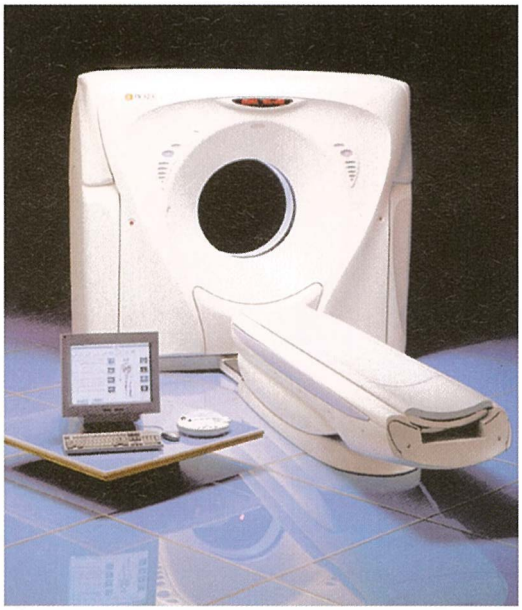
The members Executive and Advisory Boards unanimously agreed to accept three new members into the Foundation. The new members are Igor Bartenjev, MD, PhD, from the Dermatology Clinic in Ljubljana, Janez @agar, MD, MSc, from the Institute of Oncology in Ljubljana, and Rado Janša, MD, from the Gastroenterology Clinic in Ljubljana. All three new members had their biography and scientific bibliography data presented to the members of the Foundation and are welcome to take an active part in its various activities.

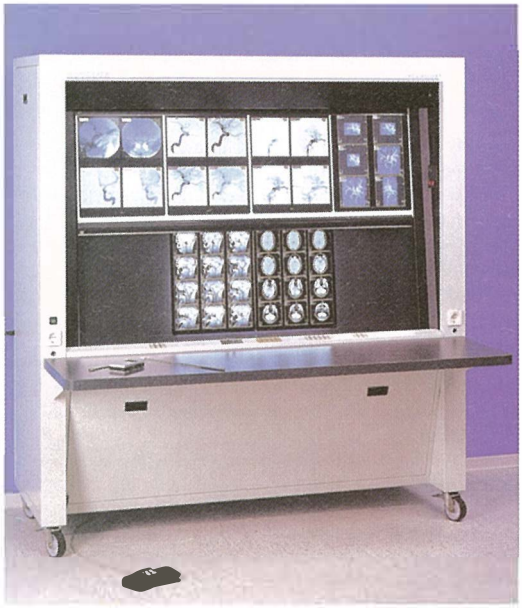
The members of the Executive and Advisory Boards are honoured to announce that on April 19th, 2001, the Honorary Award of the "Dr. J. Cholewa" Foundation for cancer research and education was presented to Mr. Anton Turnšek, in recognition of his merits associated with the activity of the Foundation. Mr. Turnšek is a highly respected businessman and an expert in food and beverages processing, and is presently the Director of the Pivovarna Laško brewery, one of the most successful and propulsive food and beverages companies, and companies in general in Slovenia. He is a recipient of many prestigious awards, including those by the Chamber of Commerce of Slovenia. Mr. Turnšek is one of the founding members of the "Dr. J. Cholewa" Foundation for cancer research and education, and especially in the beginning of the activity of the Foundation his experience in dealing with many of the related problems proved to be invaluable.

The Foundation moved back to its original headquarters in Mesesnelova Street No. 9 in Ljubljana in the beginning of the year 2001. This decision was taken to streamline the expenses associated with the day to day activity of the Foundation and was also conveyed to the relevant City of Ljubljana authorities. It is one of the measures of the Foundation taken to facilitate the access to oncology research and education support to as many interested individuals and institutions in various regions of Slovenia as possible. New approaches to achieve the enhancement of the knowledge in cancer prevention and early detection all over the country will possibly be evaluated. As it has been mentioned many times before, special attention will be given to the requests coming from the regions of Slovenia outside Ljubljana to provide grants for the participation of Slovenian oncologists and others on various educational meetings in the country and abroad.

Tomaž Benulič, MD
Borut Štabuc, MD, PhD
Andrej Plesničar, MD, MSc







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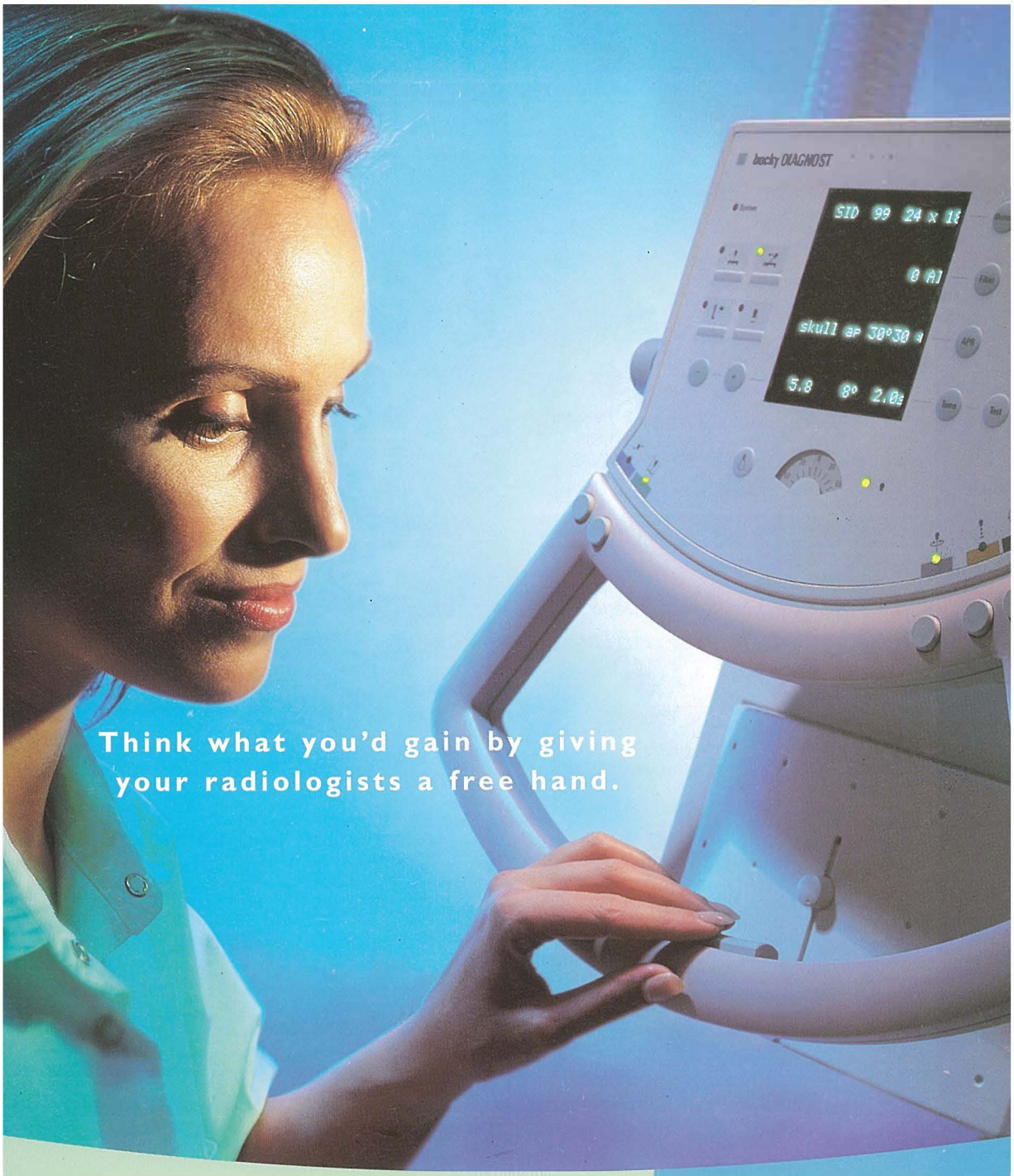

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kriptokokni meningitis	*prvi dan 400 mg,* *nato od 200 do 400 mg na dan*
vzdrževalno zdravljenje	*200 mg na dan*

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

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NOVODIRECT BIOBLOCK (Francija):
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EVL (Nizozemska):
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HÜRNER (Nemčija):
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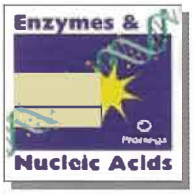
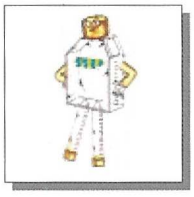
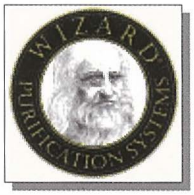
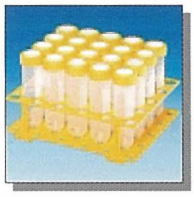






GENOMIKA - PROTEOMIKA



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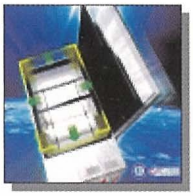
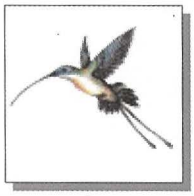


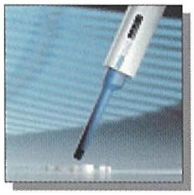
ČISTA VODA ZA LABORATORIJ

SKRINJE IN HLADILNIKI

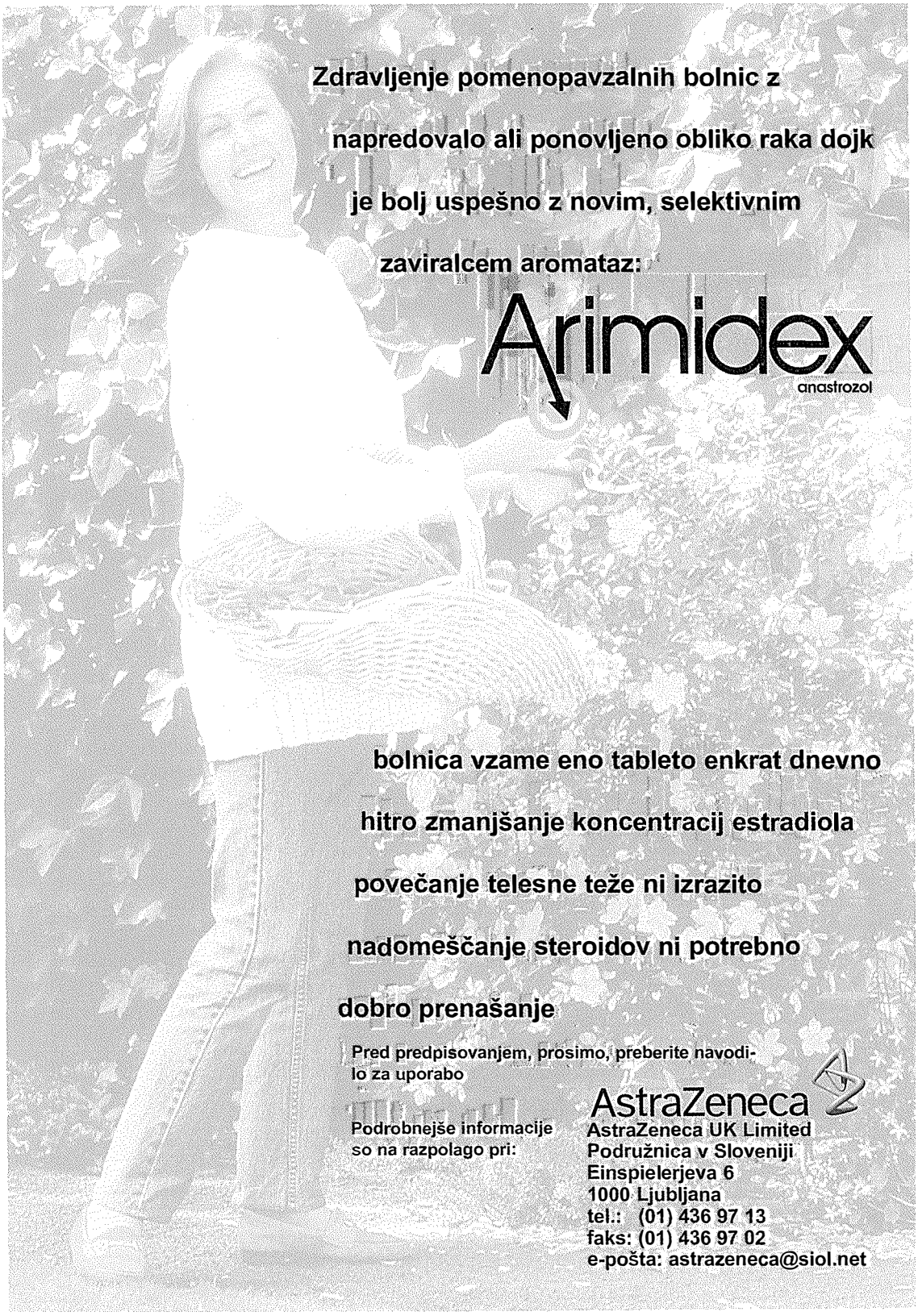
CELIČNE KULTURE

BIOHIT





ELEKTRONSKE IN MEHANSKE AVTOMATSKE PIPETE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napredovalo ali ponovljeno obliko raka dojk
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zaviralcem aromataz:
Arimidex
anastrozol
bolnica vzame eno tableto enkrat dnevno
hitro zmanjšanje koncentracij estradiola
povečanje telesne teže ni izrazito
nadomeščanje steroidov ni potrebno
dobro prenašanje
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CHALLENGE

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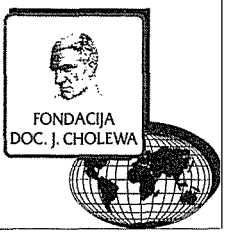

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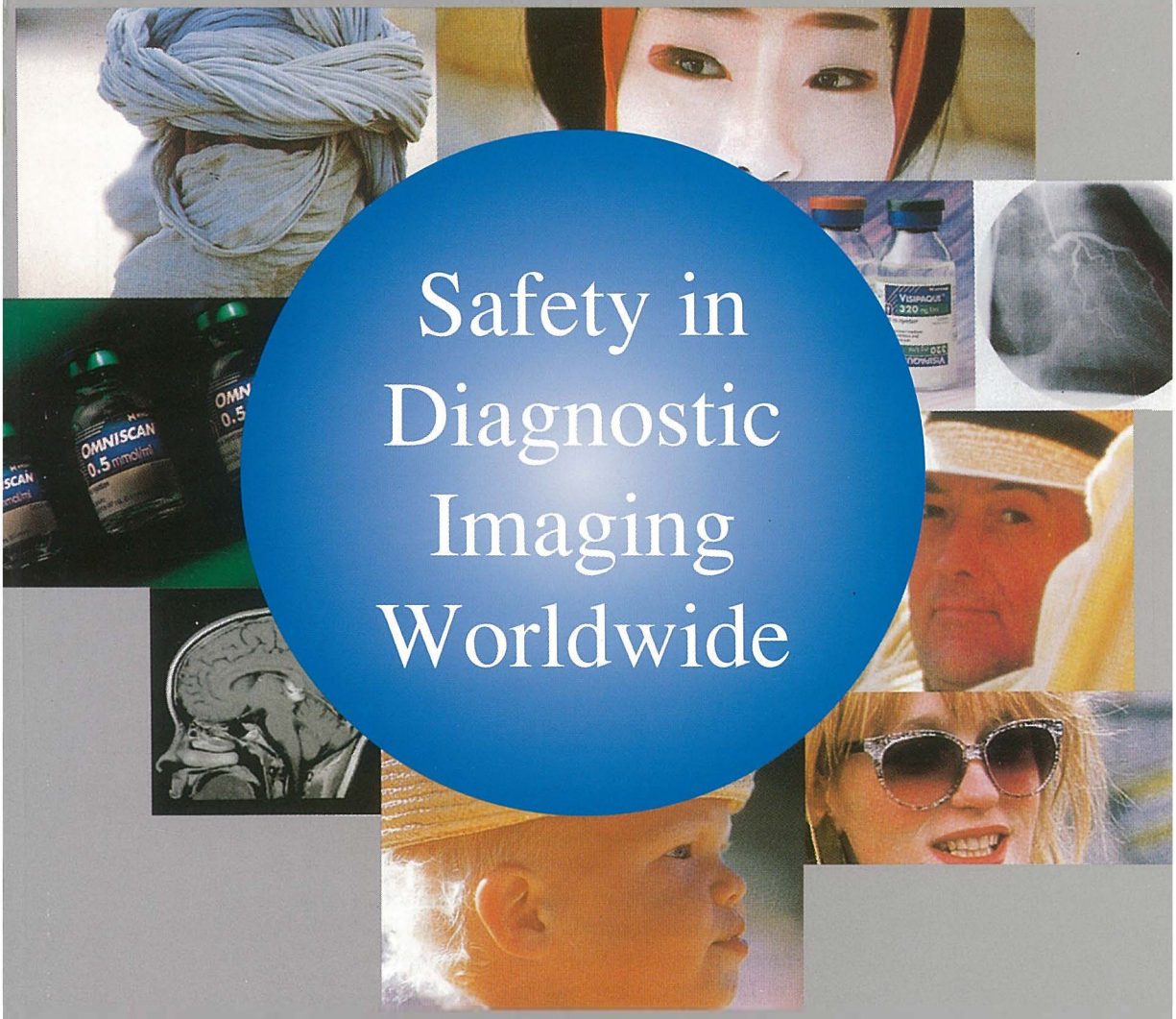

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