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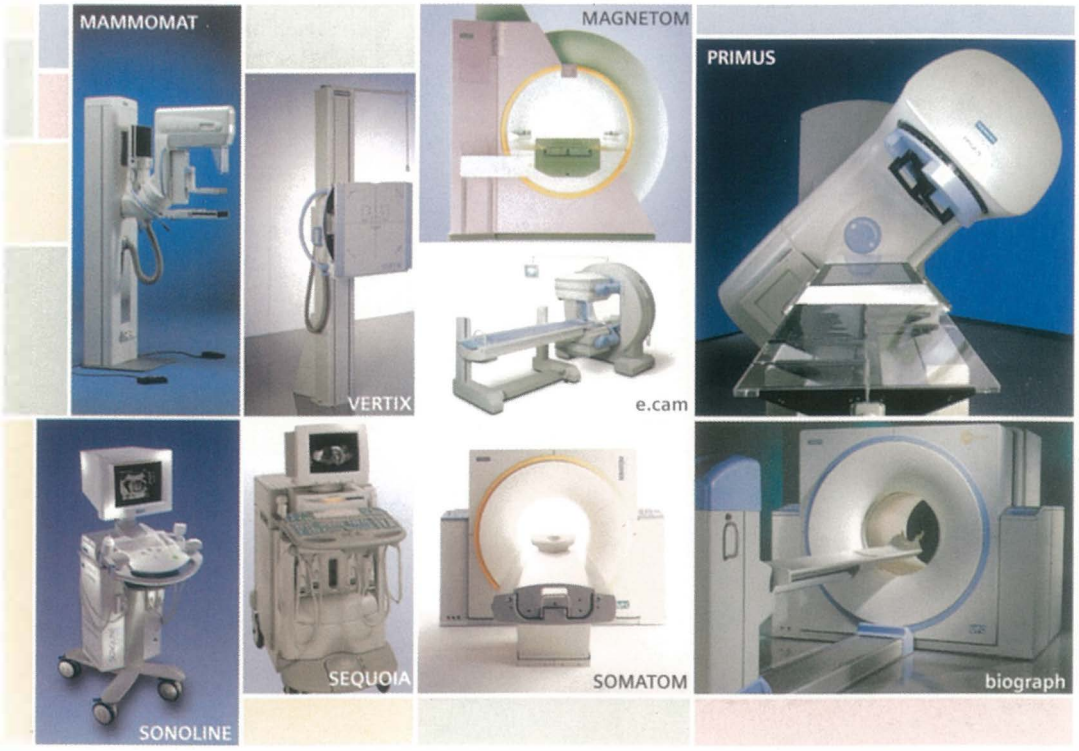

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Computer assisted diagnosis of benign bone tumours

Milan Samardziski[1], George Zafiroski[1], Vesna Janevska[2], Daniela Miladinova[3], Žaneta Popeska[4]

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Background. *The aim of this study is to determine the correlation between computer-assisted diagnosis (CAD) of benign bone tumours (BBT) and their histological type.*

Patients and method. *Altogether 120 patients were included in two groups. The retrospective group comprised 68 patients in whom the histological type of BBT was known prior to computer analysis. The prospective group comprised 52 patients in whom the histological type of BBT was unknown prior to computer analysis. Computer program was efficient and easy to use.*

Results. *Average percent of histological type confirmed with CAD in the retrospective and prospective groups was 72.06% and 76.92%, respectively. Histological confirmation of CAD in specific BBT was 91.42% for enchondroma, 96.15% for osteoid-osteoma, and 98.08% for osteochondroma. Significantly lower percentage of CAD confirmation of fibroma, chondromixoid fibroma, osteoclastoma, desmoplastic fibroma and osteobalstoma due to their adverse biological character or complex anatomic localization is understandable.*

Conclusions. *The results speak in favour of the assumption that computer assisted diagnosis of bone tumours program may improve the diagnostic accuracy of the examiner.*

Key words: bone neoplasms — pathology; diagnosis, computer - assisted

Introduction

Diagnosis and treatment of benign bone tumours (BBT) is a multidisciplinary task. Teams of diverse subspecialists are involved in the process. Good quality plain X-rays may be most helpful in 9 of 10 cases. Bone scan, CT and MRI are additionally needed for the diagnosis, staging and decision making on the management of BBT. The diagnosis of histological type can be done exclusively by a patohistyologist.[1]

In the second half of the 20th century, a digital revolution started in the USA. This led to a great advance in technology and data management. A new approach in diagnostics and decision-making process in medicine was

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inevitable. Warner was the pioneer in computer assisted diagnosis (CAD) of congenital heart diseases in 1961.[2] Lodwick in 1963 gave his preliminary results with computer assisted diagnosis of primary bone tumors.[3] Many others followed him soon after: Hall in 1971, Buzdon in 1978, Virtama in 1979, Zafiroski in 1986.[4-6] Our task in this study was to determine the correlation between computer-assisted diagnosis (CAD) of benign bone tumours (BBT) and their histological type.

Patients and methods

In this study, 120 patients with BBT were included. The observation period was 7 years. The patients were treated at the Clinic for Orthopaedic Surgery in Skopje. They were divided in two groups. The retrospective group comprised 68 patients in whom the histological type of BBT *was known* prior to computer analysis. The prospective group comprised 52 patients in whom the histological type of BBT *was unknown* prior to computer analysis. Of the total of 120 patients, 66 were males and 54 females. The age of patients ranged from 6 to 79 years old (mean 27.4 years). Two thirds (78 patients) were in the second or third decade of their life. The follow-up was from 2 to 5 years (Table 1).

Osteochondroma was diagnosed in 34.16% (41) of patients and osteoid-osteoma in 35.0% (42) of patients. Enchondroma was found in 13.33% (16) of patients and 7.5% (9) patients were diagnosed with giant cell tumours. Fibroma, desmoplastic fibroma, chondroblastoma, chondromixoid fibroma, osteoblastoma, lipoma and hemangioma were found in 12 patients (10.0%). Enchodromas were 3 times more frequent in female patients while osteohondromas, osteoid-osteomas and giant cell tumours were more often diagnosed in male patients (Table 1).

Most of the authors are using Bayes' theorem of inverse probability as a basic tool for the mathematical model in the computer program. Thomas Bayes (1702-1761) was a minister who gave the basic mathematical values to the outcome and risk, thereby founding a scientific approach to forecasting.[7]

$$Py_1\,(x_1, x_5 \ldots x_j) = \frac{Py_1\, Px_1\, y_1^{(1-\,Px5\;y1)} \ldots .\, Px_j\, y_1}{\sum_{\text{all k}} Py_k\, Px_1\, y_k^{(1-\,Px5yk)} \ldots .\, Px_i\, y_k}$$

Table 1. Patients included in the study and average follow-up

Benign bone tumors	Age (mean yrs)	Gender M	F	Number of cases	%	Follow-up (yrs)
Osteoma	30	0	2	2	1.66	4.5
Osteoid-osteoma	18.3	30	12	42	35.0	5.3
Osteoblastoma	36.5	1	1	2	1.66	5
Enchondroma	40.7	4	12	16	13.33	3.6
Osteochondroma	21.7	24	17	41	34.16	3.3
Chondrobalastoma	22	1	0	1	0.83	4
Chondromyxoid fibro.	24.5	0	1	1	0.83	3.5
Osteoclastoma (GCT)	33.8	5	4	9	7.50	4.4
Hemangioma	30	0	1	1	0.83	2
Fibroma	18.7	1	2	3	2.50	3.7
Desmoplastic fibroma	14	0	1	1	0.83	3
Lipoma	39	0	1	1	0.83	3
	Mean	Total		Total	Total	Mean
	27.4	66	54	120	100%	3.8

On **y** axis of probability matrix, all possible diagnoses (y_1, y_5,...y_j) are given, on **x** axis, all radiological characteristics of the tumours (x_1, x_5,...xj) are shown. **P** is probability, and **k** is the number of possible diagnosis included in the matrix. For an absolutely correct probability, indefinite number of cases are needed (**i**), and all variables included should be completely independent.

An adequate vocabulary, based on the radiographic manifestations of BBT, is required for the communication with the computer program.[3] The program is capable of predicting 34 different histological types of primary bone tumours and tumour like lesions.[6] The greatest task with CAD is to achieve a correct histological type of the BBT and to follow two basic principles: (1) the prediction of the diagnosis must be correct in the highest possible number of cases (ideally in all of them), and (2) if there is a mistake in the prediction, it must not influence further treatment of the lesion in a way that could harm the patient. In the decision-making algorithm, both principles are included.[8]

We compare our prior experiences of radiographic manifestations of BBT with the radiographic manifestations of the new cases. The next task in the algorithm is to eliminate as many data (diagnosis) as possible during the decision-making process. In this process, the strongest criteria for eliminating or including a certain diagnosis are the radiological grade of tumour growth. Many lesions are seen only in the radiological grades of tumour growth Ia, Ib or Ic (Figure 1).[4] During the analysis of the x-ray, the following data were included: age and gender, localisation of the

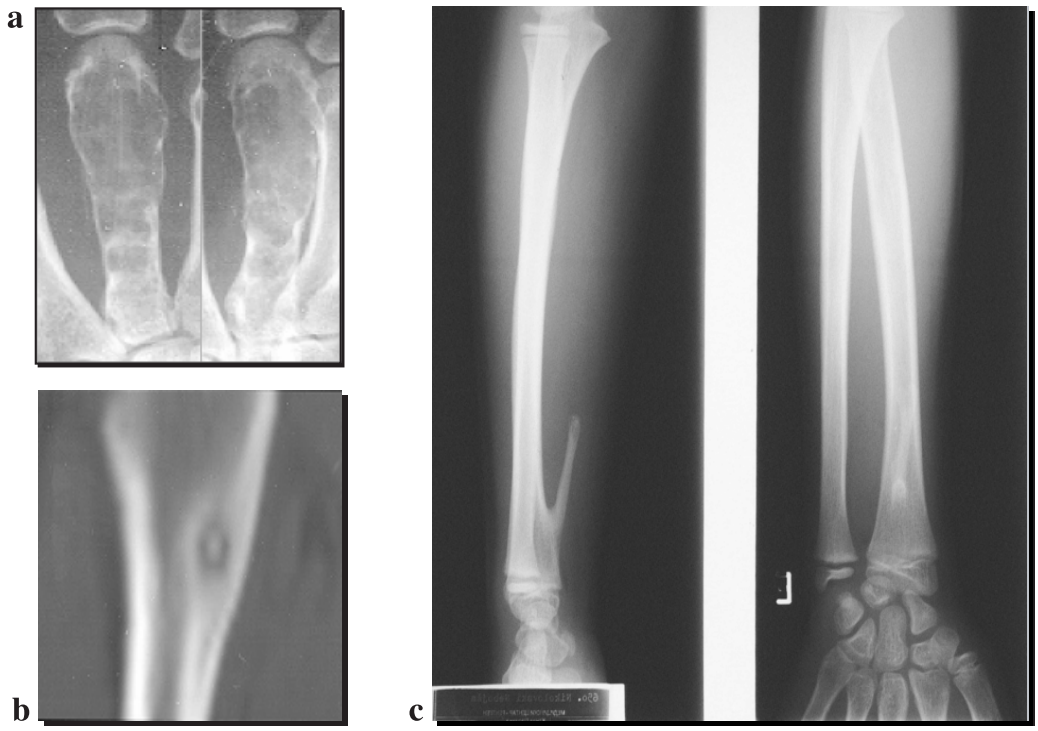

Figure 1. (a) enchondroma in the proximal phalanx of the third finger of the hand, presented with moderate pain until the fracture occurred; (b) CT imaging of osteoid-osteoma in the proximal femur, with typical "nidus"; (c) plain radiograph of the forearm showing osteochondroma of distal radius (almost not seen in frontal plane).

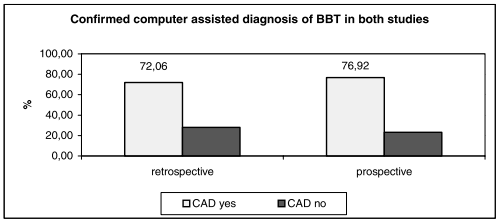

Figure 2. Percentage of confirmed computer assisted diagnosis (CAD) in the retrospective and prospective study.

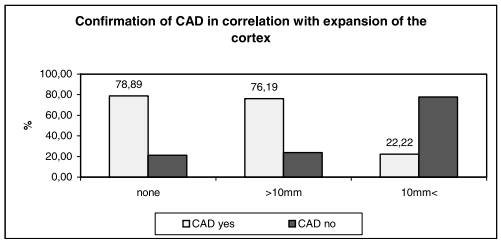

Figure 3. Percentage of confirmed computer assisted diagnosis (CAD) in correlation with the expansion of the cortex.

BBT, bone destruction, destruction of the cortex, periostal proliferation, tumour matrix mineralisation and size of the tumour.

Results

In this study CAD were compared to the final histological type of BBT. The results showed high statistical significance between the radiographic manifestations of BBT and histological type.

The percentage of confirmed CAD in the retrospective study was 72.06% and in the prospective study 76.92%. There was no statistically significant difference between these results ($\chi^2 = 0.36$; for r =0.34) (Figure 2).

The analysis of different radiographic manifestations in correlation with confirmed CAD was made on a joined number of cases from both studies (retrospective and prospective); so, the results gave greater statistic significance. Highest percentage of CAD was seen in the lesions localised in the cortex of the bone (83.10%) compared to the lesions localized in the bone medulla (61.36%) and other localizations (60.00%). Analysed parameters showed high values of χ^2 test: $\chi^2 = 7.244455$; $r = 0.026723$ for $r < 0.05$.

The highest percentage of confirmed CAD in correlation with expansion of the cortex under the pressure of growing BBT showed lesions without expansion (78.89%). The highest percentage of unconfirmed CAD showed lesions with the expansion of the cortex greater than 10 mm (77.78%). Analysed data revealed high statistic significance ($\chi^2 = 13.76689$; $r = 0.001025$ for $r < 0.05$) (Figure 3).

Size of the tumours was measured in millimetres of their longest diameter. Tumours were divided in the group with the confirmed CAD and the group with unconfirmed CAD. Standard error and standard deviation were higher in the group with unconfirmed CAD and average size of 41.8 mm. The values showed statistical significant difference for χ^2 test -21.68123; $r = 0.010638$ for $r < 0.005$.

Discussion

Most of the bone tumours originate from the medullar bone, destructing it prior to the growth of the lesion in the cortex. Unfortunately, this is not seen until 40-50% of the medullar bone is lost. In contrast to the medullar bone, the cortex shows even slightest destruction when appropriate x-ray projection is made. Slow growing and benign bone tumours produce a sclerotic reaction of the surrounding bone.[9] Analysing these manifestations together with bone tumour matrix one can easily determine the radiological grade of tumour growth. Active, aggressive and malignant should be immediately treated and latent ("live me alone") bone tumours should be regularly inspected and followed.[10] Working with this program for computer-assisted diagnosis of BBT appears to be easy, understandable and can be used by relatively

inexperienced examiner. The use of the program improves diagnostic accuracy significantly and results in improved patient management and cost-saving.[5]

CAD of BBT should be confirmed in the highest possible number of cases (ideally 100%). The average percent of confirmed CAD in retrospective study is 72.06% and in prospective study is 76.92%. This is slightly lower than those in previous studies of Enneking (77.9%) and Bumbasirevic (81.2%).[4,9] In our study, for some specific benign bone tumours as enchondroma, osteochondroma and osteoid-osteoma, the confirmation is higher than 83.33%. There was no significant influence of the examiner on the results of CAD. The analysis of the results of fibroma, chondromixoid fibroma, osteoclastoma, desmoplastic fibroma and osteoblastoma and lesions localized on scapula and pelvis was inconclusive due to their adverse biological character, low number of cases or complexity of the analysis of the specific anatomic localization.

Best results of CAD were shown when lesions were localized in the cortex, in tumours without expansion of the bone and tumours with average size of 27 mm in diameter. The results support the assumption that the computer-assisted diagnosis of bone tumours program may improve the diagnostic accuracy of the examiner. This is due to an analytic, systematic and logic approach to the analysis of the radiographic manifestations of BBT. A slightly lover percentage of confirmed CAD in the retrospective versus prospective study speaks in favour of that conclusion.

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Spontaneous perirenal and subcapsular haematoma – report of 5 cases

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Background. *Spontaneous perirenal and subcapsular haemorrhage is a rare but important clinical condition and is diagnostically very challenging. Sometimes, the aetiology of bleeding remains unclear; when all available diagnostic possibilities are exhausted, therapeutic approach still remains controversial.*

Case reports. *We present a series of 5 patients with perirenal and subcapsular bleeding. In two of among our patients, the initial or control CT scan suggested angiomyolipoma and renal cyst as the cause of the bleeding that was confirmed by pathological analyzes. In other three patients, no pathology other than haematoma itself was visualized on CT scans, nor it was discovered on pathological analyzes in two of the patients. Our CT findings closely correlated with pathological findings – whether positive or negative for the pathological substrate. Interestingly, we found not one case of renal cell carcinoma.*

Conclusions. *In literature, in as many as 50 % of cases of perirenal and subcapsular bleeding, a malignant tumour is found. Therefore, by some authors, nephrectomies in all patients are recommended, but others take more expectative approach with long-term close surveillance. We believe, that with new imaging modalities, if using optimal examination technique and follow-up protocols, the patients with bleeding due to benign disease should be recognized and unnecessary nephrectomies avoided.*

Key words: kidney diseases; haematoma, tomography, X-ray computed

Introduction

Spontaneous perirenal and subcapsular haemorrhage is a rare but important clinical condition and is often diagnostically very challenging. The appropriate treatment of these patients is based on making a fast and correct diagnosis of subcapsular and perirenal haemorrhage. Clinical symptoms are often non-specific and misleading and the radiological methods, based on ultrasound (US) and CT imaging are crucial in making the correct diagnosis. Diagnosing the haematoma itself, its extent and location is rather simple with mentioned imaging modalities, but determining the source of bleeding and defining the underlying pathological condition that caused the bleeding is more complex task.

As sometimes the aetiology of the bleeding

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still remains unclear though all available diagnostic possibilities are exhausted, the therapeutic approach to these patients is still controversial.[1-4] In clinical approach, it is necessary first to exclude trauma, anticoagulation medication, bleeding diathesis, arteritis, tuberous sclerosis or whether the patient is undergoing a long-term haemodialysis, as all these conditions are known to be associated with perirenal bleeding. The most common underlying kidney conditions include renal cell carcinoma, angiomyolipoma, AV malformation, arterial aneurysm, renal cyst, infarction and abscess. [2,5-7]

We report our experience on a series of 5 patients with perirenal and subcapsular bleeding. In our diagnostic algorithm, after the US examination that was used as a first method, the key examination was CT scanning. All examinations were performed on conventional CT scanner (Shimadzu Intellect). CT was performed [(after an i.v. contrast medium bolus administration)] from diaphragm to symphisis with the slice thickness of 10 mm and pitch of 10 mm using native sequences and sequences.[7] When needed, a selective angiography was also performed.

Case reports

Patient No. 1 was male, aged 37 years. He presented with the acute right-sided flank pain. On US examination, a perirenal haematoma was suspected and CT finding confirmed the haematoma with angiomyolipoma as a probable bleeding source (Figure 1a). Angiography (DSA) was performed and revealed pathological vascular pattern characteristic for angiomyolipoma. Nephrectomy was performed and pathohistological diagnosis confirmed the clinically suspected angiomyolipoma (Figure 1b).

Patient No. 2 was female, aged 53 years. The initial CT scan showed subcapsular renal haematoma on the left side without any other pathology (Figure 2a). Two months later, the follow-up CT scan showed substantial regression of the bleeding and renal cyst that was suspected to be a bleeding source (Figure 2b). Three months later, the follow-up CT scan showed complete regression of the haematoma (Figure 2c). Surgical exploration and pathohistological analyses confirmed the diagnosis of the renal cyst and the kidney was preserved.

Patient No. 3 was male, aged 75 years. The patient presented with an acute lumbar pain. US examination showed a heterogenic mass in the kidney that was suspected to be a bleeding renal tumour. CT scan was performed and revealed only a huge left-sided perirenal haematoma (Figure 3). Laboratory

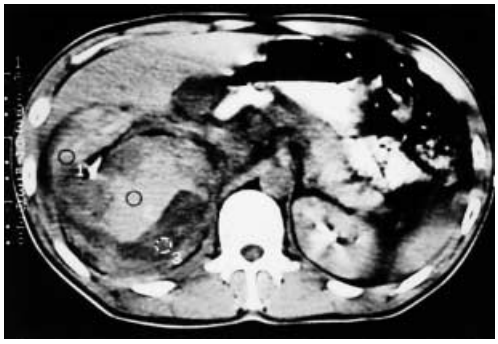

Figure 1a. The initial CT scan showed perirenal haematoma and angiomyolipoma was identified as a bleeding source.

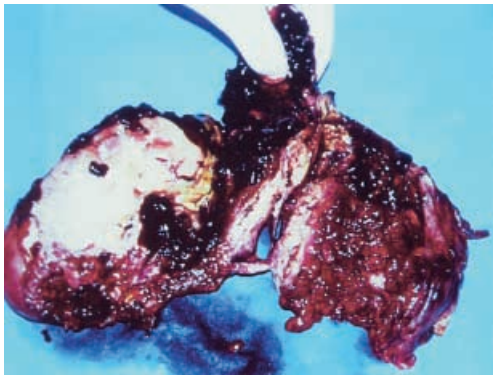

Figure 1b. Angiomyolipoma was confirmed intraoperatively.

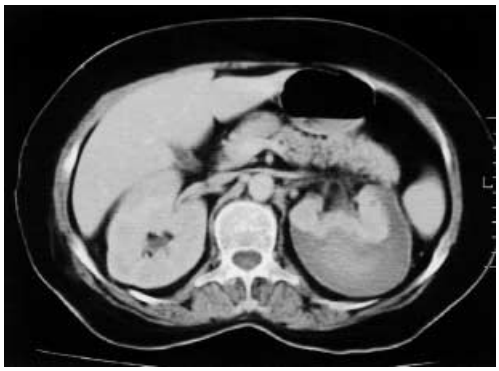

Figure 2a. The initial CT scan showed subcapsular haematoma without identifying the bleeding source.

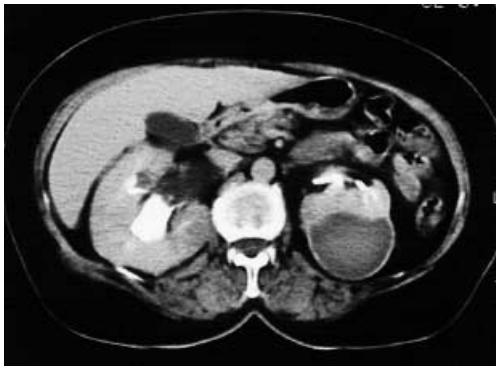

Figure 2b. The follow-up CT scan two months later showed a substantial regression of bleeding and a renal cyst that was suspected to be the source of bleeding.

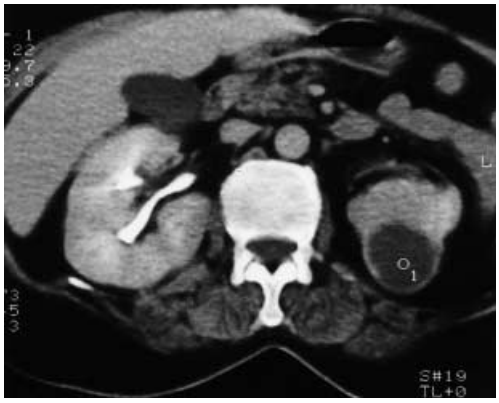

Figure 2c. The follow-up CT scan three months later showed a complete regression of the bleeding and renal cyst was confirmed.

findings indicated liver cirrhosis (elevated liver enzymes, coagulation disorder). As the patient became haemodynamically unstable urgent nephrectomy was performed. Pathohistological analyses revealed no pathological findings apart from the haematoma. We believe that coagulation disorder due to liver disease caused the bleeding in this patient.

Patient No. 4 was male, aged 63 years. He presented with a flank pain in the right lumbar region lasting for 15 days. He had similar symptoms 2 months before and was diagnosed with renal colic. US and CT examinations showed subcapsular haematoma and calculus in the right kidney with no other pathological findings (Figure 4a). Surgical exploration was performed and as the bleeding source could not be identified, the kidney was preserved. Three months later, CT scan and US was normal, as well as CT scan one year later (Figure 4b). We believe that the renal colic caused the bleeding in this patient.

Patient No. 5 was female, aged 46 years. The patient was diagnosed with rheumatoid arthritis 6 years prior to the current illness. She was admitted due to right-sided lumbar pain lasting for several months. US examination showed hyperechogenic renal mass and renal tumour was suspected. CT scan showed subcapsular haematoma and also retroperitoneal lymphadenopathy (Figure 5). Occult

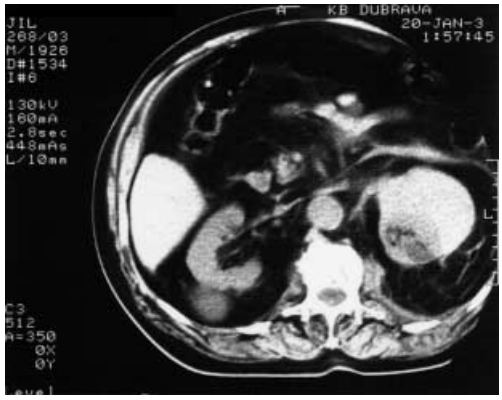

Figure 3. CT scan showed subcapsular haematoma without identifying the bleeding source.

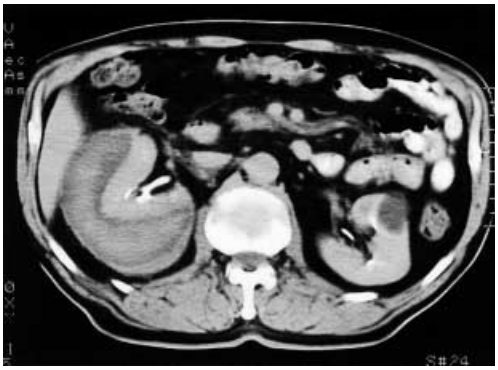

Figure 4a. The initial CT scan showed subcapsular haematoma without identifying the bleeding source.

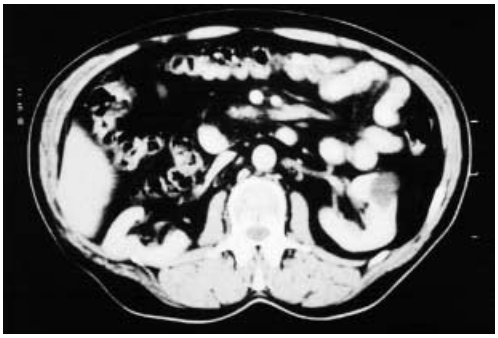

Figure 4b. The follow-up CT scan 3 months later was normal as well as the follow-up CT scan 1 year later.

renal cell tumour was suspected and nephrectomy was performed. Pathohistological diagnosis showed reactive hyperplasia of the lymph nodes and mononuclear infiltration with no malignant disease.

Discussion

In our patients, the initial or control CT scan suggested the cause of the bleeding in two patients (patients No. 1 and No. 2), angiomyiolipoma and bleeding renal cyst, respectively. These diagnoses were confirmed by postoperative pathohistological analyses. In other three patients no substrate other than haematoma itself could be visualized on CT scans. In two among them (patients No. 3 and No. 5) nephrectomy was performed and no malignancies were found on pathological analyses. In the last patient (patient No. 4), neither the initial CT nor the intraoperative examination showed bleeding source and it was decided to preserve the kidney. Even repeated CT scans, done over the period of one year, did not identify any pathological substrate; we therefore believe that the renal colic caused the bleeding in this patient.

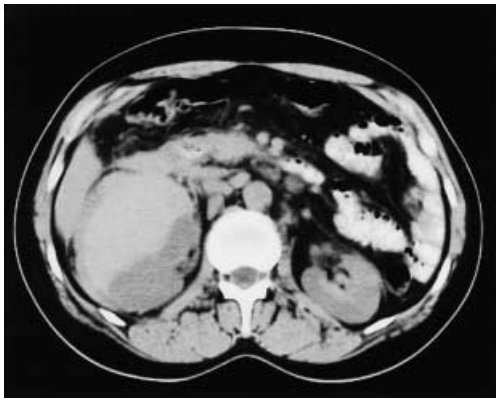

Figure 5. The initial CT scan showed subcapsular haematoma and retroperitoneal lymphadenopathy.

In our series of patients, CT findings closely correlated with pathohistologic findings – whether positive or negative for the pathological substrate. Interestingly, we did not find any case of renal cell carcinoma among our patients. In our opinion a correct CT examination technique is crucial for making a correct diagnosis. A careful search for small tumours after i.v. contrast administration is mandatory. Areas of fat within the kidney and diagnostic for angiomyolipoma should be noticed as angiomyolipomas are common causes of spontaneous haematoma.[8] If CT scan is negative for the tumour in order to exclude vascular abnormality, a selective angiography should be performed.[9] If the diagnosis of the cause of haematoma is still unclear the repeated CT scanning is advised, preferably every 6-8 weeks. It will allow enough time for the haematoma to resorb and, possibly, also for finding a small tumour that might have been present, but hidden by

the blood in the initial study. The follow-up is needed until the haematoma completely resolves or until the diagnosis is made.[2,10]

Even today, with all our sophisticated technology, the therapeutic approach to spontaneous perirenal and subcapsular haematomas is controversial. The malignant tumour, often small in size, is reported in 30% to over 50% of the patients and, according to several authors, radical nephrectomy in the absence of apparent cause of bleeding is recommended in all patients.[11-13] On the other hand, as the haemorrhage can be idiopathic or due to benign lesions, other authors[2,3,9] propose more expectative approach with long-term close surveillance in order to avoid unnecessary surgery and nephrectomias.

We believe that, with new imaging modalities, especially spiral and multidetector CT and using optimal examination technique as well as follow-up protocols, we should recognize the patients with perirenal bleeding due to benign disease and avoid unnecessary nephrectomias.

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Sonographically guided fine-needle aspiration biopsies of adrenal masses in lung cancer patients, eleven-year experience

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Purpose. *The aim of this retrospective study was to define the accuracy and safety of the ultrasonographically (US) guided fine-needle aspiration biopsy (FNAB) of the enlarged adrenals in the patients with lung cancer.*

Patients and methods. *In eleven-year period 64 patients with cytologically proven lung cancer underwent US-guided FNABs of adrenal masses. The accuracy of the method was assessed on the basis of cytology findings and the safety on the number of complications reported after the procedure.*

Results. *US-guided aspiration biopsy turned out to be accurate in 58/64 cases (91%), and very safe with only 4/64 (6%) minor complications. In 52/58 (90%) cases, the cytology sample was found to be malignant. In 6 cases (10%), isolated adrenal masses were adenomas.*

Conclusions. *We recommend US-guided FNAB as a safe and reliable diagnostic method that has many advantages over computer tomography (CT)-guided FNAB, such as safety, patient-friendliness, no X-rays and its reproducibility.*

Key words: lung neoplasms – secondary – ultrasonography – pathology; adrenal gland neoplasms; biopsy, needle

Introduction

The adrenal glands are a common site for the metastatic spread of lung cancer.[1] The metastases in the adrenal glands are often detected at the time of setting the basic diagnosis. As they are usually asymptomatic,[2] the only reliable method to confirm the metastases is diagnostic imaging. The majority of them are detected by chest and upper abdomen CT or by abdominal ultrasound (US) examination.

The improvement of US technology allows visualization of slightly enlarged adrenal glands, with the exception of the scans in obese and meteoristic persons. Any enlargement of the adrenal glands should be explained because benign changes could be detected in healthy individuals.[3,4] In addition, there are many reports on high percentage of the benign cytology findings of fine-needle as-

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piration biopsies (FNABs) from the enlarged adrenal glands in lung cancer patients.[5,6]

In the literature, the results of CT-guided aspiration biopsies[7-9] are more often analysed than the results of US-guided ones.[8-10] The purposes of these retrospective study were to obtain data on the accuracy and safety using US guided FNABs in the evaluation of enlarged adrenal glands in patients with lung cancer.

Patients and methods

In the 11-year period, from 1991 to 2001, we performed 64 US-guided biopsies of the enlarged adrenal glands in 64 patients with cytologically confirmed lung cancer. Forty-six of them were men and 18 were women, with the average age of 59 years, ranging from 42 to 82 year (SD ± 9.6).

Lung cancer was cytologically confirmed (by bronchoscopy, transthoracic FNAB, or by sputum examination). The most frequent type was adenocarcinoma (28 patients), followed by epidermoid (16), microcellular (6) and macrocellular lung cancer (6) and not otherwise specified in 8 cases. In 40 patients the tumour was localized in the right lobe and in 24 patients in the left lobe.

Sonographic examination and US-guided FNABs had been performed with Toshiba SSA 240A ultrasound scanner before 1997 and a Toshiba SSA 340A afterwards (Tokyo, Japan). A convex probe with the radius of 25 or 50 mm was chosen for subcostal or transhepatic approach, whereas the probe of 15 mm was used for intercostal approach.

US-guided aspiration biopsies were performed by flexible "Chiba" needles with the length of 16 to 20 cm and 22 G (0.7 mm) thick. A metal probe adapter with a 5 cm long guide helps to maintain the needle aligned with the scan and allowed it to hit the target easier. In all cases, the radiologist carried out the whole process by himself, holding the probe with his left hand while inserting the needle and aspirating with the right one (Figure 1).

Prior to biopsy, coagulation tests had been performed in order to check that the patient's platelets counts and prothrombin time (PT) were within normal values. Patients with platelet count of less than$100x10^9$/l and PT ratio of less than 0.60 had been excluded from the biopsy procedure.

In the patients in whom a bilateral enlargement of the adrenal glands was observed by US we anticipated the same aetiology of changes in both glands; therefore, FNAB was performed in one gland only.

Results

We performed 38 biopsies (60%) of the enlarged adrenal glands on the right side and 26 biopsies (40%) on the left side. The mean longest diameter of the enlarged glands was 5.6 ± 2.7 cm (range, 2.5-13.0 cm).

The material for cytology analysis was assessed as appropriate in 58/64 cases (91%), while in 6/64 cases (9%), it was inappropriate. Cytology examination confirmed a malignant process in 52/58 patients (90%) and a benign process in 6/58 (10%) patients. Of 52 malignant cases, 40 (77%) were diagnosed as definitely a metastatic process, and the remaining 12 were found to be malignant without further characterization.

The mean longest diameter of benign adrenal masses, which were all unilateral, was 4.2 ± 2.4 cm (range, 2.5-7.0 cm) and that of the malignant ones was 6.3 ± 2.8 cm (range, 3.5-13.0 cm). The mean longest diameter of unsuccessfully biopsied lesions (inappropriate cytology samples) was 5.7 ± 2.1 cm (range, 4.0-8.0 cm).

We carried out the majority of aspiration biopsies in the outpatient department; 50 patients (78%) were called in on the day of biopsy. Four patients complained of pains and of

sensitivity to palpation that developed immediately after the biopsy, persisted for some hours and faded away spontaneously. In these patients sonographic examination performed approximately two hours after the biopsy revealed no abnormalities.

Discussion

In view of the accuracy and safety, the literature recommends more CT than US-guided FNABs of the enlarged adrenal glands.[7,9,11] No comparative studies have been done. The studies report 80-83% primary and 90-93% secondary accuracy of CT-guided FNABs.[7,12,13] In our study, the sample was appropriate for the cytology analysis in 58 cases, which means 91% primary accuracy of the method.

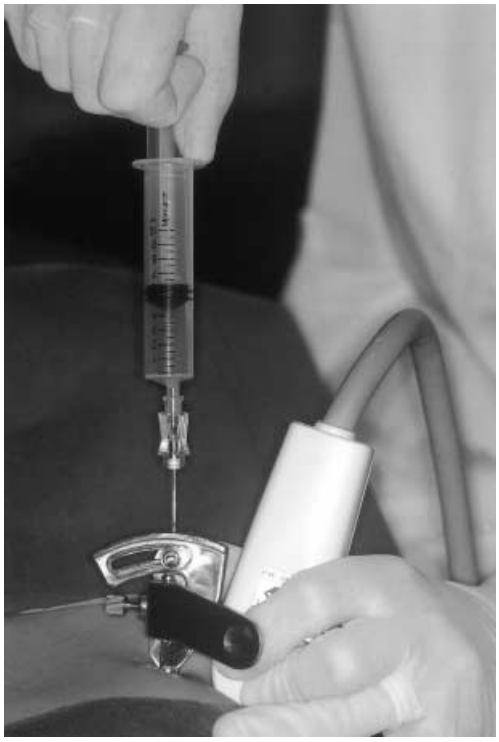

Figure 1. The puncture technique. A metal probe adapter with a 5 cm long guide helps to maintain the needle aligned with the scan and allowed it to hit the target easier. The radiologist holds the probe with his left hand while inserting the needle and aspirating with the right one.

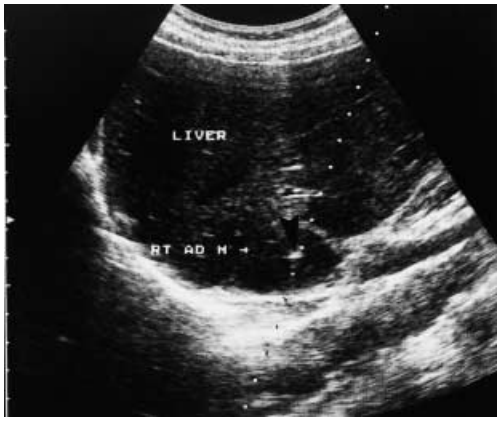

Figure 2. Right adrenal metastasis FNAB, measuring 3.5 x 2.5 cm in the patient with right upper lobe lung cancer. The tip of the needle (black arrowhead) is clearly visible in the lesion.

In 6 of our patients, cytology confirmed a benign enlargement of the adrenal gland (adenoma or hyperplasia). In these patients during follow-up period of, no metastatic spread into the adrenal glands was observed. Due to the small group conclusions referred on these data are not reliable.

CT-guided FNAB is considered to be safe;[7,11,12] the most frequent complications are pneumothorax[13] and bleeding.[7] No distinct correlation was made between the needle thickness and localization of the lesion, although Price[11] reported that no complications occurred by transhepatic approach CT-guided FNABs of the right adrenals.

Most of our patients had the biopsy performed as outpatients. After the procedure, they were observed for 2 hours. Only 14 patients (22%) underwent the FNAB as inpatients. Four of all patients complained of periodic pains at the puncture site. A key to the success of the procedure is to perform it as quickly as possible. US-guided aspiration biopsies are more flexible and adjustable if performed by a single person holding the probe with his left hand while inserting the needle and aspirating with the right one

(Figure 1). It also offers several approaches that could be chosen with regard to the anatomy. This allows better coordination, easier to hit the mass, and shortens the procedure. The needle is thus remained inside the body for only one or two breath holds (less than 1 minute), kept still and thus does not cause any additional impairments that cannot be avoided in CT-guided aspiration biopsies.

CT-guided aspiration biopsy is specifically recommended for small adrenal masses.[10] In our series, 13 biopsies were successfully performed on the glands that were smaller than 4 x 2.5 cm - the size that is considered as the limit of the anatomically normal adrenal glands (Figure 2).

In summary, the results of our study confirm that sonographically guided FNABs of the adrenal glands are just as safe and reliable as the CT-guided ones. Nevertheless, US-guided aspiration biopsy has some advantages over the CT-guided one. We believe that CT-guided aspiration biopsy should be performed only if US-guided aspiration biopsy is not safe anymore, e.g. low visibility, non-cooperative patient, or really small size of the lesion.

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Choroid plexus carcinoma: A case report

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Background. *The opinions on the value of adjuvant therapy in choroid plexus carcinomas vary. The aim of present report is to present a case of successful therapy of this rare tumor.*

Result. *A fourteen-year-old girl with third ventricle tumor had non-radical surgery and adjuvant chemotherapy and irradiation. She is alive with no evidence of disease 8.5 years after diagnosis. The role of adjuvant therapy in the context of literature data is discussed.*

Conclusion. *For choroids plexus carcinomas, adjuvant multiagent chemotherapy and craniospinal radiotherapy following surgery should be considered.*

Key words: choroid plexus neoplasms; chemotherapy, adjuvant; radioteraphy; survival analysis

Introduction

Choroid plexus tumor (CPT) is a rare neoplasm, arising from the neuroepithelial lining.[1] After its first description in 1832, more than 500 CPT patients have been described in literature.[2] Three quarters of the patients are children, with tumors most often found in the lateral ventricles. In adults, the fourth ventricle and its recesses are the most common sites of origin.[1] The histopathology of CPT ranges from a well - demarcated benign papilloma (WHO grade I) to highly anaplastic, infiltrative carcinoma (WHO grade III, choroid plexus carcinoma [CPC]). Surgical resection alone is curative for benign tumors, but the optimal adjuvant therapy for the malignant ones has not yet been defined and the prognosis is poor.[1,3] Our experience in successfully treating such a patient is therefore of interest.

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Case report

The patient was previously healty 13.8-year old girl who was admitted to the hospital in January 1996, with a six months complaint of headache and double vision when reading. Two months prior to admission she became progressively lethargic and dull resulting in a deterioration of school performance. Neurologic examination revealed bilateral papilledema, ataxia, positive bilateral Babinski

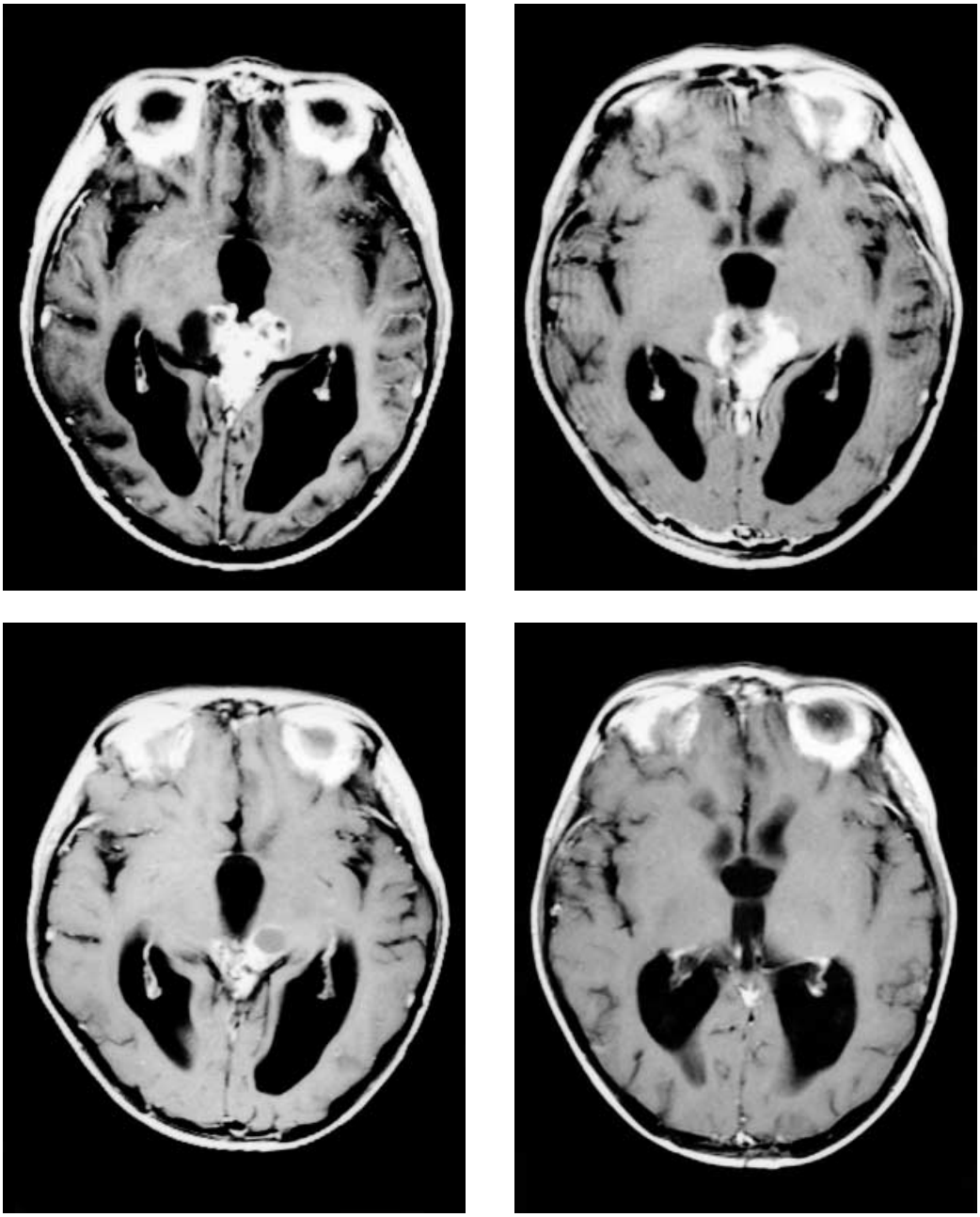

Figure 1. T1-weighted transverse postcontrast MRIs of the patient.
(A) Before surgery: partially cystic tumor mass of the third ventricle with the extension to thalamus, and dilatation of ventricular system.
(B) Two weeks after surgery and before chemotherapy: residual tumor in the third ventricle.
(C) After the second cycle of multiagent chemotherapy: marked regression of residual tumor.
(D) Five months after radiotherapy: even after gadolinium application, there is no pathologic enhancement suspicious for residual tumor mass.

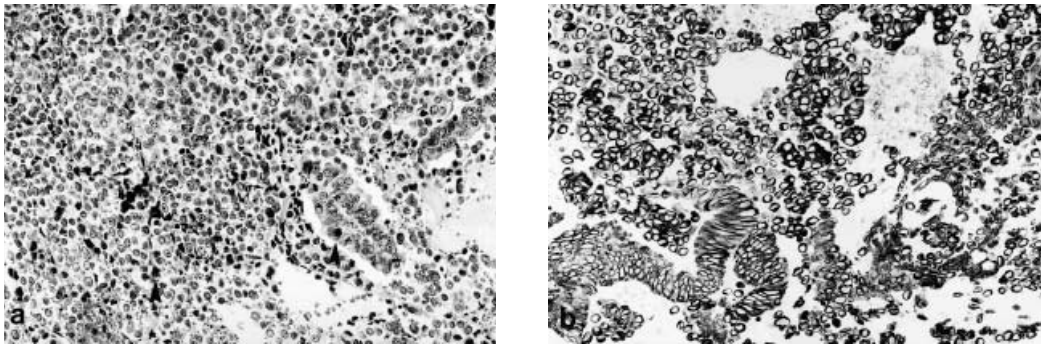

Figure 2. Histologic characteristic of resected tumor.
(A) Solid growth of carcinoma with focal papillary structures. Mitotic figures are present (arrowheads). H&E, magnification 190x.
(B) Strong cytokeratin immunoreaction is evident in all tumor cells. Immunohistochemistry, DAKO's CK 18 monoclonal antibody, magnification 190x.

signs and right-sided hyperreflexia. Two days before surgery, Parinaud syndrome developed. Computed tomography (CT) and magnetic resonance (MR) scans of the brain showed a contrast-enhancing lesion in the pineal region with extension to the thalamus and the lamina quadrigemina and dilatation of the supratentorial ventricles (Figure 1A).

External ventricular drainage was introduced first. No tumor cells were found in the cerebrospinal fluid. Tumor resection was performed one week later and a reddish granular tumor tissue overgrowing the posterior part of the third ventricle was found. It infiltrated locally and extended to the lamina quadrigemina. Histologic examination revealed a highly cellular, focally necrotic tumor composed of polygonal cells with moderately polymorphic nuclei and scattered mitoses. Tumor cells were organized in sheets or formed papillary structures lined with multiple epithelial layers. Due to pineal location, embryonal carcinoma was also taken into consideration. Strong cytokeratin and NSE labelling of tumor cells, in addition to negative AFP and PLAP, confirmed the diagnosis of CPC (Figure 2). Two days after surgery, external ventricular drainage was removed. On postoperative imaging, tumor residue was seen in the postero-inferior part of the third ventricle (Figure 1B).

Postoperatively, multiagent chemotherapy was introduced according to the so-called BEP protocol (bleomycin 15 mg/m^2 I.V., days 1-3; etoposide 100 mg/m^2 I.V., days 1-3; cisplatin 20 mg/m^2 I.V., days 4-8). After the second cycle of chemotherapy, the MRI showed a marked regression of the residual tumor (Figure 1C), and an additional two cycles of these drugs resulted in further tumor reduction. The treatment concluded with craniospinal radiotherapy of 31.5 Gy/21 fx and a local tumor boost of 22 Gy/20 fx b.i.d. The patient was irradiated five days per week, using 5 MV linear accelerator photon beams. The treatment technique consisted of posterior spinal fields with moving junction and a combination of two lateral opposing portals and one posterior portal for the brain. Two-field technique was used for boosting the tumor. Complete disappearance of the tumor was confirmed by a subsequent MR scan (Figure 1D).

To date, 8.5 years after diagnosis, there has been no evidence of local tumor recurrence or metastasis. She has no severe neurologic impairment and her Karnofsky index is 100. She finished high school, got married, and gave birth to her first child. So far, the child is normal as was the endocrine testing of his mother.

Discussion

Experience with this extremely rare malignant tumor is scanty. Surgery is, however, unequivocally considered to be the first-line therapy for all histological variants of CPTs. Surgical techniques and possible complications have been widely described in literature.[1] In CPCs, the most significant predictive factor for survival is the extent of surgery. This has been confirmed in several single-institution analyses[4-6] as well as in literature reviews.[2,3] To obtain complete tumor removal, Ellenbogen et al. and others have advocated as many surgical procedures as required.[4-6]

One of the key debates in CPC therapy relates to the value of adjuvant therapy after gross tumor resection. There are both opponents and proponents of the combined treatment approach.[2-5,7,8] A recent literature review by Wolff *et al.* found adjuvant radiotherapy to be of benefit over surgery alone.[2] Similar conclusions with regard to radiotherapy and/or chemotherapy can be drawn from numerous single-institution reports.[5,9,10]

The need for aggressive adjuvant therapy is widely recognized in the patients with residual CPC following surgery since the expected survival is half of that after gross tumor resection.[2,3,8] Even though there are anecdotal reports on successful adjuvant radiotherapy[7,9] or chemotherapy,[10] it is our impression that aggressive combined radio-chemotherapy offers the best chance for survival. Examples of beneficial effect of combined therapy, sometimes incorporating second-look surgery, can be found in the literature.[8,9,11]

The radiotherapy target volume is dictated by the propensity of CPC for subarachnoid seeding which, when confirmed, calls for adjuvant therapy *per se*, irrespective of the degree of completeness of surgical procedure. Subarachnoid seeding was found in 43% of those reported cases that were investigated for dissemination.[3] Thus, craniospinal axis irradiation to a dose of 30 Gy and a boost to the tumor bed up to 50 Gy is indicated if radiotherapy is used,[12] and seems to be more effective than chemotherapy.[3]

Due to the high risk of severe adverse intellectual and endocrinologic sequelae in very young children, early radiotherapy is an option in older age groups only. Two treatment strategies were described in the literature for young patients, both placing emphasis on multiagent chemotherapy, although this also is not entirely free of long-term side-effects.[13] To facilitate complete tumor resection as a main prognostic determinant in CPCs, St Clair *et al.* used preoperative chemotherapy to reduce tumor vascularity and bulk after initial biopsy or limited surgery. Not specifying the postresection therapy, if any, two out of four children from this program were reported to be free of disease for 30 and 39 months from diagnosis.[6] The second option was described by Duffner *et al.* Using chemotherapy for 24 months in children 0-23 months of age and 12 months in those 24-36 months of age and delayed radiotherapy, the autors reported a 3-year survival of 75%, with five of the eight patients surviving a minimum of 48 months following diagnosis.[10] The variety of chemotherapeutic agents and their combinations used by these two groups as well as in other reports indicates that an optimal chemotherapy regimen is yet to be defined.

In conclusion, our recommendation would be that for CPCs, after as extensive surgery as possible, adjuvant therapy consisting of multiagent chemotherapy and craniospinal radiotherapy, delayed in very young children, should be considered. The BEP regimen detailed above plus radiotherapy gave a good result in the patient described.

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Keratocysts in the jaws

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Background. *Jaw cysts are a common pathology; among them, the odontogenic keratocysts (OKC) represent a special group because of their aggressive growth and recurrence.*

Patients and methods. *We established retrospectively the epidemiology and clinical characteristics of OKC among all the pathohistologically confirmed jaw cysts that had been surgically cured in the past ten years (from 1994 to 2003) at the Clinical Department of Maxillofacial and Oral Surgery, University Medical Centre in Ljubljana.*

Results. *Among 992 surgically removed jaw cysts, 106 were OKC (10.6% of all). Pathohistological diagnosis of OKC was confirmed in 90 patients, in 51 men (56.7%) and 39 women (43.4%). Mean age of patients with OKC at the time of treatment was 36 years. The youngest one was 7 years old, the oldest one 83 years. Seventy-four (69.8%) of OKC were removed from the lower jaws, 32 (30.2%) from the upper jaws. As to the location, OKC (49 cases - 46.2%) predominated in the angles and vertical branches of the lower jaw. Recurrence rate after the first removal of OKC was 22.2% (in 20 patients). First recurrence occurs most frequently (in 70%) within the first 5 years after primary treatment; the mean time till the first recurrence was 4 years and 7 months. Multiple recurrences of OKC were observed in 9 patients (10% of all patients with OKC). Five of the patients with OKC had the syndrome of basal cell carcinoma (Gorlin–Goltz Sy.). We found out that one third of OKC were clinically unexpected in regard to their untypical locations in the jaws.*

Conclusions. *It is critical for the jaw cysts to be pathohistologically examined. The number of cases of OKC among all jaw cysts in our study is significantly larger (3.5-time) than in the previous epidemiological study in Slovenia; but this may be the consequence of previous underdiagnosis of that pathology entity. Our study is comparative with other similar foreign studies in literature in respect to the patient's sample and epidemiological results.*

Key words: jaw cysts – pathology; odontogenic cysts - epidemiology

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Introduction

Cysts in the facial bones are similar to other cystic changes elsewhere in the human skeleton regarding their morphology and structure. Because of the presence of the developmental dental and nondental epithelium and

the teeth with surrounding tissues in the jawbone, the cysts are much more common in the jaws than anywhere else. They occur as pathological unicentric or multicentric cavity, where the liquid, solid masses or gas accumulate, but not as the consequence of pus accumulation.[1] The cysts are usually, but not always, surrounded with the epithelium, which differs in morphogenesis and structure.[2] The most common characteristic of cysts is the bone defect – the radiolucent area on X-rays, which can cause different clinical signs predominantly because of their sizes or secondary infections. Other causes of bone defects are odontogenic and bone tumours, but they are much more rare in a jawbone than in other parts of human skeleton.[3] Among them are also very rare bone defects caused by tumour metastases, mostly of adenocarcinomas (tumours in the breasts, bronchus, kidneys).[4] They are so important because they can be the first clinical sign.

Jaw cysts are nonodontogenic and odontogenic; the latter are more common. Two thirds of odontogenic cysts are of inflammatory origin (radicular, residual cysts); follicular cysts (in approximately 15% of all cysts), keratocysts or a few others are rarer.[3]

Odontogenic keratocysts (OKC) were recognized as a special pathologic entity very late. Among the cysts, they are considered as a peculiar group because of their aggressive growth and great recurrence; they therefore require more radical surgical treatment (the removal with surrounding bone) and prolonged clinical follow-up. Pathohistologically, they are divided into para- and ortho-keratinous types of OKC. Regarding their pathogenesis, they are benign neoplasms.[5] Figures 1a and 1b show 2 typical panoramic X-rays of OKC.

In 1945, Robinson described primordial cysts as the consequence of impaired dental enamel organ. Later, their appearance was associated with the developmental disturbance of dental lamina. These cystic bone lesions were first named OKC by Philipsen in 1956, which became also their official term in the WHO classification of cysts in 1971.[1,2]

Among the jaw cysts, the frequency of OKC in different studies ranges from 3.2 to 11.25%.[2,6] The factors which influence the growth and development of OKC are still unknown; they can be either in the epithelium of a cyst or in the connective tissue of its capsula.[6] As OKC are detected in the patients

Table 1. The incidence of the pathohistologicaly proved cysts from 1994 to 2003

Cyst / Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Σ	%
Radicular	17	14	11	18	33	57	86	82	98	114	**530**	**53.5**
Dentigerous	9	5	2	2	9	17	16	5	8	16	**89**	**9.0**
Residual	2	2	2	1	6	13	19	13	8	15	**81**	**8.2**
Eruption	1	0	0	0	0	0	0	0	1	0	**2**	**0.2**
Odontogenic keratocysts	7	1	5	9	7	6	9	16	21	25	**106**	**10.6**
Gingival cyst of adults	0	0	0	0	2	0	0	0	1	0	**3**	**0.3**
Lateral periodontal	0	1	0	0	1	0	0	0	1	0	**3**	**0.3**
Calcifying odontogenic	0	0	0	0	0	0	0	0	0	1	**1**	**0.1**
Solitary bone	1	0	1	0	2	1	2	1	1	1	**10**	**1.0**
Pseudocyst	0	1	0	0	0	0	1	0	0	0	**2**	**0.2**
Nasolabial	0	0	0	0	0	0	0	1	0	0	**1**	**0,1**
Nasopalatine	0	0	0	2	2	1	1	0	3	1	**10**	**1.0**
Unknown	16	18	27	21	15	19	11	9	11	7	**154**	**15.5**
Σ	**53**	**42**	**48**	**53**	**76**	**114**	**145**	**127**	**153**	**180**	**992**	**100.0**

aged between 7 and 93 years, they can arise in any life period.[7] The size of OKC is from 0.1 to 10.0 centimetres in diameter, the mean size at the time of their detection is 4 to 5 cm.[8] They grow for 2 to 14 millimetres per year; their growth is slower after the age of 50.[9] In literature, a great possibility of recurrence after the removal of the primary OKC in the same place or in their neighbourhood was described (3 to 62%, mean possibility is 30%).[6]

In 1960, Gorlin and Goltz first described the syndrome of three mean signs: multiple cells-cells carcinomas of the skin, multiple jaw OKC and rib changes. OKC are a permanent and clinically important sign. Later, this syndrome was named nevoid basal-cells carcinoma syndrome. It is inherited dominantly autosomally and has a high level of genetic penetrance with prevalence of 1 : 60 000.[6,10]

In the differential diagnosis of OKC before pathohistologic examination, we must also consider tumour ameloblastoma, whose similarity arises from the same origin – the dental lamina; the ameloblastoma can also arise from OKC epithelium.[7] In addition, the transformation in orthokeratinous epithelium of OKC to planocellular carcinoma has also been described.[8]

The purpose of our study was to establish the frequency and characteristics of OKCs, which had been surgically cured in the past ten years (from 1994 to 2003) in Clinical Department of Maxillofacial and Oral Surgery, University Medical Centre in Ljubljana.

Patients and methods

We removed and pathohistologically examined 992 cysts in the lower and upper jaws from 930 patients from the beginning of 1994 to the end of 2003. On the basis of pathohistologic examinations, we retrospectively surveyed all medical documentation of these patients (all diagnostic procedures, treatment and post-operative controls).

We determined the basic statistical characteristics. Table 1 presents the frequency of different cysts in the observed years.

Results

In the period from 1994 to 2003, we surgically removed 992 pathohistologically proved cysts at our department. Of them, 105 were OKC, which represented 10.6% of the cysts of oromaxillofacial region (Figures 1a, 1b).

In the observed period, pathohistological diagnoses of OKC were confirmed in 90 patients. Of them, 51 were in men with the mean age of 39 years and 39 in women with the mean age of 33 years. The mean age of all patients with OKC at the time of treatment was 36 years. The youngest one was 7 years old, the oldest one 83 years. Figure 2 represents the distribution of the observed patients by sex and age.

Seventy four OKC were removed from the lower jaws (69.8% of all OKC) and 32 from the upper jaws (30.2% of all OKC). Regarding

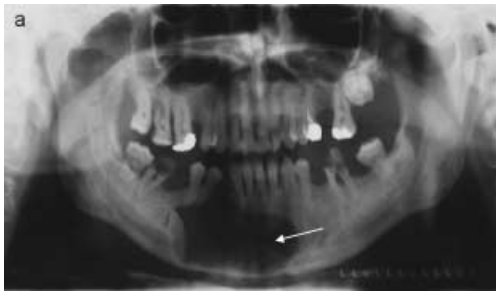

Figure 1a. PanoramicX-rays of OKC in lower jaw at 37 years-old man.

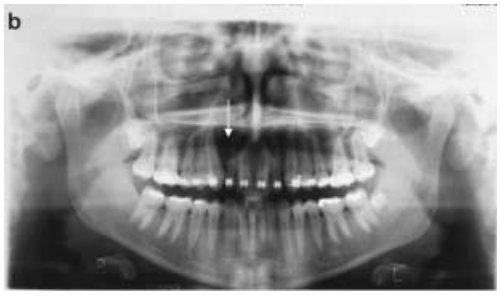

Figure 1b. PanoramicX-rays of OKC in upper jaw at 19 years-old woman.

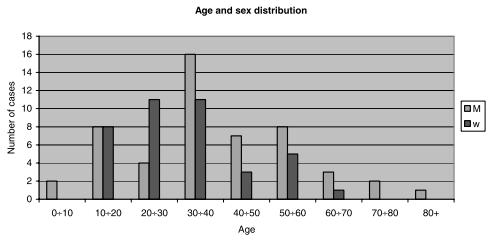

Figure 2. Patients with OKC by the sex and age intervals.

the location, they predominated in the angles and vertical branches of the lower jaw (in 49 cases, 46.2% of all OKC). The characteristic cases of that predilection location are shown in Figures 3a, 3b and 3c.

Recurrence rate after the first removal of OKC was 22.2% (20 of 90 patients). The first recurrence is the most frequent (in 70%) within the first 5 years after the primary treatment, the mean time until the first recurrence being 4 years and 7 months. The longest time between the first treatment of OKC and diagnosis of its first recurrence was 15 years. Multiple recurrences of OKC occurred in 9 patients (10% of all patients with OKC).

Among the patients with OKC, 5 had the syndrome of basal cell carcinoma (NBCCS, Gorlin–Goltz syndrome). Two of them had multiple basal-cells carcinomas. One patient, 10 years old at the time of diagnosis NBCCS, was hereditarily predisposed, as his mother had the same illness.

We established that, in 31 patients, OKC was clinically unexpected before pathohistologic examination; the pathohistologic examination then confirmed it was OKC.

Discussion

All the patients examined here were treated at the Clinical Department of Maxillofacial and Oral Surgery, University Medical Centre Ljubljana. At this institution, orodental pathologies of the patients from Ljubljana region are treated and it is also the Slovenian

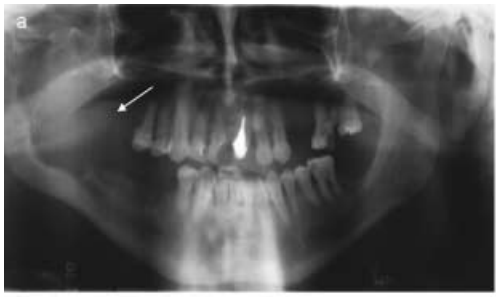

Figure 3a. The characteristic tomogram radiograph (panoramic x-ray) of OKC on predilection location (the angles and vertical branches of the lower jaws) in the right side.

referral clinic that treats the most complicated cases of orodental pathologies of the patients from the whole country. All patients treated at our clinic were included into this study, viz. also the patients with extremely large OKC or those with OKC in the neighbourhood of vitally important structures. The consequence of this is that the percentage of OKC among the jaw cysts reported here is greater than that in Slovenia's population.

The smallest OKC in our study are from 0.5 to 1 centimetre in diameter and they predominate in the upper jaws. In clinical and radiological aspects, this means that these OKC are commonly removed as inflammatory odontogenic pathology without being pathohistologically examined. In these cases, OKC are often overlooked. This also means that these overlooked OKC are not treated and controlled adequately.

At our Department, we were already studying the jaw cysts for a ten-year period from 1984 to 1993. Our research was based on pathohistological diagnostics.[11] The present study from 1994 to 2003 is the continuation of that one. We observed 3.5-times more OKC in the last decade than in the former one. During the first study, the OKC pathologies were rarely recognised; they were recognised in fewer cases than expected from the literature data. Interestingly, OKC were first pathohistologically recognised only in 1982.

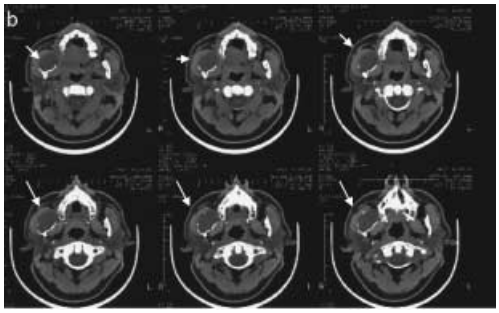

Figure 3b. The characteristic computer tomography image (axial CT) of OKC on predilection location (the angles and vertical branches of the lower jaws). CT images show perforation of OKC in the right mandibula ramus.

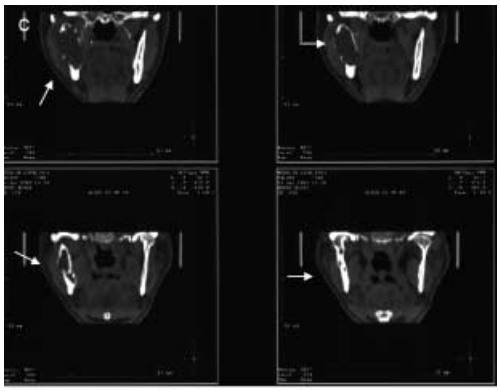

Figure 3c. The characteristic computer tomography image (coronal CT) of OKC on predilection location (the angles and vertical branches of the lower jaws). CT images show perforation of OKC in the right mandibula ramus.

Among the jaw cysts, the frequency of OKC was 10.6% in the period 1994 -2003. This percentage agrees well with the literature data of 3.2 to 21.8%;[2,6,8] in fact, it is approximately in the middle.

The ratio of men to women with OKC is 1.28 to 1; the predominance of men with OKC is mentioned also by other authors.[7,12,13] The age structure of the patients with OKC in our study is similar to other's data. In 1992, Shear reported that OKC in elderly population was often discovered late because of a few and delayed clinical signs.[2] In our study, 34.4% of patients came in our institution without any clinical signs; later, the cavities in the jaws were accidentally found on the radiographs done by their dentists.

The ratio of OKC in the lower against the upper jaw is 2.3 to 1. The higher occurrence of OKC in the lower jaws is reported throughout the literature. The ratios of OKC location in the lower to the upper jaws are from 1.9 : 1 to 4.9 : 1 according to different authors and our findings are within the described range.[7,14]

The recurrence rates of OKC after the first surgical removal differ from one author to another and are within the range of 10.4%[15] to 39%.[13] During the observed period, the recurrences of OKC were observed in 20 of our patients (22.2% of all OKC patients). The multiple recurrences were observed in 9 patients (in 10% of cases). According to the data from literature, multiple recurrences are ranging from 2.8%[7] to 4.6%.[14] The mean time until the first recurrence of OKC in our study is 4 years and 7 months, while Brannon reported that this time was 4 years and 10 months.[7]

The presence of OKC in children or adolescents before the age of 19 is, in 75% of cases, the first sign of NBCCS.[6] Four patients in our study with NBCCS had OKC before the age of 19.

According to literature, the first recurrence is the most frequent within the first 5 years after primary treatment in 75% of cases, whereas according to our data, it occurs in 70% of cases.[3,5] Some authors described the recurrence even 20 years after primary treatment.[2] In our study, the longest time until the first recurrence was 15 years. So, while the regular clinical and radiograph controls of patients with OKC in the first 5 years after the primary surgery are necessary, the patients with NBCCS have to be checked once a year throughout their lifetime.

The treatment of OKC is more radical than of the other jaw cysts. Because of the aggressive nature of OKC, it is necessary to remove the wall of the cyst and all bone adjacent to

the wall colonised by the cysts epithelium islands and buds. When the bone is totally destructed by the cyst, this can spread to the soft tissue, which must be removed entirely. In order to diminish the cases of unrecognised OKC, the pathohistologic examinations of all cyst tissue is always necessary, as in our study, there were 37 surprise cases of OKC (34.8% of all OKC) discovered through the diagnostic procedures, radiographs and clinical diagnosis of other odontogenic cysts.

Maxillofacial and oral surgeons in Slovenia have approximately 10% possibility that the jaw cyst is OKC. These cysts must be recognised by the pathohistologic examinations to be adequately treated and to assure to the patients to receive adequate clinical follow-up.

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review

Psychological distress and intervention in cancer patients treated with radiotherapy

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Background. *Common side effects of treatment with radiation therapy (RT) often cause psychophysical distress in cancer patients. Anxiety, adjustment disorders and depression (which are according to many studies experienced in about half of the oncological population) might originate some serious psychiatric forms of mood disorders and can even culminate in suicide, if not treated appropriately. There are some groups of cancer patients who are especially vulnerable and among them are cancer patients undergoing RT –they should receive special attention from medical staff. The purpose of this review is to present a variety of psychosocial interventions and illustrate some methods that are (or could be) used in psycho-oncology practice.*
Conclusions. *A large body of literature suggests that the first intervention step should be effective screening for patients in distress. In regard to these proposals the development of (computerized) screening programmes is the first measure that ought to be taken. Moreover, further systematical research of traditional, non-traditional and complementary intervention strategies in cancer patients in distress would be necessary in order to provide reliable empirical results about the effectiveness of different approaches.*

Key words: neoplasms –radiotherapy –psychology; mood disorders; adjustment disorders; distress, intervention, screening.

Introduction

The psychosocial oncology research studies indicated that significant proportion of cancer patients at all stages of the disease have been confronted with psychosocial distress.[1,2] The prevalence of some psychiatric illnesses (major depression, generalized anxiety, adjustment disorder) is higher in some groups of cancer patients (patients undergoing radiotherapy (RT) or palliative treatment, terminally ill patients and patients experiencing uncontrollable pain), which also implies an increased risk for suicidal behaviour.[3,4]

Some studies estimated that approximately 20% of cancer patients need a psychiatrist for treating major depression or anxiety during their cancer experience. Additional 15% of cancer patients need the services of a psychologist for treating distress and 25% of patients require the services of social workers to deal with financial and practical issues.[5,6]

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Since some reports emphasized that psychosocial interventions in cancer patients are not only effective but also economical, more attention should be focused on establishing routine psychosocial screening programs in order to asses psychological functioning, primarily anxiety and depression and overall Quality of Life (QoL).[7-9] Cancer patients should be targeted around the time of initial diagnosis and treatment. They should be screened for distress and common problems during the treatment trajectory. The purpose is the identification of those cancer patients who experience significant distress at early stages of therapy in order to treat them proactively and avoid future psychosocial problems.[10-14]

RT was one of the earliest cancer treatments and it still plays an important role in the care of cancer patients. It has been used in curative as well as in palliative cancer treatment in order to achieve a local control over the tumour with minimum side effects. Despite astonishing progress of modern RT technique (safe doses of radiation which are skin sparing in comparison to old techniques), the treatment causes some common physical side effects, for example: fatigue, nausea, diarrhoea, gastrointestinal symptoms and skin irritation. Some of them can persist even after the treatment. Studies revealed that cancer patients may also face some psychological problems during the treatment with RT.[11,15] A wide range of different aspects of psychological functioning and well-being can be impaired in cancer patients prior to, during, and after RT.[16,17] Therefore a better insight into the psychosocial functioning of patients undergoing RT could facilitate the identification of those who are at higher risk of developing mood disturbances. These patients should receive a full psychosocial support to manage the coping process with cancer and adopt appropriate coping strategies.[18,19]

There are many methods and techniques of psychosocial interventions that are commonly used in psycho-oncological practices. Most of them are useful in treating cancer patients undergoing RT as well.[20,21] A variety of psychosocial approaches (education in group, education on pain management, meditation training, biofeedback, relaxation training, visualization, creative therapies such as music, art or role play, peer supportive group therapy, family counselling, etc.) have been studied and approved to significantly contribute to patient's QoL. Nevertheless, many of them are ineffective if medical staff is not acquainted with the dynamic of psychological functioning of cancer patients undergoing RT and well trained for recognizing the patient's crisis. In the following review some aspects of psychosocial functioning and distress in cancer patients treated with RT will be discussed. In addition some psychosocial interventions will be described.

Distress induced by experience with cancer

Several studies clearly demonstrate that psychosocial distress occurs in one-third to one-half of all cancer patients.[3,10,11] There are some groups of cancer patients that are especially vulnerable to psychosocial distress. Particularly patients with history of chronic depression, patients with breast and genitalia cancer, patients using specific coping strategy (hopelessness/helplessness), patients without social support, children and elderly patients should be recognized at earlier stages of cancer diagnosis and treatment.[3,5,22] Although severity of emotional distress is more closely related to a patient's pre-existing vulnerability than to the characteristics of the cancer, it is more likely to occur at the following stages of patient's experience with cancer:[23-25]

Diagnosis

Investigation and diagnosis can induce anger, shock, disbelief and emotional distress in

cancer patients. Whereas these can be resolved without interventions in the most cases, especially high levels of distress at this time are predictive for onset of later emotional problems.

During treatment
Side-effects of hospital attendance, unpleasant surgery, RT and/or chemotherapy are prevailing reasons for the distress. Patients might become particularly distressed during apparent treatment failure.

End of treatment
Some patients can experience "rebound" distress associated with the fear that cancer could spread or occur again. The sense of loss and vulnerability may also appear at this point as outcome of ending the prolonged relationship with the cancer service staff.

After treatment
Many patients who survive cancer may reorder their life priorities. On the other hand others need help to overcome worries, preoccupation with loss and illness, a tendency to avoid reminders of cancer, difficulties coping with intimacy and return to work. A form of health anxiety with misinterpretation of physiological sensations and anxious seeking of reassurance may develop as a form of fears of cancer recurrence.

Recurrence
Patients who believe that they have been cured are at greater risk of severe distress if recurrence occurs. For some of them recurrence of cancer may be more distressing than receiving the initial diagnosis.

Terminal disease
Depression is common in the terminal phase, particularly in cancer patients with poorly controlled physical symptoms. Majority of cancer patients experience fear of uncontrolled pain and the process of dying. They worry what happens after death and are concerned about loved ones.

Negative or positive psychological states
Studies engaged with adjustment to cancer focused primarily on negative psychological states like depression, anxiety and general distress.[26-28] Many of them concluded that cancer could be understood as an event and an ongoing process that may physically and emotionally weaken the individual. On the other hand, the number of studies on positive consequences of the cancer experience is growing. These studies suggested that experience with cancer may result also in some positive outcomes, for example: increased self–esteem and more optimistic look, improved interpersonal relationships, re-evaluation of prior goals, altered priorities in life and new pursuits.[29-33]

Radiotherapy and psychosocial functioning in cancer patients

The results of studies comparing RT to other cancer treatments revealed few differences in psychological functioning among different treatment modalities.[11,34] The patients undergoing RT experienced a common distress –similar to patients without RT. Some studies indicated a great variability in reported results, but the global trends in psychological responses to RT prevailed. The most common reactions reported by patients before starting a course of RT, were feelings of anxiety rather than depressive symptoms. During the course of treatment, most studies indicated a decline in feelings of anxiety. An increase of depressive symptoms and negative mood was found during and after RT. It was also emphasized that the field lacks a systematic overview of the empirical data regarding psychological functioning prior to, during and after RT. [11,16,35]

Although RT is not painful it induces

many side effects, which can continue long after completion of treatment. Nevertheless, the non-invasive nature of RT can make it easier for patients to adapt, which could explain why in spite of anxiety, patients often experience RT much more positive than initially expected.[11,36] Some studies aimed to enlighten the psychosocial functioning in cancer patients undergoing RT since some unpleasant side-effects could interfere with their quality of life, namely: fatigue, skin irritation, nausea, diarrhoea, genitourinary and gastrointestinal symptoms, long-term cognitive disability in patients undergoing RT of brain, eating problems and oral complications in patients undergoing RT of head and neck, etc.[37-44]

Some recent studies reviewed the impact of RT on neuropsychological functioning in cancer patients.[38,45-48] Neuropsychological side-effects of different cancer treatments may include difficulty concentrating, impaired verbal and visual memory, difficulty organizing information, decreased motor skills, and language problems. It remains unclear to which extent intellectual and cognitive impairment in cancer patients could be linked with RT, since some patients could have already been experiencing some cognitive decline due to the effects of stress, fatigue or the sometimes toxic by-products of the cancer process itself.

It has been emphasized, that the assessment of RT side-effects either by the doctor or the patient remains subjective and often leads to different results.[49] This implied a need for establishing reliable screening system with objective parameters in assessment of psychophysical and social distress of radiooncological patients.[50-54] To provide effective psychosocial support for cancer patients undergoing RT, the screening for psychosocial status of patients should be performed during diagnostic and therapeutic procedures. A distress inventory composed of interviews; checklists and questionnaires should be applied before, during and after the course of RT.

First intervention step: screening for cancer patients in distress

Depressive and anxiety disorders often remain unrecognised. In this regard an active screening by simply asking patients about symptoms of anxiety and depression may be helpful. How can an oncologist screen for patients in distress? One research group reported that single-item screening was sensitive and specific for depression – an oncologist must simply ask a question: *"Are you depressed most of the time?"*[3] Usually the questionnaire for assessing patients' anxiety and depression includes questions like: *"How are you feeling in yourself?"; "Have you felt low or worried?"; "Have you ever been troubled by feeling anxious, nervous, or depressed?"; "What are your main concerns or worries at the moment?"; "What have you been doing to cope with these?"; "What effects do you feel cancer and its treatment will have on your life?"; "Is there anything that would help you cope with this?"; "Who do you feel is helping you at the moment?"* Doctors should also be aware that patients might be distressed because of factors unrelated to cancer.[23,55,56]

Additional check-up for some risk factors that underlie psychiatric disorders is also required in cancer patients. Risk factors associated with patient (history of psychiatric disorder, social isolation, dissatisfaction with medical care, poor coping), cancer (limitation of activities, disfiguring, poor prognosis) and treatment (disfiguring, side-effects) should be taken into consideration.[8,57]

It is common to use diagnostic tools or (computerized) screening programs to provide a better insight into patient's crisis. Several agencies developed screening guidelines or books of standards in order to provide distress screening for each patient. Most widely used tools are: Brief Symptom Inven-

tory (BSI), Hospital Anxiety and Depression Scale (HADS), General Health Questionnaire, QoL Questionnaires and distress thermometer.[9] A large amount of studies on psychometrical characteristics of these screening tools is available on-line.

Review of literature showed that more than 45 tools/instruments have been used to measure psychological distress.[58] Unfortunately none of them is able to identify patients who are highly distressed without clinical symptoms of anxiety and depression. Therefore, the development of a reliable screening mechanism seems appropriate and may help in identifying patients who specifically warrant the intervention. Distress-screening tool may also assist health professionals to provide patient-specific-intervention processes if the distress level and cause could be identified.

Several groups of scientists are dealing with development of screening mechanism for distress induced by RT. A group of German scientists (Klinikum Grosshadern, Munchen) developed questionnaire SIRO (The Stress Index RadioOncology).[50] A group in Canada has been developing a computerized QoL program for clinical use in palliative RT.[5,59] In recent studies two instruments were tested for benefits in screening process: a short and structured interview procedure PRIME-MD (Primary Care Evaluation of Mental Disorders) and BCD (Brief Case-Find for Depression).[10,60] Both instruments were found to quickly and reliably identify the prevalence and types of mood disorders (depressive disorders: major depression, minor - subsyndromal depression/adjustment disorder, dysthymia, bipolar disorder; anxiety disorders: panic disorder, generalized anxiety disorder). When compared to the PRIME-MD diagnosis of depression the BCD had greater sensitivity. No specific training is needed to administer PRIME-MD and BCD; their application is quick and therefore convenient for screening by oncologist.

Second intervention step: post-screening intervention strategies

Interventions usually assume the following common strategies: psycho-education, cognitive-behavioural training (group or individual), supportive therapy (group or individual).[5] They target different points on the illness trajectory: diagnosis/pre-treatment, immediately post-treatment or during extended treatment (such as RT or chemotherapy) and disseminated disease or death. Certain modalities of intervention strategies have been proven to be more efficacious at one or more of these time periods. For example, psycho-education may be most effective during the diagnosis/pre-treatment period, when patient searches for information. Group support may be more effective at later stages to cope with more advanced disease.[61,62] Cognitive-behavioural techniques such as relaxation, stress management and cognitive coping could be most useful during extended treatments.[63,64] Relaxation and imagery have been shown to be effective in controlling nausea and vomiting associated with chemotherapy treatment,[65] and furthermore, these techniques can also help patient to decrease the usage of pain medications.[66]

Many studies have focused on the efficacy of group interventions. It seems that group therapies have repeatedly been shown to be as effective as individual treatment.[63,67] Because of the reduced cost of group therapies (the greater number of patients who can be treated at the same time) many researchers identify group therapy as the preferred route for treating distress in cancer patients. Several specific group therapy interventions have been standardized and proven efficacious, for example: supportive expressive therapy for metastatic early stage breast cancer,[68,69] mindfulness-meditation based stress reduction[70,71] and standardized group psycho-education for patients with different types of cancer diagnoses.[72]

On the other hand recent surveys confirm the popularity of non-traditional therapies among cancer patients. 23% – 81 % of U.S. and Canadian, 22% – 52% of Australian, 16% – 32% of British and 10% – 61% of mainland European cancer patients used at least one such therapy.[20,73,74] Psychological therapies (e.g., relaxation, meditation, visual imagery, and hypnotherapy) are among most popular non-traditional therapies. More than 50% of Australian and up to 29% of U.S. and 10% of European and Canadian cancer patients have reported the use of at least one type of psychological therapy.[75,76] Patients have high expectations of these therapies: in one study, up to 25% of participants expected the psychological therapy to cure their cancer and 75% – 100% expected it to assist their traditional therapies.[76]

Moreover, alternative/complementary therapies are increasingly used to reduce side effects of cancer treatment, without convincing evidence of their effectiveness.[77] Some studies are in favor of using complementary therapy in order to reduce the stress and anxiety in cancer patient.[78,79] A study of patient's perceptions of the benefits of reflexology on their QoL revealed that reflexology interventions were perceived to impact positively on psychophysical functioning.[80,81]

Further indications for effective acupuncture treatment of patients with radiation-induced xerostomia came from study with patients undergoing RT for head and neck cancer.[82,83] Some national institutes of health support the use of acupuncture for chemotherapy-induced nausea and vomiting.[84] The nurse practitioners are obligated to be knowledgeable about the use of these and other effective complementary treatments in order to provide the best care. Used in conjunction with current antiemetic drugs, acupuncture and acupressure have been shown to be safe and effective for relief of the nausea and vomiting resulting from chemotherapy.

Application of psychological interventions has been found in many studies to improve the QoL in cancer patients. These is hypothesized to be mainly due to reducing their psychological symptoms and distress, enhancing psychological and functional adjustment and rehabilitation as well.[85] However, the relevance of psychosocial interventions on survival from cancer has been widely criticized. In the recent review all identifiable publications about psychological therapies used by cancer patients have been critically and systematically analysed.[20] Despite of extensive body of literature authors could not make strong recommendations about the effectiveness of psychological intervention strategies at improving cancer patient's outcomes. The results of this review were considerably less enthusiastic about the likely benefits of psychological therapies for cancer patients compared to the results of other recent reviews. While many studies recommended widespread and routine use of psychological therapies to improve patient's psychosocial, side effect, survival and immune outcomes, this study emphasized that the most beneficial are group therapy, education, structured and unstructured counselling and cognitive behavioural therapy. Furthermore, some long-term cost studies have proven that psychosocial intervention programs have also beneficial economical value.[5,86]

Cancer patients undergoing RT can engage in all above described intervention programs. Some findings about psychosocial side effects of RT, discussed in previous section have also got practical implications for medical staff in oncology practice.[87] Namely, it is very important that patient is well informed what to expect during the treatment period. The aim of the RT should be explained and misperceptions eliminated (role models that underwent the RT could be used for education of patients). This is not important only because of the cooperation between the patient and medical staff, but also because talking often reduces the anxiety that ascends from specific, unknown and uncontrollable situation. In addition, after completed treat-

ment with RT patients show high need for information – particularly about the psychophysical changes they could experience after completing RT. They are also interested how they could best ask their physicians questions, which agencies they could call when they need help and how they could cope with painful emotions. Therefore providing an information booklet in form of a self-management package seems to be an effective intervention.[88]

Conclusions

Although recent studies comparing different cancer treatments suggested that the psychological impact of RT is not superimposed to other treatments, some measures have to be taken to avoid further psychiatric complications (anxiety, depression, adjustment disorders and suicide) in cancer patients undergoing RT. [3,10,11,34] The first step is to effectively screen for patients in distress throughout the treatment process (patients should be screened at the initial visit and at appropriate intervals).[10-14] A multidisciplinary approach that includes psychological as well as medical assessment and intervention should be carried out. Otherwise psychological care might be neglected by the medical focus on cancer treatment. Consequently screening programmes for those patients who are likely to show psychological dysfunction and helping them to cope with treatment and cancer related problems should be the constituent part of cancer managment.[5,36,86]

The knowledge of the coping process with cancer and some fundamental strategies in screening for distress is substantial for medical staff working with patients undergoing RT.[86] What is expected before starting a course of RT? The majority of patients will experience anxiety (which will probably decline during the treatment).[11,16,35] They will be distressed mostly by fears of possible side-effects and by the fact of being irradiated. An effective intervention strategy at this stage is psycho-education (providing information about RT and its side effects). The visualization and the relaxation training are also useful for reducing the anxiety. In contrast to the anxiety an increase of depressive symptoms is expected during and after RT. At this point the group-supportive therapy might be appropriate.[61-69] To conclude: different psychological interventions evoke different effects according to the specific stages of the cancer treatment.

In general, five types of therapies were established due to increasingly active participation by the recipient: providing information, emotional support, behavioral training in coping skills, psychotherapy and spiritual/existential therapy.[72] The widespread usage of nontraditional psychological and complementary therapies[20,73-84] is a big challenge to the traditional medical and psychological approaches to cancer experience. The field lacks a systematic overview of different approaches and their contributions to the QoL as well as to the cancer prognosis.

Patients are most often willing to participate in the therapeutic process of cancer, yet the psychological aspect of medication might be underestimated by the patient. Therefore oncologist should also notice if a patient needs some further psychological or psychiatric consultations. Quick and reliable screening tools could be useful for this purpose. Although there are some available instruments for such purposes (BSI, HADS, PRIME-MD, etc.),[9,10,58] many findings suggest that the screening process for cancer patients experiencing distress while undergoing RT requires additional empirical analysis.

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review

Use of preneoplastic lesions in colon and liver in experimental oncology

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The present article gives a brief overview on the use of altered hepatic foci (AHF) and aberrant crypt foci (ACF) in the colon in experimental cancer research. These foci are easily detectable preneoplastic lesions, which have been discovered approximately 30 years ago. AHF and ACF are valuable tools for the detection of cancer - initiating and promoting compounds, and for the detection of chemoprotective agents. They were also successfully used in numerous studies aimed at elucidating the molecular mechanisms of early neoplasia, such as alterations of the expressions of oncogene and tumor suppressor genes, and changes in the activities of cancer associated enzymes.

Key words: preneoplastic lesions; liver neoplasms; colonic neoplasms

Introduction

Preneoplastic lesions are used in experimental research since more than thirty years. They consist of morphologically or functionally altered populations of cells that are precursors of neoplasms. In contrast to long term experiments in which tumor formation is used as an endpoint, they have the advantage that they can be detected after comparatively short time periods (after 2-5 months) and that the number of animals, which are required are relatively small (usually 8-10 animals are used per experimental group). Preneoplastic lesions have been identified in a number of organs, for example in the skin (epidermal dysplasia and hyperplasia, epithelial papillomas), lung (alveolar and focal hyperplasia, nodular lesions), pancreas (atypical acinar foci), kidney (tubules with irregular epithelium), mammary gland (hyperplastic alveolar nodules) and also in liver and colon (for overview see[2]). The present article is focused on hepatic altered foci (AHF) and aberrant crypt foci (ACF) in the colon, which have been used extensively in the last years for the detection of carcinogens, for the identification of chemoprotective agents and also in mechanistic studies. It describes their mor-

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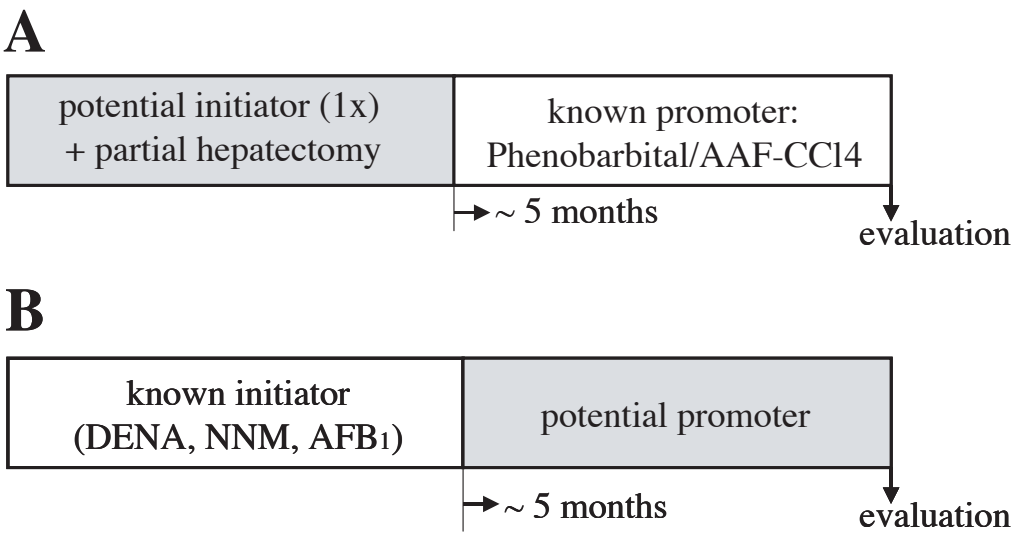

Figure 2A,B. Different treatment schedules for the detection of initiating and promoting carcinogens for experiments in which AHF are used as biological endpoint.

phology and molecular characteristics and their use in the identification of initiating, promoting and protective agents and the development of new techniques.

Altered hepatic foci – morphology and phenotypes

The use of altered hepatic foci started in the 1970's. In the early years, a classification system was developed, which was based on the staining behaviour and included clear, acidophilic, intermediate, tigroid, basophilic and also mixed cells of AHF.[2] In subsequent years, it was shown that the expression of a variety of enzymes of AHF differs from that of the normal tissue, and based on this observations, histochemical methods were developed which enable the detection of enzymatically altered AHF (for review see [1]). An overview on the different markers is given in the article of Pitot.[3] At present, the most widely used endpoint is the expression of the placental form of glutathione-S-transferase ($GSTp^+$), which can be detected by immunohistochemistry. About 80% of all foci stained positive for $GSTp^+$.[3] Another frequently used marker is γ-glutamyltranspeptidase. Figure 1 depicts a GSTp+ foci.

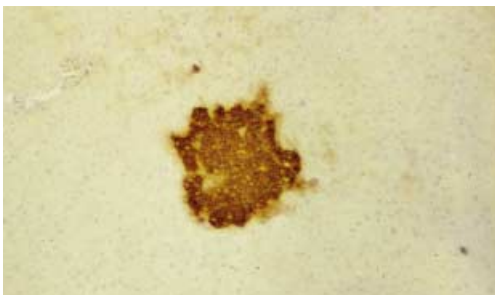

Figure 1. A GSTp+ focus.

Methodological aspects

AHF can be used to detect tumor initiating (Figure 2A) and promoting properties (Figure 2B) of chemicals. To distinguish between these characteristics, the test animals are treated with the compounds according to different schedules.[4]

Initiators and promoters of AHF

Numerous synthetic and natural compounds have been identified, which either initiate or promote the formation of AHF.[4] Typical examples for initiators are nitrosamines (which are the most frequently used carcinogens in mechanistic studies), urethane, aflatoxin B1, heterocyclic aromatic amines, and haloethans.[5] Also polycyclic aromatic hydrocarbons such as benzo(a)pyrene cause formation of AHF in rats, although the liver is not a target organ for tumor induction of this compound.

Typical examples for compounds which promote the growth of AHF in the liver are barbiturates (phenobarbital etc.), steroid hormones such as dexomethazone and testosterone, hypolipidemic drugs and polychlorinated biphenyls (for review see[4]).

Inhibition of foci formation

Numerous investigations have been conducted to identify compounds, which prevent the formation of liver foci. These agents were either protective at the initiation level (*i.e.* when administered before and/or simultaneously with the carcinogen) or at the promotion level (after carcinogen treatment). Examples for anti-initiators are food additives such as butylated hydroxyanisole, which protects against AFB_1[6] and butylated hydroxytoluene, which inhibited the foci formation caused by 2-acetyl-aminofluorene.[7] Also glucosinolates, contained in cruciferous vegetables were found protective towards AFB_1 and cruciferous plants themselves inhibited foci formation induced by the heterocyclic aromatic amine (HAA) IQ.[8-13]

A number of compounds were identified which prevent the development of foci when administered after the carcinogen treatment. For example acetaminophen and aminophenol were protective against formation of foci that had been induced by a nitrosamine in the liver[4] and flavonone reduced significantly areas of placental $GSTp^+$ foci induced by aflatoxin B1 during the phenobarbital- induced promotion step.[14]

A very interesting observation was made in experiments with rats in which the restriction of dietary calories reduced the number and volume of AHF by 85% in 3 month; food restriction lowered DNA replication but increased apoptosis. When treated with a tumor promoter (nafenopin) after food restriction, only half as many hepatocellular adenomas were found as in animals fed ad libitum throughout their lifetime. The authors concluded that restricted calorie intake preferentially enhances apoptosis of preneoplastic cells.[15]

Mechanistic aspects

It is well documented that AHF increase in number and size with continued exposure to both, genotoxic and non-genotoxic carcinogens.[16-18] Some of the phenotypical abnormalities of AHF are stable, however under specific conditions some phenotypical characteristics are lost ("phenotypic reversion").[19] In rats, it is well documented that AHF develop by the clonal expansion of individual cells.[19] As a result of sustained growth, AHF develop into nodular lesions.[20,21] If these nodules are neoplasms, as suggested by some studies,[22] AHF truly represent preneoplastic lesions.

A number of studies have been conducted in which the ratio between cell division and programmed cell death during development of liver cancer was investigated. It was shown, that the cell division rates are increased in AHF compared to normal tissue; in adenomas and carcinomas even higher division rates were observed. Also the death rates (apoptosis) increased gradually from normal to preneoplastic to adenoma and carcinoma tissue.[23] Further studies showed, that the prenoplastic tissue is more susceptible to stimulation of cell replication and cell death;[24,25] and that tumor promoters evidently act as survival factors by inhibiting apoptosis in

preneoplastic liver cells, thereby stimulating growth of preneoplastic lesions. Interestingly, withdrawal of tumor promoters led to excessive elimination of preneoplastic lesions, whereas normal tissue was less affected.[24]

New developments

Grasl-Kraupp and coworkers[25] developed recently an *ex vivo* cell culture model, with initiated rat hepatocytes. Following treatment of the rats with a nitrosamine (N-nitrosomorpholine), hepatocytes were isolated after 22 days (maximal occurrence of $GSTp^+$-cells) and cultivated *in vitro.* Then the cells were either treated with the mitogen cypoterone acetate or with transforming growth factor (TGF-β) for 1-3 days. In culture, the rate of DNA-replication of $GSTp^+$-cells was compared to that of normal hepatocytes. It was found, that $GSTp^+$-cells show an inherent growth advantage and a preferential response towards the effects of TGF-β and cypoterone acetate as in the *in vivo* situation. Based on these results, the authors stress that this *ex vivo* system may provide a useful tool to elucidate biological and molecular changes during the initiation stage of carcinogenesis.

Aberrant crypts in the colon – morphology

In 1987[27], Bird discovered that the treatment of rats with a colon carcinogen (dimethylhydrazine, DMH) leads to formation of morphologically aberrant foci, which can be visualized with methylene blue stain. ACF consist of altered cells, which exhibit cytoplasmic basophilia, a high nuclear to cytoplasmic ratio, prominent nucleoli, loss of globlet cells, loss of polarity, and in the upper part of the crypt they exhibit increased proliferative activity.[28] Figure 3A and 3B depict typical aberrant crypts, which are abnormally large, darkly

Table 1. Biochemical and immunohistochemical alterations of ACF.[30,33-42]

Endpoint	Comment	Reference
Hexosaminidase increased	gene closely located to the APC gene 95% of ACF in rats stain positive, not a marker for human ACF	Boland *et al.*, 1992 Pretlow *et al.*, 1993
Carcinoembryonic antigen (CEA)	intracellular adhesion molecule in human ACF altered (93%) but not a marker for dysplasia	Pretlow *et al.*, 1994
P-Cadherin E-Cadherin	cell adhesion molecules P-c expressed in ACF prior to and independent from E-c and β-catenin	Hardy *et al.*, 2002
β-Catenin	transcriptional activator in ACF nuclear expression increased (see also chapter: development for new markers)	Hao *et al.*, 2001
Inducible nitric oxide synthase (iNOS)	increased in dysplastic but not in hyperplastic ACF	Takahashi *et al.*, 2000
Cyclooxygenase 2 (COX-2)	overexpression in ACF	Takahashi *et al.*, 2000
Cell proliferation markers Ki-67, proliferating cell nuclear antigen (PNCA) $P16^{INK4a}$	several studies show altered patterns in ACF	Renehan *et al.*, 2002 Cheng *et al.*, 2003
Placental form of GST	might be associated in humans with K-ras expression, induced in human ACF and CRC	Miyanishi *et al.*, 2001
Changes in mucin production	alteration of mucin-patterns seen in ACF in rats and in humans	Uchida *et al.*, 2001 Bara *et al.*, 2003

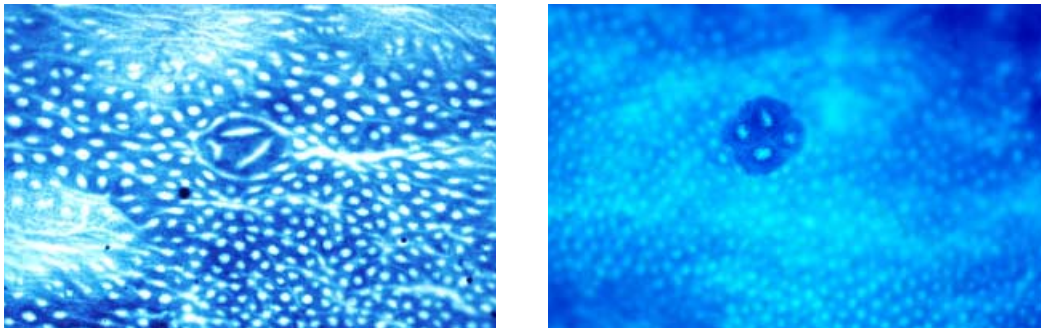

Figure 3A,B. A- An aberrant crypt focus with a high level of dysplasia , which is microscopically elevated with a slit-shaped luminal opening. B- A crypt with oval openings. A GSTp+ focus.

staining and slightly elevated. Dysplastic crypts with a slit-shaped luminal opening are shown in Figure 3A; Figure 3B depicts non-dysplastic crypts with a larger pericryptical zone.[29]

ACF show variable features – ranking from mild hyperplasia to dysplasia, and are generally divided into three groups, namely dysplastic, non-dysplastic (atypic) and mixed type (for details see[30]). In ACF without dysplasia, the crypts are enlarged (up to 1,5-fold) and have slightly enhanced nuclei, no mucin depletion and crypt cells staining positive for PNCA and Ki-67 remain in the lower part of the crypts. In ACF with dysplasia, crypts are more elongated, and the nuclei enlarged. PNCA and Ki-67 stain is extended to the upper part of the crypts. Mixed type ACF show combinations of the features of pure adenomatous pattern (with dysplasia) and hyperplastic characteristics.

In humans, ACF were first described in 1991.[31,32] They resemble those seen in rodents induced by carcinogens[27] and several lines of evidence support the assumption that they are precursors of colorectal tumors (for details see Cheng et al.).[30]

Biochemical and immunohistochemical alterations of ACF

A number of biochemical alterations are typical for ACF. The most important features are listed in Table 1.

Table 2. Epigenetic and genetic alterations in ACF.[43-50]

Alteration	Remarks	Reference
K-ras mutation	in ACF in rats, identified in many studies also in humans	Stopera *et al.*, 1992 Losi *et al.*, 1996
APC mutation	deleted in human ACF – but lower rates as in adenomas/carcinomas	Smith *et al.*, 1994 Nascimbeni *et al.*, 1999
hMSH2 mutation	mismatch repair gene alteration in ACF in mice colons	Reitmair *et al.*, 1996
CpG island methylation	in 53% of ACF of humans with sporadic CRC but only in 11% of FAP patients	Chan *et al.*, 2002
Microsatellite instability	detected in animal models and in humans in ACF	Augenlicht *et al.*, 1996
Fragile histidine triad (FHIT) candidate tumor suppressor gene	lost in CRC (40%) – only few ACF showed reduced expression; the loss correlated with the extent of dysplasia	Hao *et al.*, 2000

Table 3. Compounds, which act as tumor promotors in the colon and cause increased formation of ACF.[58-66]

Compound	Result	Reference
Thermolysed protein	increasing thermolysis of casein increases AOM induced foci numbers and size	Zhang *et al.,* 1992
Thermolysed sucrose (5-hydroxymethyl-2-furaldehyde)	increases the size of AOM induced foci weakly initiating carcinogens	Zhang *et al.,* 1993
Fat (beef tallow)	AOM experiments with mice:increases 3-5 times the size of chemically induced foci	Corpet *et al.,* 1990
Refined sugars (sucrose, fructose, dextrin) induced foci in rats	increased formation of AOM induced foci sucrose and dextrin enhance no. of AOM	Stamp *et al.,* 1993 Poulsen *et al.,* 2001
Progastrin (PG)	ACF significantly more common in AOM treated mice overexpressing PG	Cobb *et al.,* 2004
Haemoglobin, haemin	especially haemin but also haemoglobin were potent ACF promoters in AOM treated rats, when fed a low-calcium diet	Pierre *et al.,* 2003
Chenodeoxycholic acid (CDCA)	AOM induced foci as well as crypt multiplicity significantly increased in rats	Ghia *et al.,* 1996 Sutherland *et al.,* 1994

Genetic and epigenetic alterations

Different genetic alterations have been identified in ACF in humans and also in chemically induced ACF in rats; a detailed overview is given in the article of Cheng *et al.*[30] Many genes, which are considered to be involved in colon carcinogenesis, were found to be altered in ACF; this supports the assumption that they (ACF or specific subpopulations) represent indeed preneoplastic lesions. Table 2 lists up different alterations which were identified in ACF.

Methodological aspects

As in AHF-experiments, ACF-studies allow to discriminate between initiating and promoting compounds. The treatment schedule is more or less identical as that used for the detection of liver foci, but other model chemicals are used.

Only a few compounds have been detected, which are initiators of colon cancer and aberrant crypts. The most frequently used agents are DMH and its metabolite azoxymethane (AOM).[51] Both compounds lead to DNA methylation and to formation of ACF, which become apparent[5-7] weeks after the administration.[52] Also heterocyclic aromatic amines (HAs), which are found in fried meat cause formation of ACF[28,53,54] and were used in a number of chemoprevention studies (for review see Dashwood[55] and Schwab *et al.*[56]). Other agents which cause ACF are N-methyl-N-nitrosurea (MNU) and 3,2-dimethyl-4-aminobiphenyl (DMABP), but these compounds were hardly ever used in mechanistic and chemoprevention studies.[57]

Use of the ACF-model to detect factors which act as tumor promoters in the colon

The ACF-model was intensely used in studies aimed at detecting dietary factors which cause tumor promotion in the colon. Table 3 lists up a number of studies.

Use of the ACF-model for the detection of chemoprotective compounds

Numerous studies have been conducted aimed at identifying compounds which are protective towards colon cancer with the ACF model. Recently, Corpet and Tache[57] have published a review on this topic. They

found in total 137 articles and results for about 186 complex mixtures and individual compounds are available (the data can be downloaded from: http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html). The establishment of a ranking order of protective potency showed, that the most potent were pluronic, polyethylene glycol, perilla oil containing β-carotene and indole-3-carbinol (for details see[57]). In addition, many other dietary constituents were found protective, for example vitamins, lactobacilli in fermented foods, different glucosinolates in Brassica vegetables, carotinoids and fibers to name only a few.[57]

In most of the studies, DMH or AOM were used to cause foci formation and the putative protective compounds were added either before or after administration of the carcinogen. The prevention during the foci "initiation" phase might be either due to inactivation of DNA-reactive molecules, inhibition of metabolic activation or induction of DNA-repair processes[67] and is compound specific. Since humans are not exposed to DMH and its metabolite AOM, chemoprotective effects seen in such experiments cannot be extrapolated to the human situation. On the other hand, it is assumed that the further development of preneoplastic cells (promotion, progression) is triggered by molecular processes which are independent from the chemical carcinogen used.[68] Therefore antipromoting effects seen in the AOM/DMH ACF model might be considered relevant for humans.

HAs are formed during cooking of meats.[69] They cause cancer in the colon of rodents, and in other organs as well[70] and evidence is accumulating that HAs are involved in the etiology of colon cancer in humans.[71] HAs were used in a number of chemoprevention studies in which inhibition of ACF formation was used as an endpoint[55,56,] and a number of dietary components such as fibers, chlorophyllins, Brassica vegetables and lactobacilli were found protective. In this context it is interesting that epidemiological studies indicate that consumption of these factors is also inversely related with the incidence of colon cancer in humans.

One of the problems of the use of HAs in ACF studies is that the foci yield is relatively low, even when the animals are treated with high doses (up to 100 mg/d for several days). The foci frequency could be substantially increased by feeding the animals a high fat and fiber free diet, which facilitates the detection of putative protective effects.[72] In contrast to AOM or DMH it is not possible to induce ACF with a single HA-dose, therefore it is not possible to distinguish clearly between anti-initiating and anti-promoting effects in these experiments.

Corpet and Pierre[51] published an article on the correlation between the results of chemoprevention studies using ACF as an endpoint, and data from experiments with the *Apc*$^{Min/+}$ mouse model (these animals have a mutated *Apc*-gene and therefore highly increased rates of intestinal spontaneous tumors, and are often used as a model for human hereditary colon cancer). Comparison of the efficacy of protective agents in the *Apc*$^{Min/+}$ mouse and in the ACF rat model showed a significant correlation ($p<0,001$). Furthermore, the authors also compared the results of rodent studies with clinical intervention studies. For a number of compounds, which were protective in the animal models, also chemopreventive properties were seen in humans.

New developments

Although numerous studies show that ACF detect colon carcinogens and have been used extensively for the identification of dietary factors enhancing or reducing the risk for colorectal cancer, some results suggest that misleading results may be obtained with certain compounds.[73] For example it is well documented that cholic acid, a primary bile acid, is a strong tumor promoter in the colon, whereas it significantly decreases the number of

ACF.[74,75] A similar contradiction was seen with the xenoestrogen genistein.[76-78]

It was repeatedly postulated by Japanese groups[79-82] that β-catenin acculmulating crypts (BCAC), which are independent from ACF, are more reliable biomarkers for colon cancer development. They show that cholic acid increases the frequency of AOM-induced BCAC in rats. In a critical comment of Pretlow and Bird[83] it is stated that BCAC represent in fact specific dysplastic ACF. In a subsequent paper of Hao *et al.*[37], human ACF were analyzed for β-catenin expression and in approximately 56% of dysplastic ACF, cytoplastic β-catenin was increased, whereas in ACF with atypia, β-catenin in the cytoplasm was only seen in 2% of the total number.

As mentioned above, Magnuson and coworkers[74] also found that the number of ACF at early time points did not predict tumor incidence in rats treated with cholic acid. Therefore the authors suggest that crypt multiplicity should be measured in future studies, due to the fact that it was a consistent predictor of tumor outcome in their study.

Another potential short-term endpoint for colon cancer might be mucin-depleted foci (MDF). In AOM-treated rats such foci could be visualised with high-iron diamine Albicon blue.[84] Their frequency was lower than that of ACF and they were histological more dysplastic than mucinous ACF. In a recent article, it was shown that the number of MDF-foci declined in AOM treated rats, after piroxicam (a colon cancer inhibiting drug) administration, whereas their frequency increased after treatment with cholic acid.[84]

Conclusions

In the last years, highly effective molecular techniques (e.g. microarray based methods) have been developed, which can be employed to elucidate the mechanisms of carcinogenesis. These approaches can be used to analyze gene expression patterns *in vitro* in cell culture models, and also in tumors and can be compared with histological endpoints related to neoplasia. The predictive values of results obtained in in vitro models is often restricted, since the indicator cells which are used lack often characteristic features which are important for the in vivo situation. Typical examples are chemoprevention studies in which metabolically incompetent cell lines may give misleading results, as they do not reflect the activation/detoxification of DNA-reactive carcinogens.[85] On the other hand, the use of tumor formation in animal experiments as endpoints is hampered by the high costs and the time requirement and in case of human studies additionally by the limited availability of material. These shortcomings underline the value of preneoplastic foci models, which represent early stages of the neoplastic process. It has been shown that many compounds, considered as human carcinogens, can be detected with these models in rodents and also that protective agents which were identified in such foci experiments prevent specific forms of cancer in humans. Furthermore, the foci models are also useful to monitor the time course of biochemical and genetic alterations in neoplasia. On the basis of the important information created by the use of these foci models, it is likely that they will be also important tools in future research activities.

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Diagnosis and classification of spontaneously developed and radiation-induced murine haematopoietic neoplasms. The murine models for the research on the human haematopoietic neoplasms

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The Haematopathology Subcommittee of Mouse Models of Human Cancer Consortium (MMHC) proposed a classification that can be readily compared with the human WHO classification 2001 [1] and appropriately delineates the diseases that occur in mice. The mouse lymphoid and nonlymphoid neoplasms develop spontaneously in certain strains and in genetically engineered mice (GEM) or follow induction with ionising radiation or chemical carcinogens or viruses. In the study, the haematopoietic neoplasms that developed in the three investigated mouse strains were identified according to the above classification. They can be useful as mouse models of human lymphoid and nonlymphoid haematopoietic neoplasms.

Key words: T-cell lymphoma, B-cell lymphoma; models, mice

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Introduction

Uniform classification of tumours of murine haematopoietic system has been extensively studied.[1,2] The precise diagnosis will make it possible to compare and contrast murine diseases with human lesions and enable modelling human haematopoietic neoplasms in mice.

Classifications of murine haematopoietic neoplasms has been changing over the last decades. The first classification formulated

by Dunn (1954) was based on the morphology of neoplastic cells and showed similarities to Rappaport's (1966) nomenclature of human lymphomas.[3,4]

In 1981, Pattengale and Taylor proposed a histopathological and immunological scheme of murine lymphomas based on the concept stating that human and murine lymphoid cells of neoplasms represent neoplastic conversion of T or B cell lineage.[5,6] That classification showed a very close relation to Lukes and Collins' (1974) and Kiel's classification (1981).[7,8] Pattengale and Taylor adopted the term of "lymphoid neoplasm" for all haematopoietic neoplasms containing transformed cells that have fully or partially differentiated into T-cells or B-cells or natural killer cells and showing monoclonal proliferation.

The latest classification of murine lymphoid neoplasms was recommended by Haematopathology Subcommittee of MMHCC (Mouse Models of Human Cancers Consortium) and published by Morse *et al.* (2002).[9] It is worth stressing that the classification can be compared with the latest WHO classification of human haematopoietic neoplasms.[1] The classification is also known as "Bethesda proposals for classification of lymphoid neoplasms in mice".[9]

In 2002, the same Subcommittee of MMHCC formulated the latest classification for murine nonlymphoid haematopoietic neoplasms. It was published by Scott C. Kogan *et al.* and it is known as "Bethesda proposals for classification of nonlymphoid neoplasms in mice".[10] The term "nonlymphoid haematopoietic neoplasm" was adopted for haematopoietic neoplasms arising from other lineages than lymphoid ones. The Haematopoietic Subcommittee of MMHCC recommends recognition of the following types of murine lymphoid neoplasms:

B-cell neoplasms
Precursor B-cell neoplasm
Precursor B-cell lymphoblastic lymphoma/leukaemia
Mature B-cell neoplasms
Small B-cell lymphoma
Splenic marginal zone B-cell lymphoma
Follicular B-cell lymphoma
Diffuse large B-cell lymphoma
- Centroblastic
- Immunoblastic
- Histiocyte associated
Classic Burkitt's lymphoma
Burkitt's-like lymphoma
Plasma cell neoplasm
B natural killer cell lymphoma
T-cell - neoplasms
Precursor T-cell neoplasms
Precursor T-cell lymphoblastic lymphoma/leukaemia
Mature T-cell neoplasm
Small T-cell lymphoma
T-natural killer cell lymphoma
T-cell neoplasm, character undetermined
Large cell anaplastic lymphoma

The marked types were not recognized in Pattengale and Taylor classification as separate categories. *E.g.*, the diffuse large B-cell lymphoma was a subtype of follicular centre cell lymphoma from large cells.

It is also worth pointing out that some types of murine lymphomas occur only in mice as special models. E.g. B-natural killer lymphomas can develop only in thymectomized (SL/Kh x AKR/Ms) F1 mice.[11]

The Haematopoietic Subcommittee of MMHCC recommends also four categories of murine nonlymphoid haematopoietic neoplasms with subtypes:

1. Nonlymphoid leukemias
- Myeloid leukemias (granulocytic leukemia)
- Erythroid leukemia
- Megakaryocytic leukemia
- Biphenotypic leukemia
2. Nonlymphoid haematopoietic sarcomas
- Granulocytic sarcoma
- Histiocytic sarcoma
- Mast cell sarcoma
3. Myeloid dysplasias
4. Myeloid proliferations (nonreactive)

The diseases represented in that classification are not very readily compared with human lesions. It is due to the fact that some nonlymphoid haematopoietic neoplasms have not been clearly described in mice. Additional murine models of human nonlymphoid haematopoietic neoplasms are still anticipated.

The purpose of this paper is to show that the murine haematopoietic neoplasms developed in our three investigated mouse strains and identified according to the latest classification can be recognized as murine models of human haematopoietic neoplasms.

Material and methods

Tumours

The murine haematopoietic neoplasms developed:

- spontaneously in recombinant congenic strain OcB/Dem – 20 cases. The OcB/Dem mice were bred from the pairs of mice sent to Cancer Centre in Warsaw from the Netherlands Cancer Institute,[12]
- spontaneously in AKR/W mice carrying endogenous ecotropic provirus which induced potential lymphomas – 46 cases, [13]
- in back-cross (CcS17 x CcS2) x CcS/Dem mice exposed to γ radiation – 72 cases. Mice were exposed to four whole-body γ irradiation with the doses of 1.7 Gy at one week intervals.[14]

All mice were sacrificed when they were visibly sick with poor grooming, hunched posture, weight loss and enlargement of the thymus, lymph nodes or/and spleen detected by palpation.

Pathological procedures

Autopsies were done on each animal. The thymus, mesenteric lymph nodes, spleen, liver as well as other organs with visible neoplastic lesions were fixed in EAFS (ethanol, acetic acid, formol, 0.9% NaCl), and embedded in paraffin; 4 μm thick paraffin sections were stained with H&E or prepared for immunohistochemistry.

Immunophenotyping was performed using two techniques of immunohistochemistry ABComplex and MOM® (Mouse on Mouse) – (immunodetection kit designed to localize murine primary antibodies on mouse tissue), and flow cytometry with the appropriate monoclonal antibodies.

The specific monoclonal antibodies (MAbs) for flow cytometry were conjugated with FITC (CD90.1, CD90.2, CD3ε, CD8, CD5, CD19, CD45R) or PE (CD4, TCRαβ, RAM KAPPA – (rat anti mouse κ), and for immunohistochemistry, they were biotin or pure (anti IgM, anti IgD, anti Igκ, anti Igλ1λ2λ3, Gr-1).[15] All antibodies were produced by PharMingen Germany.

Additionally, two histochemical stainings were performed on the air-dried imprints of tumours, of the spleen, liver or of other organs with neoplastic lesions: naphtol ASBI method - acid phosphatase focal staining is considered to be a specific marker for T lymphoblasts and ASD method - assessment of chloroacetate esterase activity is needed if granulocytic leukemia is to be diagnosed.

Blood smears were stained with Giemsa and the number of neoplastic haematopoietic cells was estimated.

Results

We recognized three types of lymphoid and two types of nonlymphoid haematopoietic neoplasms among 138 classified haematopoietic neoplasms:

LYMPHOID NEOPLASMS:
T-cell derived lymphoma:
- precursor T-cell lymphoblastic lymphoma/leukaemia

B-cell derived lymphoma:
- follicular B-cell lymphoma

- diffuse large B-cell lyphoma subtype centroblastic (CB)

NONLYMPHOID HAEMATOPOIETIC NEOPLASMS:

- granulocytic leukaemia
- granulocytic sarcoma

Precursor T-cell lymphoblastic lymphoma

Human counterpart of mouse precursor T-cell lymphoblastic lymphoma is the lymphoma of the same nomenclature. The microscopic characteristic of examined lymphomas was as follow:

- cells were monomorphic, medium size with scant cytoplasm;
- nuclei were round with fine immature chromatin;
- cells exhibited numerous mitosis;
- 1-2 nucleoli were placed in the centre of the nucleus;
- the spleen was filled up with sheets of neoplastic lymphoid cells;
- in the liver - sheets of neoplastic cells were placed in sinusoids and/or around the vessels.

The detailed immunophenotypes of the examined precursor T-cell lymphoblastic lymphomas are demonstrated in Table 1. The lymphomas exhibited one out of three immunophenotypes (CD4/CD8)$^+$; CD4$^+$/CD8$^-$; CD4$^-$/CD8$^+$. The double positive phenotype was the most frequent conversely phenotype CD4$^-$/CD8$^-$. The expression of CD4 or/and CD8 and CD90 demonstrated by FACS scan analyses is shown in Figures 1A, B, C. Those lymphomas were positive for acid phosphatase staining. Representative images of T-cell lymphoblastic lymphoma are shown in Figures 2A, B, C.

Follicular B-cell lymphoma

Human counterpart is also follicular B-cell lymphoma.

Microscopic changes were as follow:

- diffuse pattern of lymphoma;
- neoplastic cells were small – centrocytic or large – centroblastic;
- cytoplasm was scant;
- nuclei were cleaved, usually with characteristic "heart" shape or noncleaved, round;
- 2-3 nucleoli were prominent and adherent to the nuclear membrane;
- mitoses were visible only among centroblastic cells.

Follicular B-cell lymphomas showed immunophenotype of B-cells – sIg$^+$, B220$^+$, CD19$^+$. Clonality was confirmed by the ex-

Table 1. Immunophenotypes of tested mouse haematopoietic neoplasms

Marker	T-cell derived lymphomas	B-cell derived lymphomas	Granulocytic leukemia / Granulocytic sarcoma
CD90/Thy.1.	+	–	–
CD3ε	+	–	–
CD4	+ or –	–	–
CD8	+ or –	–	–
CD5	+	–	–
TCRαβ	+	–	–
IgM	–	+	–
IgD	–	+/–	–
Igκ / RAM KAPPA	–	+	–
Igλ1λ2λ3	–	–/+	–
CD19	–	+/–	–
CD45R B220	–	+	–
Gr-1	–	–	+

+ - positive
+/– - more often positive than negative
–/+ - more often negative than positive
– - negative

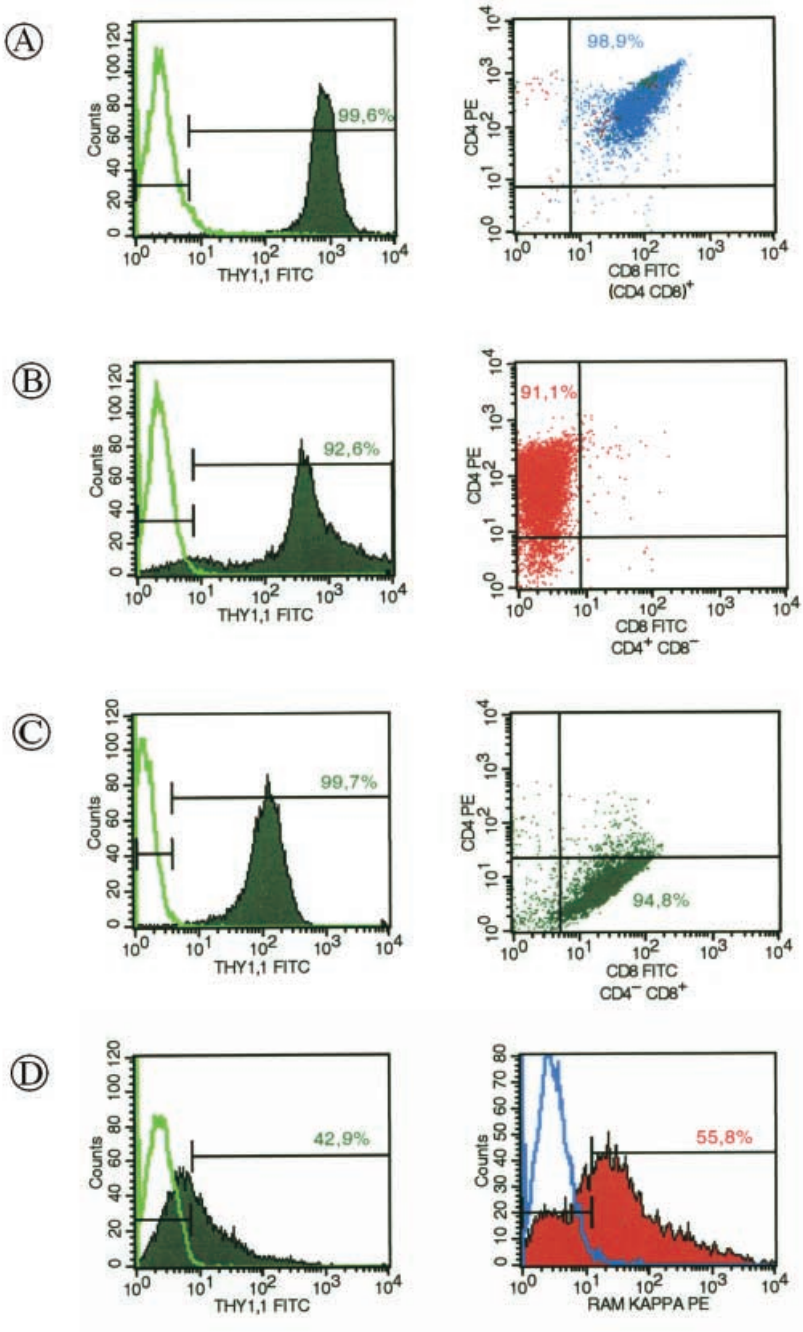

Figure 1. FACS analysis:
Tumor of thymus, T-cell lymphoma (A), (B), (C).
Positive reaction with CD 90.1 (Thy 1.1) FITC (left) co-expression $(CD4/CD8)^+$ or expression CD4+ $CD8^-$ or CD4– $CD8^+$ (right).
Tumor of mesenteric lymph nodes, B-cell lymphoma (D).
Negative with CD90 FITC (left) and positive reaction with RAM KAPPA PE (right).

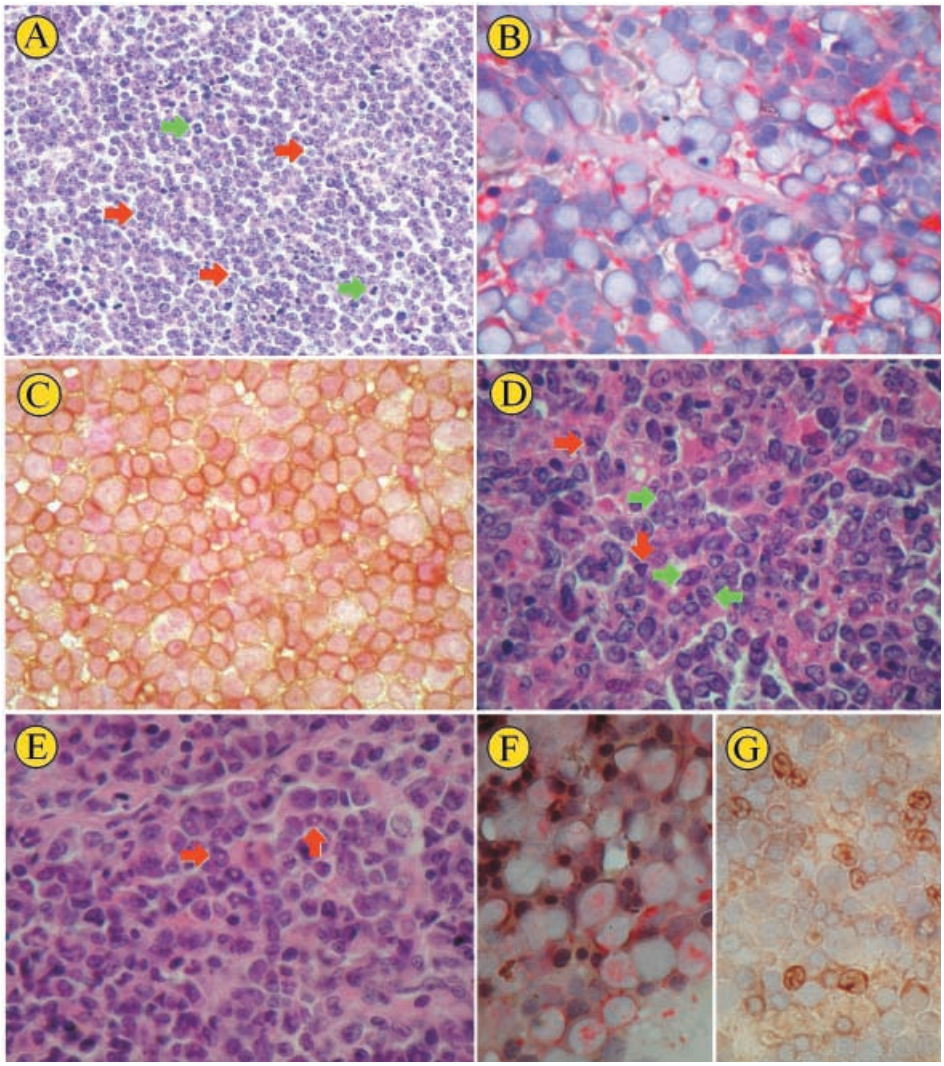

Figure 2. Precursor T-cell lymphoblastic lymphoma/leukaemia (A), (B), (C).
(A) Tumor of thymus - uniform population of medium sized cells with central prominent nucleoli (red arrow) and numerous mitosis (green arrow). H&E x400.
(B) Tumor of mesenteric lymph nodes - focal positive acid phosphatase reaction on air-dried imprint ASBI method x1000.
(C) Tumor of thymus - immunohistochemical staining on air-dried imprints positive for CD90. ABC method x1000.
Follicular B-cell lymphoma (D).
Tumor of mesenteric lymph nodes. Population of large centroblasts (green arrow). and cleaved "heart" shaped centrocytes (red arrow) H&E x1000.
Granulocytic leukaemia (E), (F), (G)
(E) Tumor of mesenteric lymph nodes – infiltration of ring forms of granulocytes (red arrow) H&E x1000.
(F) Tumor of mesenteric lymph nodes – ASD positive staining for chloroacetate esterase activity on air-dried imprint. ASD method x1000.
(G) Spleen – numerous ring shaped forms of granulocytes; positive reaction with Gr-1. ABC method x1000.

pression of one or two heavy chains of immunoglobulin μ, δ (IgM or IgD) and one of light chains κ, λ (Igκ or Igλ).

The detailed immunophenotype of follicular B-cell lymphoma is shown in Table 1. Those lymphomas exhibited the expression of RAM KAPPA and no expression of CD90 (Thy 1.) (Figure 1D). Representative image of follicular lymphoma is shown in Figure 2D.

Diffuse large B-cell lymphoma

The human counterpart is also diffuse large Bcell lymphoma – variant centroblastic. We classified B-cell derived lymphomas with more than 50% of neoplastic lymphoid cells as diffuse large B-cell lymphoma – centroblastic. Those lymphomas showed immunophenotype of mature B-cell lymphoma sIg+, B220+, CD19+, Igκ/RAM KAPPA+.

Granulocytic leukemia

The most severely affected organs were the spleen and mesenteric lymph nodes. The thymus was not involved. The immature forms of granulocytes were found in the peripheral blood and in the periportal, sinusoidal liver and around the liver vessels. Infiltration into the kidney and lung was not observed in our material. Leukaemic cells were bean or, more often ring-shaped and were in one stage of maturation. Representative images of granulocytic leukemia are shown in Figures 2E, F, G.

Granulocytic sarcoma

The lesion was primarily a solid tumour developed in a mesenteric lymph node mass without "spillover" to the peripheral blood. Granulocytic leukaemia and granulocytic sarcoma exhibited positive staining for chloroacetate esterase and showed the expression of Ly-6G Gr-1 in ABC method (Table 1).

Assessment of murine tumours of the investigated mouse strains as a model of human haematopoietic neoplasms

The vast majority of examined haematopoietic neoplasms were derived from lymphoid lineages -127 cases, while nonlymphoid haematopoietic neoplasms developed only in 11 cases. The occurrence of haematopoietic neoplasms in examined strains is shown in Table 2.

In all examined strains, a T-cell derived lymphoma – a precursor T-cell lymphoblastic lymphoma - was the prevalent type of lymphoid neoplasms - 106 cases.

As expected, in the AKR/W mice that type occurred in significantly higher proportion than in the other strains, due to the fact that the AKR/W mice are the most appropriate mouse models of the human precursor T-cell lymphoblastic lymphoma.

Two types of B-cell derived lymphomas, follicular B-cell lymphoma and diffuse large B-cell lymphoma occurred in 21 cases. Those lymphomas developed in the OcB and irradiated Bc(CcS17x CcS2)xCcS2/Dem strains more frequently than in the AKR/W mice. Both mouse strains could be recommended as mouse models for studying human counterpart of those B-cell derived lymphomas.

Granulocytic leukaemia and granulocytic sarcoma were diagnosed mainly in the Bc(CcS17xCcS2)xCcS2/Dem strain. Those

Table 2. The occurrence of neoplasms with given immunophenotype in examined mouse strains

Mouse strains	Nº of tumours	T-cell derived lymphoma	B-cell derived lymphoma	Nonlymphoid haematopoietic neoplasms
OcB/Dem	20	12	7	1
AKR/W	46	45	1	0
Bc (CcS17 x CcS2) x CcS2/Dem	72	49	13	10
TOTAL	138	106	21	11

animals were prepared especially to test the genetic control of susceptibility to radiation induced B-cell derived lymphomas and granulocytic leukaemia. Therefore, the nonlymphoid haematopoietic neoplasms developed in that strain could be the potential mouse model of human neoplasms of the same nomenclature.

Discussion

The mouse precursor T-cell lymphoblastic lymphoma is a very appropriate and well-known counterpart of human lymphoma of the same nomenclature, observed especially in children and young adults.[16] However, it should be stressed that the nuclear convolution, often observed in the human lymphomas, is not seen in the analogous murine lymphomas.

Those lymphomas have been extensively studied in the AKR mice.

Follicular B-cell lymphomas, which developed spontaneously in the OcB/Dem mice and, as a result of irradiation, in the Bc (CcS17 x CcS2) x CcS2/Dem mice, showed a diffuse pattern. While that pattern is common in mice, the follicular structure is usually recognised in human, and the diffuse variant is seen very rarely. Despite those differences, the cytology of these murine and human lymphomas is similar.

The other described type of B-cell derived lymphoma – diffuse large B-cell lymphoma in mice always requires a differential diagnosis with the progression of follicular B-cell lymphoma or progression of splenic marginal zone lymphoma.[17]

It is worth stressing that there is an obstacle in confirmation of clonality of B-cell derived lymphomas in mice, due to the fact that most (approximately 95%) murine light chains are the κ type. Therefore, more informative is the restriction to IgM or IgD than the restriction to light chain κ.

There is also the difficulty in the diagnosis of granulocytic leukemia and granulocytic sarcoma because, in mice, extramedullary haematopoiesis continues in the spleen throughout life. The infiltration in the liver parenchyma by immature forms of granulocytes is more informative than the sheets of immature granulocytes in the spleen. Unfortunately, in our material, in some cases, the liver was not involved and there were no immature granulocytes in the peripheral blood. In those cases, the restriction to one stage of maturation of granulocytes in the spleen was the only criterion for diagnosis.

Due to the fact that the investigated strains developed haematopoietic neoplasms that can be identified according to the classification proposed by the Haematopathology Subcommittee of Mouse Models of Human Cancer Consortium, they can be used as murine models of the human diseases. The observations made on these haematopoietic neoplasms can be translated to their human counterparts.

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Comparison of Wistar vs. Fischer rat in the incidence of 1,2-dimethylhydrazine induced intestinal tumors

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Background. *Many investigators have observed differences in the susceptibility to induce intestinal tumors by 1,2-dimethylhydrazine (DMH) between various strains of rodents. The results are difficult to compare because of the different regimes used for induction. The purpose of our study was to evaluate the influence of strain on DMH-induced intestinal tumors between Wistar and Fischer rats.*

Materials and methods. *We used 29 Fischer and 30 Wistar male rats that were injected subcutaneously DMH, weekly, at a dosage of 25 mg/kg-body weight for 20 weeks. After 25 weeks from the beginning of the experiment, the animals were sacrificed and autopsied. The complete length of colorectum and all macroscopic changes were examined histologically.*

Results. *The induction of intestinal tumors was 97% in Fischer rats and 100% in Wistar rats. In Wistar rats 184 tumors were found: 133 adenomas, 50 tubular adenocarcinomas and 1 signet-cell carcinoma. 77% of carcinomas were found in colorectum and 23% in the small intestine. In Fischer rats, 126 tumors were found: 94 adenomas, 26 tubular adenocarcinomas, 5 signet-cell carcinomas and 1 mucinous carcinoma; 42% of carcinomas were found in the colorectum and 58% in the small intestine. The strain difference in the incidence of all induced tumors was statistically significant (P=0.001). The differences in the occurrence of the malignant and benign tumors was also significant (P<0.001; P=0.011). Extra intestinal tumors were not found.*

Conclusions. *Wistar rats showed greater percentage of colorectal tumors, and also the distribution of tumors in colorectum resembled more the distribution found in human pathology. That is why we recommend Wistar rat rather than Fischer rat for the research work on the colorectal tumors.*

Key words: intestinal neoplasms – chemically induced; 1,2 dimethylhydrazine; rats, inbred F344; rats Wistar

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Introduction

Colorectal carcinoma (CRC) is one of the leading causes of cancer mortality in the USA.[1] With respect to its incidence as well as mortality rate, CRC takes the second place in Slovenia.[2] This was the reason for much in-

terest in the research of this disease and for highlighting the need for animal models that would be comparable to human disease and would help in the study of etiology, pathogenesis and therapy of the human disease.

Some studies compared the incidence of experimentally induced intestinal tumors between different species of experimental rodents and different strains among the species and demonstrated that susceptibility to carcinogen and the incidence and distribution of tumors which developed is species-, strain-, and sex-dependant.[3-8] Wistar and Fischer rats are among the most commonly used strains of rats in the research of intestinal cancer.[9] The published information on the strain-related differences between them is scarce. Besides the results are difficult to compare because different carcinogenic substances, doses, application regimes and application sites are used. So, we decided that this issue is worth of further studies.

Materials and methods

Animals

We used 29 Fischer (344) and 30 Wistar (Hannover) male rats from The Medical Experimental Center, Ljubljana, Slovenia. They were 8-10 weeks old. The experiment was carried out in accordance with the permission of The Veterinary Administration Board of The Republic Slovenia.

At the onset of the experiment the weight of Wistar rats ranged between 170–340 g and that of Fischer rats between 180–290 g. The experiment was carried out at a room temperature of 20–23°C, humidity 40–70%, and at a natural light cycle. The animals were provided pelleted M-K-02 food (Biotechnical Faculty, Ljubljana) and tap water *ad libitum.*

Carcinogenic agent

CRC was induced by means of 1,2-dimethylhydrazine (DMH) (Fluka Chemie, Switzerland) prepared according to the standard method[10]: DMH-HCl was dissolved in 0.001 M EDTA and pH value adjusted to 6.5 using 0.1 M NaOH solution. Fresh solutions were prepared once weekly.

Study design

The dose of DMH was adjusted accordingly, so that it always amounted to 25 mg/kg of body weight. The solution was injected subcutaneously into the skin fold on the hip once weekly throughout a period of 20 weeks. The animals were left to live four weeks after completed DMH injection and thereupon sacrificed by CO_2 inhalation. The body weight was controlled every two weeks.

Morphology

During autopsy, all internal organs except the central nervous system were examined. Attention was paid also to the possible presence of tumors in the outer auditory canal. The stomach was opened via the major curve while the intestine was approached longitudinally on the antimesenterial side. After opening, the organs were rinsed with water. The distal part of the ileum, large intestine, anus and neoplasms in the small intestine were spread over a polystyrene board, with intestinal mucosa facing upwards, and fixed in 10% buffered formaldehyde. The total length of colorectum and all macroscopically visible lesions were sampled for the histological examination. The tissue samples were paraffin embedded and cut into 4.5 μm thick histological sections. The sections were stained by Kreyberg trichrome method. In the cases when histological picture or tumor stage could not be determined from a single section, stepwise deeper sections were made. All intestinal lesions were assessed according to histological criteria used in human pathology and the stages of carcinomas defined following Duke's staging system:

- Stage A: tumor is limited to the intestinal wall;

Table 1. Distribution and number of intestinal tumors

	TUMOR LOCATION No (%)			
	Small intestine	**Colon ascendens**	**Colon transversum**	**Colon descendens with rectosigmoid**
FISCHER	21(17)	16(13)	47(37)	42(33)
WISTAR	7(4)	14(8)	57(31)	106(57)

- Stage B: tumor grows through the lamina muscularis propria;

- Stage C: tumor grows through the lamina muscularis propria and disseminates into the lymph nodes;

- Stage D: distant metastases.[11]

Histological criteria for the diagnosis of adenoma were: (1) cytological – increased mitotic activity, polymorphism and hyperchromatism of the nuclei, basophilia of the cytoplasm, decreased mucine excretion and (2) histological – stratification of the nuclei, irregular proliferation of the glandular formations. Smaller tumor lesions composed of 2-5 crypts (microadenomas), seen only histologically, were also statistically processed.

The criterion for diagnosis of carcinoma was the evidence of tumor growth through the muscularis mucosa. In the case the lesion was suspected of being malignant while there was no clear evidence of tumor growth through the muscularis mucosa, the following additional histological criteria for carcinoma were used: a sharp transition of normal epithelium to severely dysplastic epithelium, the presence of significant necrosis on the surface of tumor and desmoplastic stromal reaction.

Statistical methods

The significance of strain-related difference in the numeric results was tested for the difference between proportions by computer software StatGrafics®Plus.

Results

Number and distribution of intestinal tumors

All animals survived throughout the duration of the experiment. In the intestine of Fischer and Wistar rats 126 and 184 tumors were found, respectively. The tumors were induced in 97% of Fischer rats and 100% of Wistar rats, while the tumors of the colorectum were induced in 48% of Fischer and in 83% of Wistar rats (Table 1). The strain difference in the incidence of all induced tumors was statistically significant (P=0.001). Extraintestinal neoplasms were not found.

The microadenomas that were evaluated by the systematic histological examination of the whole length of the colorectum represented 70% of tumors in Fischer and 60% of tumors in Wistar rats.

In Fischer rats, 25% of the induced tumors were carcinomas that were mostly found in the small intestine (58%), followed by the as-

Table 2. Histological types and stages of intestinal tumors according to Duke's system

	HISTOLOGIC TYPES OF TUMORS												
	Adenomas	**Tubular adenocarcinomas**				**Signet-ring cell carcinomas**				**Mucinous carcinomas**			
		A	B	C	D	A	B	C	D	A	B	C	D
FISCHER	94	19	7	0	0	3	2	0	0	0	1	0	0
WISTAR	133	41	8	0	1	1	0	0	0	0	0	0	0

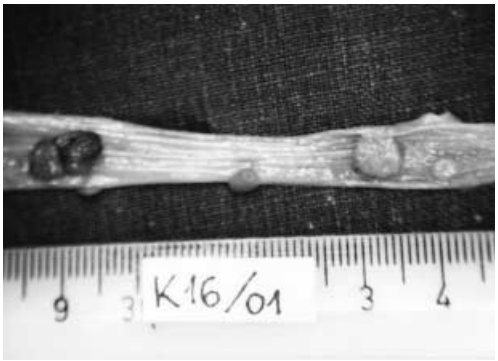

Figure 1. Segment of the large bowel with five tumors giving the appearance of chain-like arrangement.

cending colon (23%), descending colon with rectosigmoid (16%) and the transverse colon (3%).

In Wistar rats, 30% of tumors were carcinomas and were located in the transverse colon (39%), descending colon with rectosigmoid (37%), small intestine (14%) and ascending colon (10%). The most of the small intestinal tumors were found in duodenum.

Macroscopic appearances and histological examination

Macroscopically, tumors grew as plaques or as polypoid lesions on stalk or formed "napkin ring" masses. In 73% of Wistar rats, multiple colorectal tumors were found. The majority of those tumors was strung closely together and gave the appearance of "chain of tumors" (Figure 1). The latter consisted of 3-8 tumors and were mostly located in the transverse and the descending colon with rectosigmoid. Five Wistar rats presented such chains, while none was found in Fischer rats.

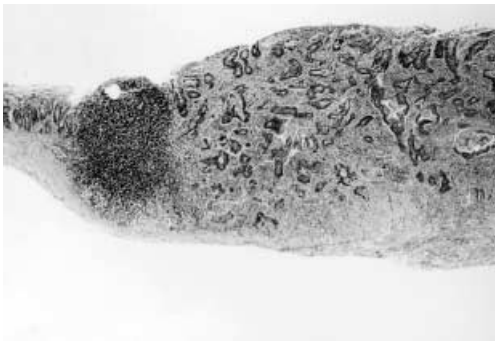

Figure 3. Adenocarcinoma stage Dukes B. On the left site there is a large bowel wall with a lymphatic follicle next to tumor tissue that invades the whole bowel wall (40X magnification).

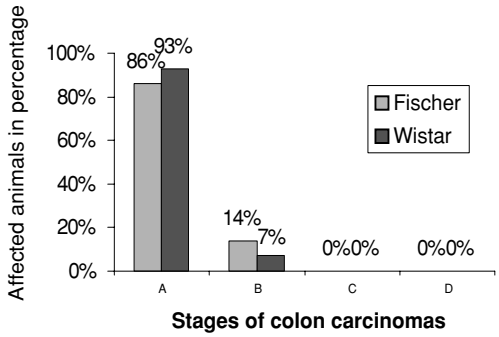

Figure 2. Comparison of colonic tumor stages in Wistar and Fisher rats.

In the review of histological samples in Wistar rats 133 adenomas, 50 tubular adenocarcinomas and 1 signet-ring cell carcinoma were found. In Fischer rats, the histological examination revealed 94 adenomas, 26 tubular adenocarcinomas, 5 signet ring-cell carcinomas and 1 mucinous carcinoma (Table 2).

Most tubular adenocarcinomas were well-differentiated lesions. They grew mostly as polypoid or papillary growths into the lumen. On the contrary, signet-ring cell carcinomas were mostly small, plaque-like lesions with prominent invasion into the deeper levels of the bowel wall. In both strains, signet-ring cell carcinomas were found in the ascending colon with only one tumor being located in the small intestine.

The difference in the occurrence of the malignant and benign tumors between the strains was statistically significant ($P<0.001$; $P=0.011$).

We also found a relation between intestinal lymphoid tissue and tumor location. More than a half of the carcinomas were found in the vicinity of the lymphoid follicles. In one Wistar rat, intussusception connected with tumor in the transverse colon was observed.

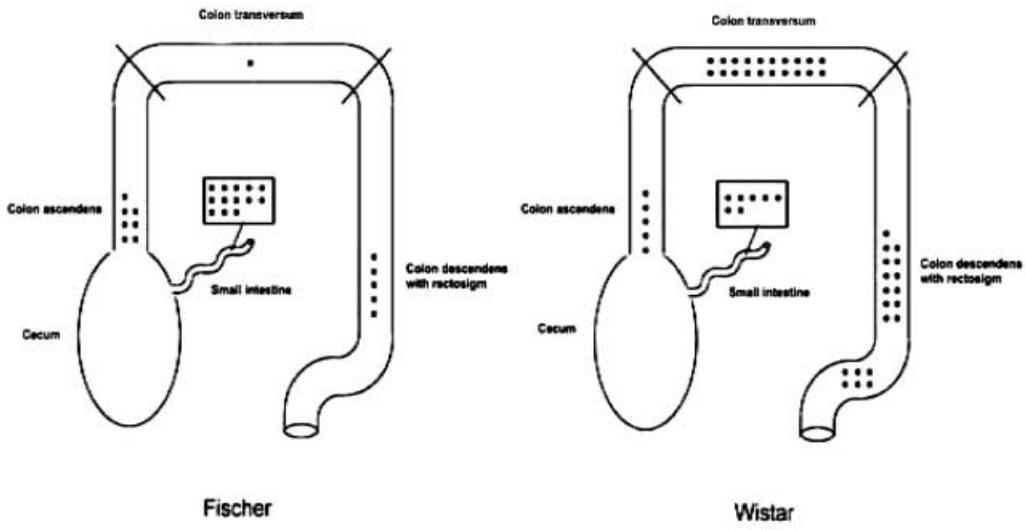

Figure 4. Distribution of intestinal carcinomas in Fischer vs. Wistar rats (each spot represents one tumor).

Staging of the intestinal carcinomas

In Wistar rats, the majority of tumors (82%) were found in stage A, 16% were in stage B (Figure 3), and 2% in stage D according to Duke's system (Table 2). Only 3% of tubular adenocarcinomas stage A were found in the small intestine, while 46% were found in the transverse colon, 41% in the descending colon with rectosigmoid and 10% in the ascending colon. The adenocarcinomas stage B were found mostly (63%) in the small intestine, 25% in the descending colon with rectosigmoid and 12% in the transverse colon. Only one signet-ring cell carcinoma was found in the ascending colon. In one rat, we found a carcinosis of the liver and peritoneum (Dukes D). The comparison of stages of only colorectal carcinomas between different strains of rats is shown in Figure 2.

In Fischer rats, 68% of carcinomas were stage A, 32% stage B, while other stages were not found; 56% of adenocarcinomas stage A and 75% stage B carcinomas were found in the small intestine, while others were located in the descending colon with rectosigmoid (22%), transverse (10%) and the ascending colon (10%). The adenocarcinomas in stage B were similarly distributed: small intestine (75%), descending colon with rectosigmoid (12.5%), and ascending colon (12.5%). The signet-ring cell carcinomas presented 12.5% of all carcinomas in Fischer rats and all were found in the ascending colon. The distribution of induced intestinal carcinomas in Fischer and Wistar rats is schematically presented in Figure 4.

Discussion

DMH injected subcutaneously is one of the most effective CRC inducers in small rodents. This substance has been studied in large-scale experiments[12-19], but the incidence of experimentally induced tumors in different strains of animals was not clearly defined. No data can be found in literature comparing DMH-induced tumors in Wistar and Fischer strains, although those are most often used for experimental purposes.[9]

The intestinal tumors were induced in 97% of Fischer and 100% of Wistar rats. Though there was no significant difference in the share of animals affected with tumors between the two strains , the incidence of intestinal tumors was significantly higher in Wistar rats.

Nevertheless, we have to emphasize that the microadenomas containing 2-5 aberrant crypts were also included in analysis. Microadenomas presented almost 70% of all tumors found and their frequency supports the likelihood that CRC develop from adenomas.[5,6,21-23] Because of the inclusion of microadenomas, the total number of induced tumors in our study somewhat exceeded the number of tumors induced by the same dose and number of applications by other authors.[6,7,23-25]

Fischer rats developed markedly less carcinomas than Wistar rats; 58% of them were found in the small intestine, others were equally distributed in the ascending and descending colon. There were, however, less tumors found in the transverse colon than reported by other authors.[9,23-25] The tumors of the small intestine, which were mainly well differentiated adenocarcinomas, developed most often in the proximal part of the small intestine. Macroscopically, both strains developed polypoid, cauliform lesions and also ring-like lesions with elevated edges that were comparable with human disease. Sessile tumors exhibiting endophytic growth pattern were rare.

In our study, the histological types of intestinal tumors in rats are consistent with those of other authors who report the greatest number of well differentiated adenocarcinomas and some signet-cell carcinomas, while poorly differentiated adenocarcinomas were rarely found.[20-23,26]

Our results of tumor stage analysis were comparable with those obtained by other authors, according to which a majority of colorectal tumors (75%) were in stage A.[20-23,26] Our comparison of carcinoma stage by strain has shown noteworthy differences. Fischer rats developed twice as much stage B tumors than Wistar rats. The tumors found in Fischer rats were showing more invasiveness and were usually growing deeper in the bowel wall. Likewise some other authors, we also found a case of stage D tumor, with peritoneal carcinosis and distant metastases.[5, 20-22]

The analysis of the small intestinal tumors revealed differences between the two strains in regard to stages: well or moderately differentiated adenocarcinomas stage B predominated in Wistar strain and well differentiated adenocarcinomas stage A in Fischer rats. Most of the macroscopically visible small intestinal tumors were located in the proximal part (duodenum, proximal jejunum), which is consistent with the carcinoma of the small intestine in humans.

An association of DMH-induced rat colorectal tumors with colorectal lymphoid follicles was observed previously, but not quantified. Our experiment revealed that more than 50% of carcinomas developed in the immediate proximity of the intestinal lymphoid tissue. This is supposed to be an immunologic answer to antigenic components present in the tumor and simultaneously because of the more rapid replication of the epithelial cells in the vicinity of lymphatic tissue.[27-29]

Tumors found in both Wistar and Fischer strain histologically resembled those found in human pathology. Wistar rats have developed a greater incidence of colorectal tumors and distribution of tumors resembled more the distribution as it is seen in human pathology than those in Fischer rats. Therefore we recommend Wistar rats rather than Fischer rats for the research work on the colorectal tumors.

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Multileaf collimator in radiotherapy

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Background. *Basic goal of radiotherapy treatment is the irradiation of a target volume while minimizing the amount of radiation absorbed in healthy tissue. Shaping the beam is an important way of minimizing the absorbed dose in healthy tissue and critical structures. Conventional collimator jaws are used for shaping a rectangular treatment field; but, as usually treatment volume is not rectangular, additional shaping is required. On a linear accelerator, lead blocks or individually made Cerrobend™ blocks are attached onto the treatment head under standard collimating system. Another option is the use of multileaf collimator (MLC).*
Conclusions. *Multileaf collimator is becoming the main tool for beam shaping on the linear accelerator. It is a simple and useful system in the preparation and performance of radiotherapy treatment. Multileaf collimators are reliable, as their manufacturers developed various mechanisms for their precision, control and reliability, together with reduction of leakage and transmission of radiation between and through the leaves. Multileaf collimator is known today as a very useful clinical system for simple field shaping, but its use is getting even more important in dynamic radiotherapy, with the leaves moving during irradiation. This enables a precise dose delivery on any part of a treated volume. Intensity modulated radiotherapy (IMRT), the therapy of the future, is based on the dynamic use of MLC.*

Key words: radiotherapy dosage; radiotherapy; multileaf collimator, field shaping

Introduction

Basic goal of radiotherapy treatment is the irradiation of a target volume while minimizing the amount of radiation absorbed in healthy tissue. Shaping of the beam is an important way of minimizing the absorbed dose in healthy tissue and critical structures.

Conventional collimator jaws are used for shaping a rectangular treatment field; but, as usually the treatment volume is not rectangular, additional shaping is required. On a linear accelerator, lead blocks or individually made Cerrobend™ blocks are attached onto the treatment head under standard collimating system. Another option that will be described in detail here is the use of multileaf collimator (MLC).

The MLC has movable leaves, which can block some fractions of the radiation beam.

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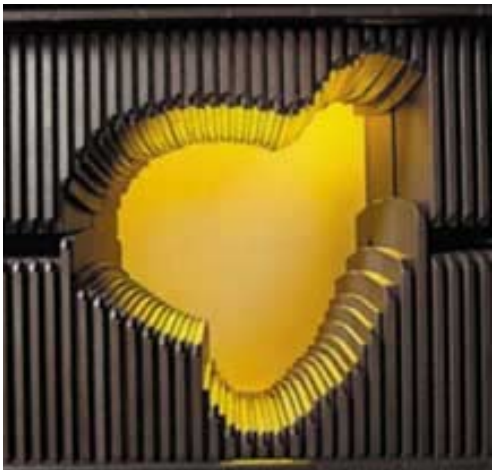

Figure 1. Multileaf collimator Varian Millenium MLC120.

Typical MLCs have 40 to 120 leaves, arranged in pairs (Figure 1). By moving and controlling a large number of narrow, closely abutting individual leaves, one can generate almost any desired field shape.[1]

The advantages of MLCs are simple and less time consuming preparation, use without needing to enter the treatment room, and simple change or correction of field shape. The therapy expenses are lower because individual shielding blocks are not needed, thus eliminating the need to handle the Wood's alloy, which is toxic. With MLC, we shorten the therapy time, and thus also the period during which patient must remain in still position. Other advantages are constant control and continuous adjusting of the field shape during irradiation in advanced conformal radiotherapy.[1-5]

MLC has also some disadvantages, which include a stepping edge effect, radiation leakage between leaves, wider penumbra, and problems with generating some complex field shapes.[2]

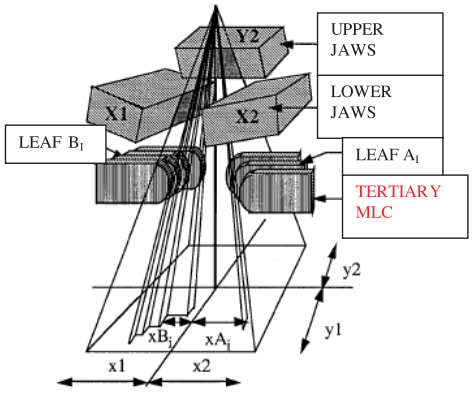

Figure 2. MLC and standard collimators positions in treatment head used in third level configurations.

MLC Configurations

MLC configurations may be categorized as to whether they are total or partial replacements of the upper jaws, the lower jaws, or as tertiary collimation configurations.

Upper jaw replacement

This configuration entails splitting the upper jaw into a set of leaves. In this design (used by Elekta™), the MLC leaves move in the y-direction (parallel to the axis of rotation of the gantry). A "back-up" collimator located beneath the leaves and above the lower jaws augments the attenuation provided by the individual leaves. The back-up diaphragm is essentially a thin upper jaw that can be set to follow the leaves if they are arranged together to form a straight edge, or else, set to the position of the outermost leaf if the leaves form an irregular shape.

The primary advantage of the upper jaw replacement configuration is that the range of motion of the leaves required to traverse the collimated field width is smaller. This allows a shorter leaf length and therefore a more compact treatment head diameter. The disadvantage of having the MLC leaves so near the source of radiation is that the leaf width must be somewhat smaller and the tolerances on the dimensions of the leaves and the leaf travel must be tighter than in other configurations.[1]

Leaves of this collimator have total travel

distance 32.5 cm, which means they can extend 12.5 cm across the centre line.

Lower jaw replacement

The lower jaws can be split into a set of leaves as well. This design is used by Siemens™ and is double-focused. Both leaf ends and leaf sides match the beam divergence. That means that the collimator leaves move along the circumference of a circle centred at the x-ray target of the linear accelerator, such that the end of the collimator is always tangential to the radius of the circle.[1]

The leaves of Siemens MLC can extend 10 cm across the field centreline, which allows a maximum leaf travel of 30 cm.

Third level configurations

MLC can be positioned just below the level of the standard upper and lower adjustable jaws (Figure 2). This design is used by Varian™ and was chosen to avoid lengthy downtime in the event of a MLC system malfunction. Using this approach, it is possible to move leaves manually out of the field should a failure occur. The treatment can continue after the replacement Cerrobend™ individual blocks have been manufactured. The major disadvantage of placing the MLC below the standard jaw system is the added bulk and clearance to the mechanical isocentre.

Moving the MLC further away from the x-ray target requires increasing the leaves size and a longer travel distance.[1]

The leaves in the Varian collimator travel on a carriage that serves to extend their movement across the field. However, the distance between the most extended leaf and the most retracted leaf on the same side can only be 14.5 cm.

Materials and properties

The material of choice for leaf construction is tungsten alloy because it has one of the highest densities of any metal. Tungsten alloys are also hard, simple to fashion, reasonably inexpensive, and have a low coefficient of thermal expansion.

Interleaf transmission

There are two situations to consider for interleaf transmission: (1) between the sides of adjacent leaves, and (2) between the ends of the leaves.

In order to minimize the leakage between the sides, it is necessary to overlap the leaves usually by specially shaped side profile that steps out and then steps back again.[6]

To minimize leakage between the ends of closed opposite ends, it is important to know that the transmission decreases with increasing the off-axis distance.[7]

Leaf end shape

Multileaf collimators that are double focused (Siemens design) have flat leaf ends that follow the beam divergence. The leaf ends of Elektra and Varian MLC design are rounded.

There are two concerns over collimation by non-focused leaf ends. First, the penumbra

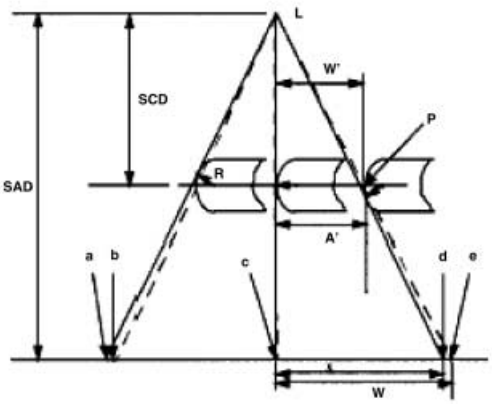

Figure 3. Rounded leaf ends and their influence on penumbra based on the position in the field.

width is larger than the penumbra generated by a focused or divergent edge. Second, the penumbra width might change as a function of the distance of the leaf end from the field midline (Figure 3). The measurements on the Elekta and Varian configurations have shown that these designs result in a little variation in the penumbra width as a function of leaf position and that the penumbra at any position is within 1-3 mm of that obtained with a focused system or with alloy blocks with divergent sides.[6-10]

MLC control features

MLCs produced by various manufacturers employ special mechanisms to move the leaves accurately to their prescribed positions.

Detection of the leaf position

The leaf position must be detected in real-time to achieve a safe and reliable position control. Linear encoders and video optical systems are most commonly used for detection.

Linear encoders

We can use many different linear encoders, but for detection of leaf positions in MLC systems high precision potentiometers are commonly used. These potentiometers can detect positions of any individual leaf in the system.

For safer work two potentiometers with correlated readings are used in this system.

Video-optical system

This system of detection uses the same light source for patient positioning and for leaf position recognition. A retro-reflector is mounted near the end of each leaf, and the light is reflected from it back to the camera. The obtained signal is digitized and processed with an image processor in the MLC controller.

The mechanism that drives a leaf

Each leaf has a small motor, which drives it precisely in the directions from the main unit. These rotations must than be translated to linear motion which moves the leaf to the desired position. Linear screw bars are normally used to translate rotations to linear motion. The speed of the leaf travel varies between 0.2 mm/s to as high as 50 mm/s, depending on the design.[1]

Clinical applications

Leaf placement strategies

To realize potential benefits of MLC, it is important that its use is incorporated into the

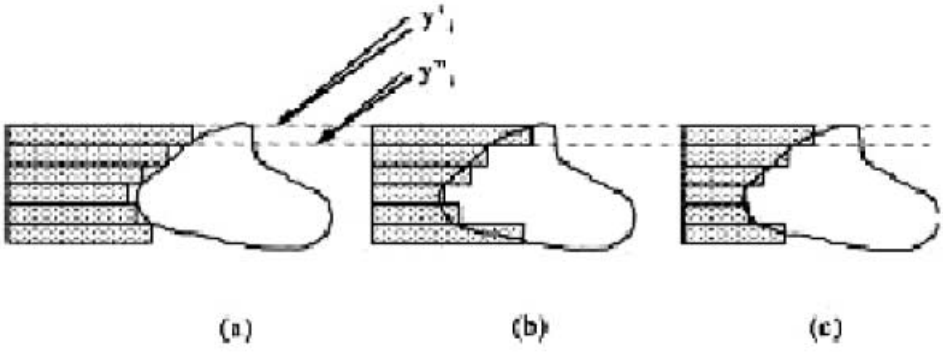

Figure 4. Three leaf coverage strategies in relation to the PTV, (a)"out-of-field" strategy; (b)"in-field" strategy; c)"cross-boundary" strategy.

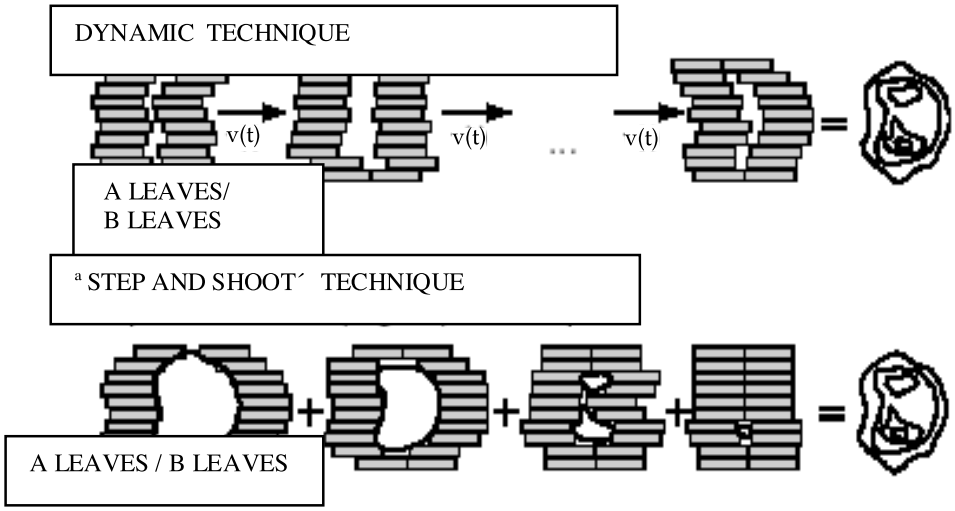

Figure 5. IMRT techniques with the use of MLC.

treatment planning process as efficiently as possible.

During the treatment planning process, manual placement of each of the 40-120 leaves is not acceptable due to time constraints. Therefore some automated method must be used in a treatment planning system (TPS). That way in TPS, the position of each leaf is defined so that the field encompasses the planning target volume (PTV). More specifically, the determination of the MLC positions is carried out by means of the following steps:

Definition of target area

Treatment planning system facilitates shaping leaves around PTV, as defined by a radiation oncologist. An accurate definition of PTV is crucial for the success of the therapy.[11]

Optimization of MLC conformation

To place automatically the leaves of MLC in conformity with the target contour shape, three leaf coverage strategies can be used (Figure 4).

Each strategy uses different position of the leaf in relation to the contour of the field that we want to irradiate.

The "out of field" strategy (4a) avoids shielding any part of the planning target volume-PTV, which is than irradiated completely.

When using the "in field" strategy (4b), PTV is not irradiated completely, but any part out of PTV stays shielded.

The most widely used method is cross-boundary technique indicated in panel (c) of Figure 4. One condition for optimizing the leaf positions was criterion that the in-field area was equal to the out-of-field area.[4]

Optimization of collimator rotation

One can optimize matching the leaf shape to target volume by rotating the collimator, and therefore, the direction of leaf travel. An example is the alignment of the leaf faces with the spinal cord axis, when the cord is close to the target volume. Brahme, in his conclusion of work said, that optimal direction for the leaf motion is the direction along the narrower axis. For a simple ellipse, the optimal leaf direction is parallel to the short axis.[12]

Intensity modulated radiotherapy (IMRT) with multileaf collimator

The basic goal of IMRT treatment is precise

dose delivery on any part of treated area thus avoiding the surrounding healthy tissue. In IMRT treatment, the leaves of MLC, while moving during the irradiation, ensure the appropriate dose that is delivered on the parts of treated area (Figure 5).

From the differences between the dose volumes delivered during the whole treatment and the dose volumes in which the leaf is shielding some part of the treated area, we can determine what dose has been delivered on this particular part. MLC for intensity modulation should be very precise, motion of leaves must be fast and constant, leaves should be precisely controlled and must have a long reach in the field. Three dimension (3D) treatment planning systems must be used for IMRT.

Two strategies of IMRT with multileaf collimator are used. One is dynamic technique, with continuous movement of leaves during the treatment; the second is step and shot technique with moving the leaves when radiation is stopped. Both strategies with this travel determine dose delivered on the parts of treatment volume.[2]

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Radiol Oncol 2004; 38(3): 165-9.

Diagnosticiranje benignih kostnih tumorjev s pomočjo računalnika

Samardziski M, Zafiroski G, Janevska V, Miladinova D, Popeska Ž

Izhodišča. Namen raziskave je bil določiti uspešnost diagnosticiranja benignih kostnih tumorjev z računalnikom glede na različno histološko zgradbo tumorjev.

Bolniki in metode. V raziskavo smo vključili 120 bolnikov in jih razdelili v dve skupini. V retrospektivni skupini je bilo 68 bolnikov, ki je imelo pred računalniško analizo že znano histološko diagnozo. V drugo, prospektivno skupino pa je bilo vključenih 52 bolnikov, ki še niso imeli znane histološke diagnoze. Uporabljali smo uporabnikom prijazen računalniški program.

Rezultati. V retrospektivni skupini smo s pomočjo računalnika potrdili histološko diagnozo benignega kostnega tumorja v povprečju v 72,06%, v prospektivni skupini pa v 76,92%. Glede na posamično vrsto benignega tumorja smo bili najbolj natančni pri enhondromih (v 91,42%), osteoidosteomih (v 96,15%) in osteohondromih (v 98,08%). Značilno nižji procent pravilne diagnoze smo dosegli pri fibromih, hondromiksoidnih fibromih, osteoklastomih, dezmoplastičnih fibromih in osteobalstomih, kar si razlagamo z različnimi biološkimi značilnostmi in anatomsko lokalizacijo teh tumorjev.

Zaključki. Rezultati so potrdili pričakovanje, da lahko s pomočjo računalnika izboljšamo natančnost slikovne diagnostike pri ugotavljanju benignih kostnih tumorjih.

Radiol Oncol 2004; 38(3): 171-5.

Spontani perirenalni in subkapsularni hematomi – poročilo o 5 bolnikih

Vukelić-Marković M, Huzjan R, Marušić P, Brkljačić B

Izhodišča. Spontana perirenalna in subkapsularna krvavitev je redko, vendar pomembno klinično stanje, ki lahko predstavlja za diagnostika velik izziv. Včasih ostaja etiologija krvavljenja nepojasnjena, čeprav so bili narejeni vsi razpoložljivi diagnostični postopki. V takšnih primerih ostaja tudi odločitev za določeno vrsto zdravljenja kontraverzna.

Prikaz primerov. Poročamo o 5 bolnikih z perirenalno in subkapsularno krvavitvijo. V 2 primerih sta prva in kontrolna CT preiskava kazali, da sta verjetni vzrok krvavitve angiomiolipom in ledvična cista, kar je potrdila tudi patohistološka preiskava. V ostalih 3 primerih pa je CT preiskava pokazala le spremembe, ki so kazale na hematom brez druge patologije in pri 2/3 bolnikih je to potrdil patohistološki pregled. Ugotovitve s CT preiskavo so zelo korelirale s patohistološkimi ugotovitvami tako pri potrditvi kot izključitvi vzroka bolezenskih sprememb. Zanimivo je, da v nobenem primeru nismo našli ledvičnega raka.

Zaključki. Po literature je kar v 50% vzrok perirenalne in subkapsularne krvavitve maligni tumor. Zato nekateri avtorji v vseh primerih svetujejo odstranitev ledvice, drugi pa svetujejo bolj zadržan pristop z dolgotrajnejšim skrbnim sledenjem bolnika. Menimo, da nam lahko nove slikovne metode, če jih optimalno uporabljamo, in dodatno sledenje bolnika omogočajo, da prepoznamo krvavljenje zaradi benignega obolenja ter se na ta način izognemo nepotrebni odstranitvi ledvice.

Radiol Oncol 2004; 38(3): 177-80.

Ultrazvočno usmerjene tankoigelne aspiracijske biopsije nadledvičnih mas pri bolnikih s pljučnim rakom, enajst let izkušenj

Igor Kocijančič

Izhodišča. Namen retrospektivne raziskave je ugotoviti zanesljivost in varnost ultrazvočno usmerjene tankoigelne biopsije povečanih nadledvičnic pri bolnikih s pljučnim rakom.
Bolniki in metode. V enajstih letih smo naredili tankoigelno biopsijo nadledvičnih mas pri 64 bolnikih s citološko dokazanim pljučnim rakom. Zanesljivost metode smo ocenjevali na osnovi citoloških izvidov, varnost pa na osnovi zabeleženih zapletov po posegu.
Rezultati. Ultrazvočno usmerjene tankoigelne aspiracijske biopsije so se pokazale kot zanesljive v 58/64 primerov (91%), in zelo varne s samo 4/64 (6%) manjšimi zapleti. V 52/58 (90%) primerov je bil citološki vzorec maligen. V 6 primerih (10%) je nadledvična masa predstavljala adenom.
Zaključki. Ultrazvočno usmerjeno tankoigelno aspiracijsko biopsijo priporočamo kot varno in zanesljivo metodo. V primerjavi z računalniško tomografsko vodeno tankoigelno aspiracijsko biopsijo ima kar nekaj prednosti - je varnejša, ponovljiva, prijaznejša bolniku in brez ioniziračega sevanja.

Radiol Oncol 2004; 38(3): 181-5.

Karcinom horoidnega pleteža: prikaz primera

Strojan P, Popović M, Šurlan K, Jereb B

Izhodišče. Mnenja o vlogi adjuvantnega zdravljenja pri karcinomu horoidnega pleteža niso enotna. Namen tega poročila je predstaviti primer uspešnega zdravljenja te redke vrste tumorja.
Rezultat. Štirinajstletna deklica s tumorjem tretjega ventrikla je bila zdravljena z neradikalno operacijo in adjuvantno kemoterapijo ter radioterapijo. Bolnica je 8,5 let po postavitvi diagnoze živa in brez znakov bolezni. V prispevku razpravljamo o vlogi adjuvantnega zdravljenja v kontekstu razpoložljivih podatkov iz literature.
Zaključek. Pooperativna adjuvantna kombinirana kemoterapija in kraniospinalna radioterapija ima svoje mesto v zdravljenju karcinoma horoidnega pleteža.

Radiol Oncol 2004; 38(3): 241-8.

Radiol Oncol 2004; 38(3): 187-92.

Keratociste v čeljustnicah

Lipovec A, Ihan Hren N

Izhodišča. Ciste v čeljustnicah so pogosta patološka sprememba. Med njimi predstavljajo odontogene keratociste (OKC) posebno skupino zaradi svoje agresivne rasti in ponavljanja.
Bolniki in metode. Retrospektivno smo ugotavljali pogostnost in značilnosti OKC med vsemi patohistološko potrjenimi cistami, ki smo jih kirurško zdravili na Kliničnem oddelku za maksilofacialno in oralno kirurgijo Kliničnega centra v Ljubljani v zadnjem desetletju (od začetka leta 1994 do konca leta 2003).
Rezultati. Med 992 cističnimi spremembami v čeljustnicah smo operativno odstranili 106 OKC (10,6% vseh cist). Patohistološka diagnoza OKC je bila dokazana pri 90 bolnikih, od tega 51 moških (56,7%) in 39 ženskah (43,3%). Povprečna starost bolnikov z OKC v času njihovega zdravljenja je bila 36 let. Najmlajši bolnik je bil star 7, najstarejši 83 let. V spodnjih čeljustnicah je bilo odstranjenih 74 (69,8%), v zgornjih čeljustnicah pa 32 (30,2%) histološko dokazanih OKC. Po lokaciji so prevladovale v področju kotov in navpičnih vej spodnje čeljustnice, kjer jih je bilo 49 (46,2%). Ponovitev OKC smo po prvi odstranitvi zasledili pri 20 bolnikih (22,2%). Prva ponovitev OKC je bila najpogosteje (v 70%) odkrita v prvih petih letih po prvem zdravljenju, povprečni čas do prve ponovitve je bil 3 leta in 9 mesecev. Večkratne ponovitve OKC so bile pri 9 bolnikih (10% vseh z OKC). Med pregledovanimi bolniki z OKC je bilo obolelih s sindromom bazalnoceličnega karcinoma 5 bolnikov. Ugotaljali smo tudi tretinski delež OKC, ki so bile klinično nepričakovane.
Zaključki. Ker je delež klinično nepričakovanih OKC znaten in povezan z netipičnimi lokacijami v čeljustnicah, se je potrebno pri vseh cistah v čeljustnicah odločati za patohistološko dokazovanje. Delež OKC navidezno kaže na znatno povečanje (kar 3,5-kratno) te patologije glede na prejšnje epidemiološke podatke v Sloveniji, vendar je to posledica predvsem prej nepoznane patološke entitete. Naša raziskava je tako po vzorcu bolnikov kot po epidemioloških rezultatih primerljiva s poznanimi raziskavami v literaturi.

Radiol Oncol 2004; 38(03): 139-203.

Psihološka obremenjenost in pomoč bolnikom z rakom, ki se zdravijo z radioterapijo

Šoštarič M, Šprah L

Izhodišča. Stranski učinki zdravljenja z radioterapijo (RT) pogosto povzročajo psihofizično obremenjenost pri bolnikih z rakom. Le-ta se kaže v obliki anksioznosti, težav v prilagajanju in depresiji ter se lahko v primeru neustreznega pristopa sprevrže v resne psihiatrične razpoloženjske motnje in v določenih primerih celo v samomor. Mnoge študije so pokazale, da se naštete oblike psihofizične obremenjenosti pojavljajo pri približno polovici vseh onkoloških bolnikov. V tej populaciji so določene skupine bolnikov, ki so še posebej ranljive. Med njimi so bolniki, ki se zdravijo z RT in potrebujejo posebno pozornost. V članku je predstavljena široka paleta psihosocialnih intervencij in nekaterih metod, ki so namenjene uporabi v psihoonkološki praksi.
Zaključki. Kot je navedeno v številnih objavah, bi prvi korak intervencije moral predstavljati učinkovit presejalni postopek. V ta namen bi bilo potrebno razvijati (računalniško podprte) presejalne programe. Potrebne bi bile tudi sistematične raziskave tradicionalnih, netradicionalnih in komplementarnih intervencijskih strategij pri obravnavi bolnikov z rakom, ki doživljajo psihofizične obremenitve. Le z zanesljivimi empiričnimi rezultati bi namreč lahko dobili vpogled v učinkovitost različnih pristopov.

Radiol Oncol 2004; 38(3): 205-16.

Uporaba preneoplastičnih lezij debelega črevesa in jeter v eksperimentalni onkologiji

Ehrlich VA, Huber W, Grasl-Kraupp B, Nersesyan A, Knasmüller S

Članek daje pregled o uporabi spremenjenih jetrnih lezijah (altered hepatic foci- AHF) in spremenjenih kriptah v debelem črevesu (aberrant crypt foci (ACF) v raziskavah eksperimentalne onkologije. Te lezije so lahko zasledljive preneoplastične lezije, ki so jih odkrili že pred tridesetimi leti. AHF in ACF so pomemben pripomoček za odkrivanje raka, snovi, ki injicirajo in promovirajo nastanek raka in za odkrivanje kemopreventivnih snovi za nastanek raka. Uporabljajo se tudi pri ugotavljanju molekularnih mehanizmov nastanka zgodnjih neoplastičnih lezij, kot je spremenjeno izražanje onkogenov in tumorskih supresorskih genov in spremembe v delovanju, ki se pojavljajo v rakavih celicah.

Radiol Oncol 2004; 38(3): 217-25.

Diagnoza in razvrstitev mišjih hematopoetskih tumorjev, ki so nastali spontano ali kot stranski učinek obsevanja: mišji modeli so lahko temelj za raziskovanje človeških hematopoetskih tumorjev

Szymańska H, Piskorowska J, Krysiak E, Skurzak H, Czarnomska A, Demant P

Hematopatološki pododbor za mišje modele pri Konzorciju za rakave bolezni pri človeku (The Haematopathology Subcommittee of Mouse Models of Human Cancer Consortium - MMHC) je predlagal razvrstitev bolezni pri miših, ki je primerljiva z razvrstitvijo bolezni pri ljudeh, kakršno je leta 2001 odobrila Svetovna zdravstvena organizacija WHO. Ta razvrstitev ustrezno označuje bolezni miši. Pri posameznih miših, pri miših vzgojenih z genetskim inženiringom ter pri miših, ki so bile izpostavljene ionizirajočemu sevanju, karcinogenim kemijskim sredstvom ali virusom, se limfoidni in nelimfoidni tumorji razvijejo spontano. V raziskavi smo v skladu s predlagano razvrstitvijo določali hematopoetske tumorje, ki so zrasli na treh omenjenih linijah miši. Menimo, da so tako razvrščeni mišji modeli lahko odlična osnova za raziskovanje človeških limfoidnih in nelimfoidnih hematopoetskih tumorjev.

Radiol Oncol 2004; 38(2): 227-34.

Primerjava incidence črevesnih tumorjev povzročenih z 1,2-dimetilhidrazinom med sevoma podgan Wistar in Fischer

Večerić Ž, Cerar A

Izhodišče. Pri eksperimentalni indukciji intestinalnih tumorjev z 1,2-dimetilhidrazinom (DMH) so raziskovalci opazovali različno občutljivost posameznih sevov podgan. Rezultate je težko primerjati zaradi uporabe različnih režimov indukcije. Naš namen je bil oceniti vpliv sevov Wistar in Fischer podgan na indukcijo intestinalnih tumorjev z DMH.

Materiali in metode. Uporabili smo 29 samcev seva Fischer in 30 samcev seva Wistar. Črevesne tumorje smo inducirali s podkožno aplikacijo DMH v dozi 25 mg/kg, enkrat tedensko, 20 tednov zapored. Po 25 tednih smo živali žrtvovali in jih obducirali. Histološko smo ovrednotili vse makroskopske najdbe ter celotno dolžino debelega črevesa.

Rezultati. Indukcija črevesnih tumorjev je uspela pri 97% živali seva Fischer in 100% seva Wistar. Pri sevu Wistar smo našli 184 tumorjev, od tega 133 adenomov, 50 tubulnih adenokarcinomov in 1 pečatnocelični karcinom; 77% karcinomov smo našli v kolorektumu, 23% pa v tankem črevesu. Pri sevu Fischer smo našli 126 tumorjev, od tega 94 adenomov, 26 tubulnih adenokarcinomov, 5 pečatnoceličnih karcinomov in 1 mucinozni karcinom. V tankem črevesu smo našli 58% karcinomov, 42% pa v kolorektumu. Zunajčrevesnih tumorjev nismo našli pri nobenem sevu. Razlika med sevoma v pojavnosti vseh črevesnih tumorjev je bila statistično značilna ($P=0,001$). Značilni sta bili tudi razliki v pojavnosti malignih ($P<0,001$) in benignih ($P=0,011$) tumorjev.

Zaključki. Pri živalih seva Wistar smo ugotovili statistično značilno večjo pojavnost tumorjev debelega črevesa. Tudi razporeditev tumorjev v debelem črevesu pri sevu Wistar je bila bolj podobna razporeditvi pri človeku. Zato se nam zdi sev Wistar primernejši kot sev Fischer za eksperimentalni model za študije tumorjev debelega črevesa.

Radiol Oncol 2004; 38(3): 235-40.

Večlistni kolimator v radioterapiji

Jeraj M, Robar V

Izhodišča. Osnovni namen obsevalnega zdravljenja je obsevanje tarčnega volumna s predpisanim odmerkom in hkrati čim nižjim odmerkom v okolnem zdravem tkivu in kritičnih organih. To dosežemo s primernim oblikovanjem polja.
Za oblikovanje pravokotnih obsevalnih polj uporabljamo standardne kolimatorske čeljusti. Volumen, ki ga želimo obsevati, običajno ni pravokotne oblike, zato moramo polje dodatno oblikovati. Pri obsevanju z linearnim pospeševalnikom polja dodatno oblikujemo s svinčenimi bloki ali z individualnimi zaščitami iz zlitine Cerrobendô, ki jih pritrdimo na pladenj pod obsevalno glavo. Novejša možnost za oblikovanje polja je uporaba večlistnega kolimatorja.
Zaključki. Večlistni kolimator danes postopoma nadomešča starejše načine oblikovanja polja, saj se je izkazal kot enostavno orodje tako pri pripravi kot pri samem obsevanju. Večlistni kolimatorji so dovolj zanesljivi, saj so proizvajalci na različne načine zagotovili njihovo natančnost in nadzor ter zmanjšali preveliko puščanje med listi in skozi posamezne liste. Večlistni kolimatorji se uporabljajo za enostavno oblikovanje polja, še bolj pa so uporabni pri dinamičnih terapijah, kjer se listi večlistnega kolimatorja premikajo med obsevanjem. Na ta način lahko odmerek sevanja prilagodimo obliki področja, ki ga želimo obsevati. Na dinamičnem obsevanju z večlistnim kolimatorjem temelji intenzitetno modulirana radioterapija (IMRT) kot obsevalno zdravljenje prihodnosti.

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.*

Radiobiology

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

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

Lung cancer

September 23-25, 2004

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

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

Radiation therapy

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ASTRO Annual meeting will be held in Atlanta, USA.

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Radiation oncology

November 7-12, 2004

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

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Radiation oncology

November 25-28, 2004

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

See http://www.isro.be

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Radiation oncology

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See http://www.isro.be

Lung cancer

July 3-6, 2005

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

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Radiation oncology

September - October, 2005

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

See http://www.isro.be

Oncology

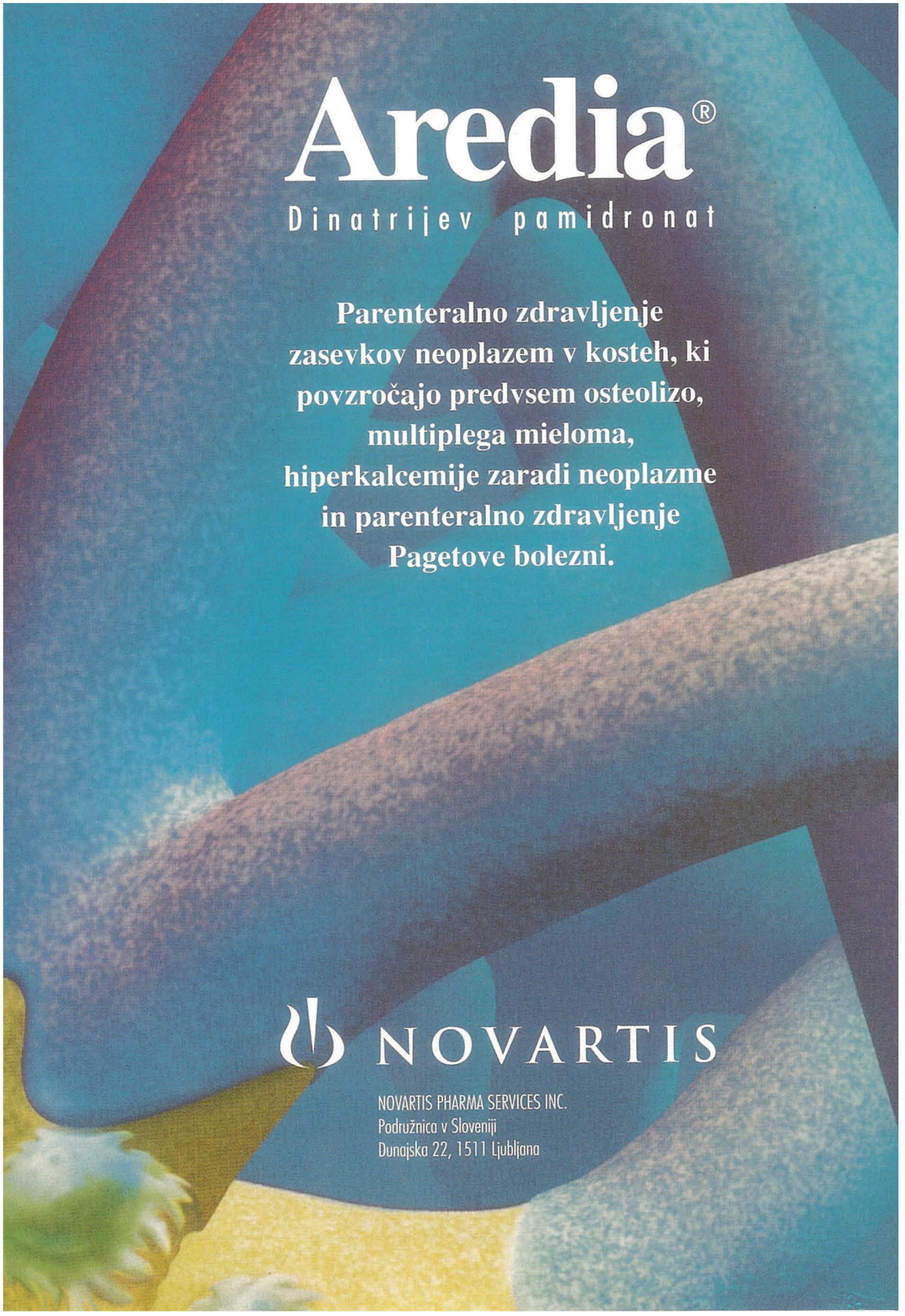
October 30 – November 3, 2005

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

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

As a service to our readers, notices of meetings or courses will be inserted free of charge.

Please send information to the Editorial office, Radiology and Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia.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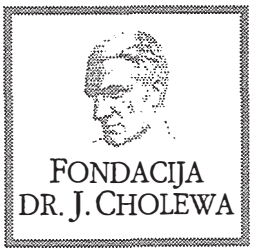

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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education - A Report for the Third Quarter of 2004

The Dr. J. Cholewa Foundation for Cancer Research and Education has conitinued to support various activities associated with cancer research and education in Slovenia throughout the period up to the last quarter of 2004. Several study and research grants were bestowed to researchers from various scientific fields associated with oncology in Slovenia. It is worth mentioning that many of them were also given grants and means to attend scientific meetings, congresses, conferences and symposia dealing with oncology worldwide. However, a decision has been taken not to support passive participation on such events in the future. The Foundation will also continue to support the regular publication of "Radiology and Oncology" international scientific journal, which is edited, published and printed in Ljubljana, Slovenia, as it has done over the last years.

It was decided at the meetings of the Supervisory and Executive Boards of the Foundation that it will start to support the organisation of the ďIn memoriam dr. Dušana RejeĒ seminars. These seminars are to be organised by the Slovenian Cancer Association on an annual basis and will represent another possibility of spreading up to date knowledge in oncology to interested experts and other individuals.

Although it remains the fact that various public and privately owned enterprises find it more and more difficult to contribute financially to help running day to day operations of the Foundation and its many scopes of activity, several new initiatives and suggestions were discussed and evaluated during the recent meetings of the Foundation. It is important to note that the KRKA Pharmaceutical Company from Novo Mesto, Slovenia, remains steadfast in its support for the Dr. J. Cholewa Foundation for Cancer Research and Education and its activities.

Andrej Plesničar, MD
Tomaž Benulič, MD
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Datum priprave besedila: marec 2003

Podrobnejše informacije so na voljo pri proizvajalcu.

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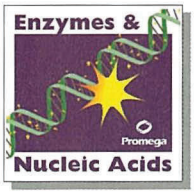

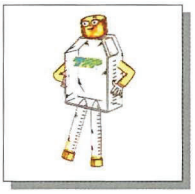

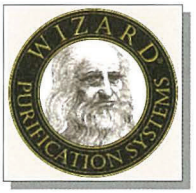

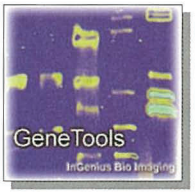

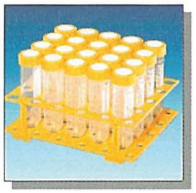

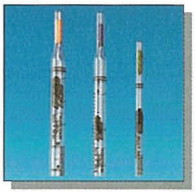

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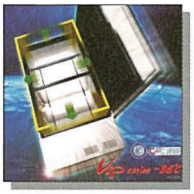

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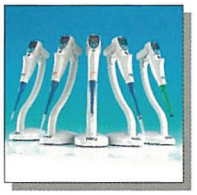

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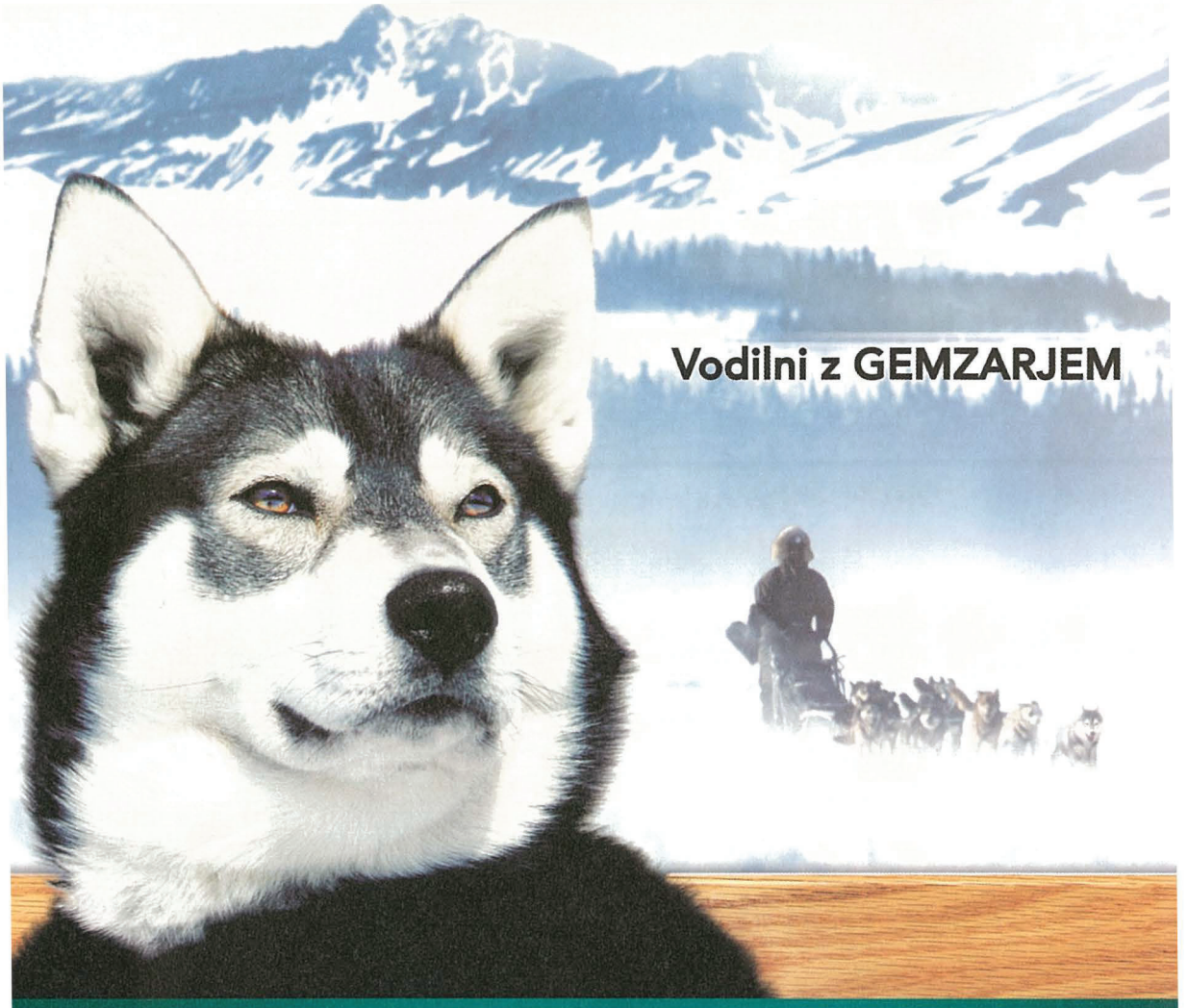
Odmerjanje in način uporabe: Rak dojk in rak jajčnikov: 50 mg/m2 i.v. 1x na vsake 4 tedne. Kaposijev sarkom: 20 mg/m2 i.v. na vsaka dva do tri tedne. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero od pomožnih snovi; dojenje **Posebna opozorila in previdnostni ukrepi:** Pri vseh bolnikih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



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Results should be presented clearly and concisely without repeating the data in the tables and figures. Emphasis should be on clear and precise presentation of results and their significance in relation to the aim of the investigation.

Discussion should explain the results rather than simply repeating them and interpret their significance and draw conclusions. It should review the results of the study in the light of previously published work.

Illustrations and tables must be numbered and referred to in the text, with appropriate location indicated in the text margin. Illustrations must be labelled on the back with the author's name, figure number and orientation, and should be accompanied by a descriptive legend on a separate page. Line drawings should be supplied in a form suitable for high-quality reproduction. Photographs should be glossy prints of high quality with as much contrast as the subject allows. They should be cropped as close as possible to the area of interest. In photographs mask the identities of the patients. Tables should be typed double spaced, with descriptive title and, if appropriate, units of numerical measurements included in column heading.

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Dent RAG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.

Chapman S, Nakielny R. *A guide to radiological procedures.* London: Bailliere Tindall; 1986.

Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

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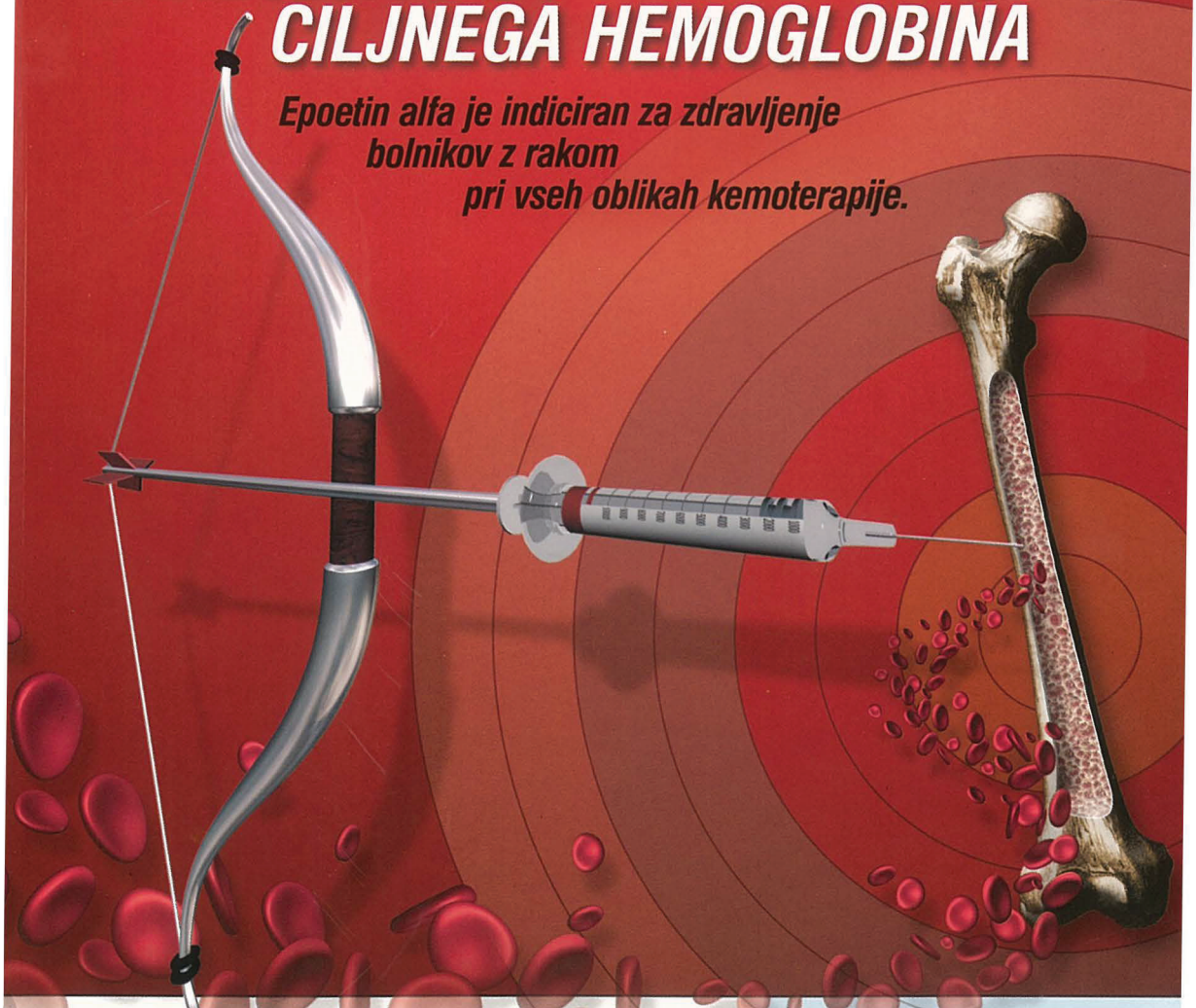
Epoetin alfa je indiciran za zdravljenje bolnikov z rakom pri vseh oblikah kemoterapije.



Sestava: epoetin alfa: 1000 i.e./ 0,5ml, 2000 i.e./0,5 ml, 3000 i.e./0,3 ml, 4000 i.e./0,4 ml, 5000 i.e./0,5 ml, 6000 i.e./0,6 ml, 7000 i.e./0,7 ml, 8000 i.e./0,8 ml, 9000 i.e./0,9 ml, 10.000 i.e./1,0 ml. Pomožne snovi: natrijev dihidrogenfosfat dihidrat, dinatrijev hidrogenfosfat dihidrat, natrijev klorid, polisorbat 80, glicin in voda za injekcije. **Terapevtske indikacije:** Zdravljenje anemije in zmanjšanje potreb po transfuziji pri odraslih bolnikih, pri katerih s kemoterapijo zdravimo solidne tumorje, maligni limfom ali multipli mielom in pri tveganju za transfuzijo, ki ga ocenimo glede na bolnikovo splošno zdravstveno stanje. Zdravljenje anemije, posledice kron. odpovedi ledvic pri otrocih in odraslih zdravljenih s hemodializo in odraslih zdravljenih s peritonealno dializo. Zdravljenje hude anemije zaradi bolezni ledvic pri bolnikih, ki še niso na dializi. Povečanje proizvodnje avtologne krvi pri bolnikih v programu samoobdarovanja krvi pred operacijo. Zmanjšanje izpostavljenosti alogenim transfuzijam krvi pred večjimi elektivnimi ortopedskimi kirurškimi posegi. **Kontraindikacije:** Nenadzorovana arterijska hipertenzija, preobčutljivost za katero od sestavin zdravila, ter bolniki, ki ne morejo dobiti ustrezne antitrombinske profilakse. Subkutano injiciranje zdravila je kontraindicirano samo pri bolnikih s kron. ledvično odpovedjo. Pri bolnikih, pri katerih se po zdravljenju z epoetinom razvije čista aplazija rdečih krvnih celic ustaviti zdravljenje z Eprexom ali drugim epoetinom. Pri bolnikih v programu avtolognega zbiranja krvi upoštevati vse kontraindikacije povezane s programom za kasnejše avtotransfuzije. Zdravilo je kontraindicirano pri bolnikih pred večjim elektivnim kirurškim posegom s koronarno, cerebrovaskularno, karotidno ali periferno arterijsko boleznijo ali nedavnim miokardnim infarktom ali cerebrovaskulamim dogodkom. **Posebna opozorila in previdnostni ukrepi:** Potrebno je skrbno spremljati in po potrebi nadzorovati krvni tlak. Previdna uporaba epoetina alfa je potrebna pri nezdravljeni, neustrezno zdravljeni ali slabo nadzorovani hipertenziji. Pri bolnikih, zdravljenih z epoetinom alfa, je treba redno meriti koncentracije hemoglobina, dokler ni dosežena stabilna vrednost, zatem pa se meritve opravljajo periodično. Epoetin alfa je treba previdno uporabljati tudi pri bolnikih z epilepsijo in kronično odpovedjo jeter. V posameznih primerih se lahko pojavi hiperkaliemija. Med zdravljenjem z epoetinom alfa se lahko pojavi zmerno, prehodno, od odmerkov odvisno povečanje števila trombocitov. Preučiti je treba še druge vzroke anemije in jih zdraviti pred začetkom zdravljenja z epoetinom alfa. Zagotoviti je treba ustrezne zaloge železa. Pri ocenjevanju primernosti zdravljenja z epoetinom alfa (bolniki, ki jim grozi transfuzija), je treba upoštevati 2-3-tedenski zamik med dajanjem eritropoetina ter tvorbo rdečih krvnic, ki jo izzove eritropoetin. **Interakcije z drugimi zdravili:** O vplivu zdravljenja z epoetinom alfa na metabolizem drugih zdravil ni dokazov. Ker pa se ciklosporin veže na rdeče krvne celice, je možna interakcija med njim in zdravilom. **Odmerjanje in način uporabe:** Pr odraslih bolnikih z rakom (npr. Hb 105 g/l), ki prejemajo kemoterapijo je uporabimo subkutani način dajanja. Začetni odmerek je 150 i.e./kg subkutano, trikrat na teden. Če vrednost Hb naraste za najmanj 10 g/l, ali se število retikulocitov poveča za 40,000 celic/ l nad osnovno vrednost po 4 tednih zdravljenja, se naj še naprej uporablja odmerek 150 i.e./kg. Če je zvečanje Hb < 10 g/l in je število retikulocitov naraslo za <40.000 celic/ l nad osnovno vrednost, zvečajte odmerek na 300 i.e./kg. Če je po dodatnih 4 tednih zdravljenja s 300 i.e./kg, vrednost Hb narasla na 10 g/l, ali se je število retikulocitov zvečalo na 40,000 celic/ l, naj ostane odmerek 300 i.e./kg. Če se je vrednost Hb zvečala za <10 g/l, število retikulocitov pa je naraslo <40.000celic/ l nad osnovno vrednost, odziv ni verjeten in je treba zdravljenje prekiniti. **Neželeni učinki:** Nespecifični kožni izpuščaji, "gripi podobni" simptomi (glavobol, bolečine v sklepih, slabost, vrtoglavica, utrujenost), trombocitoza (zelo redko), hipertenzija. **Posebna navodila za shranjevanje:** Shranjujte zaščiteno pred svetlobo, pri temperatur od 2° do 8°C. Zdravila ne zamrzujte ali stresajte. **Način izdajanja zdravila:** H/Rp.

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Podrobnejše informacije in navodila o predpisovanju so vam na voljo pri:
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