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PENACTAM®

injekcije im./iv., tablete, prašek za pripravo suspenzije

antibiotik širokega spektra –
rešitev problema bakterijske rezistence

- ampicilin, zaščiten s sulbaktamom – zato odporen proti delovanju beta laktamaz
- razširja antibakterijsko delovanje ampicilina na po Gramu pozitivne bakterije, ki izločajo penicilinazo, na po Gramu negativne in anaerobne bakterije, vključno Bacteroides fragilis, ter tako povečuje klinično uporabnost in učinkovitost ampicilina
- visoko učinkovit v ambulantnem in bolnišničnem zdravljenju infekcij zgornjih in spodnjih dihal, sečil, rodil, kože ter mehkih tkiv
- možnost oralne in parenteralne uporabe
- izključuje potrebo po kombiniranem zdravljenju
- učinkovito preprečuje pooperativne infekcije
- dobro prenašanje

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Correspondence address
Radiology and Oncology
Institute of Oncology
Vrazov trg 4
61000 Ljubljana
Slovenia

Phone: +38 61 120 068
Fax: +38 61 114 180

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Olga Shrestha

Design
Monika Fink-Serša

Key words und UDC
Eva Klemenčič

Secretaries
Milica Harisch
Betka Savski

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Pneumoperitoneum of the lesser sac following gastric and duodenal surgery

Ivan Lovasić, Milivoj Dujmović, Miljenko Uravić, Lidija Dimitrovski

Clinical Hospital Center Rijeka, Clinical Department of Radiology, Surgery Clinic, Croatia

Reports on inflammatory effusions in the lesser sac of various causes, and very heterogeneous, sometimes inadequate terminology, are well-known in literature. But, we have not found descriptions of pneumoperitoneum of the lesser sac following gastric and duodenal surgery. Five patients with localized effusion in the lesser sac with fluid level and an air vesicle above it, found 8 to 15 days postoperatively, are reported. The patients claimed no discomfort and the finding spontaneously disappeared up to the fourth week following surgery.

Key words: stomach-surgery; duodenum-surgery; pneumoperitoneum, radiology

Introduction

"Bursitis omentalis" implies the inflammatory effusion in the lesser sac or fluid content collection of other genesis. Gas content is usually present together with the fluid giving characteristic radiological feature. Fluid level with an air bubble above it, localized behind the stomach, has been the typical finding. In case of effusion without the presence of gas content, radiological feature is characterized by round shadow intensity of soft particles between the lesser curvature of the stomach, liver and diaphragm. Inflammatory diseases of the pancreas, perforation or penetration of gastric and duodenal ulcus and the diseases of other adjacent organs surrounding the lesser sac (liver, transverse colon and small intestine) have been prevailing features in the aetiology. With regard to such dissimilar aetiology, various terms are found in literature concerning this state (bursitis omentalis, pneumoperitoneum of the lesser sac, empyema of the lesser sac, lesser sac abscess, even pancreatic pseudocyst).[1, 2, 3]

We have found only one detailed report in the literature presenting localized lesser sac effusion as an unspecific complication following gastric and duodenal surgery, without proved dehiscence of the surgical suture and without signs of the adjacent organ involvement.[4]

The purpose of this study was to point out this radiological entity, a thorough understanding of which could be of great significance for differential diagnosis in postoperative complications at the lesser sac area.

Correspondence to: Prof. dr. sci. Lovasić Ivan, Klinički bolnički centar Rijeka, Klinički zavod za radiologiju, 51000 Rijeka, Tome Strižića 3, Croatia.

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Patients and methods

A smaller series of cases with the lesser sac effusions following gastric and duodenal surgery, verified in a long-term period, have been reported. Checkups covered all the patients within 8 to 15 days postoperatively because of undefined discomfort and the surgical intervention itself.

All of them underwent upright abodominal X-ray and classical radiological barium-enema examination.

Results

The first case represents a patient after Billroth I surgery. Upright abdominal X-ray showed a large fluid level with an air containing bubble beneath the left and right dome of the diaphragm on the fourth day postoperatively (Figure 1a). Control checkup on the eighth day following surgery showed a great hypotonic gastric pouch full of secretion, with aggravated emptying (Figure 1b). A small, well tonicized gastric pouch with regular emptying, but still containing lesser sac fluid level was revealed on the fifteenth postoperative day (Figure 1c).

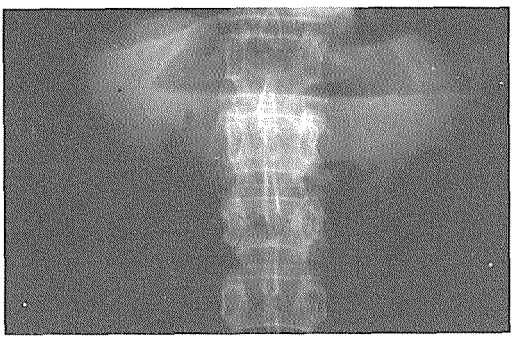

Figure 1a. A large fluid level with air collection beneath the diaphragm on the fourth day postoperatively.

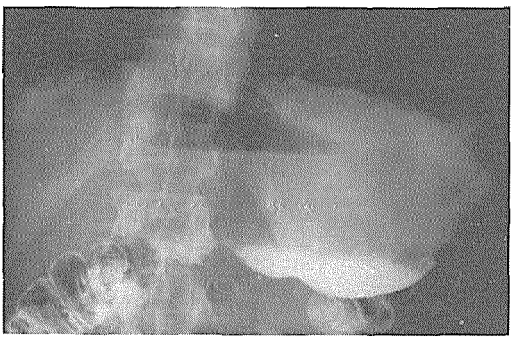

Figure 1b. The same patient 8 days after surgery. Large atonic gastric pouch (Billroth I) and the fluid level in the lesser sac.

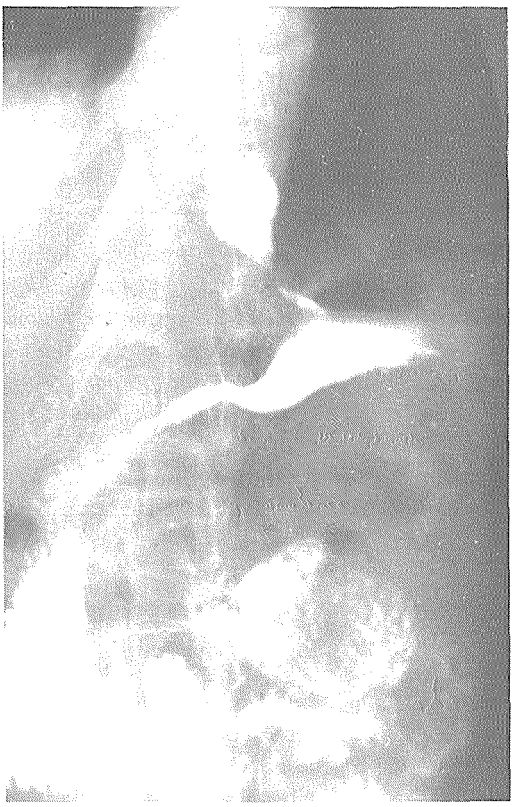

Figure 1c. The same patient 15 days postoperatively. A small well tonicized gastric pouch with regular emptying. Very low fluid level in the lesser sac.

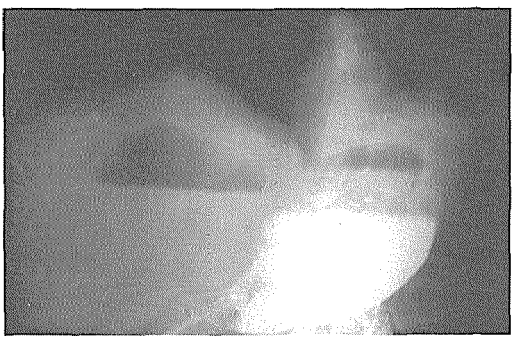

Figure 2. Billroth I operated patient. Effusion in the vestibular area of the lesser sac.

Figure 3. A large effusion in the lesser sac following gastric Billroth II surgery.

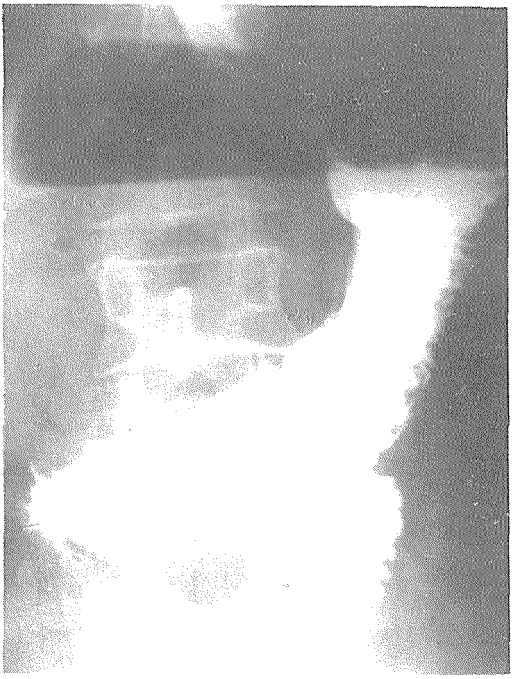

Figure 4. Typical effusion feature in the lesser sac following vagotomy and pyloroplasty (see. Finney).

The second case is a patient after Billroth I surgery, with visible effusion in the vestibular area of the lesser sac (Figure 2).

The third case shows a typical large postoperative effusion in the lesser sac following Billroth II gastric surgery, with normal appearance of the gastric pouch and stoma on the twelfth day postoperatively (Figure 3).

The fourth and the fifth patients underwent vagus- and pylorus-surgery. Routine checkup on the eighth postoperative day verified the lesser sac effusion associated with typical gastric and duodenal appearance and regular emptying (Figure 4, 5).

The reported patients were not operated on urgently because of perforation. None of the examined patients experienced any particular postoperative discomfort. No signs of dehiscence within the surgical area were found. All the verified effusions in the lesser sac were treated conservatively and disappeared in the course of one month postoperatively.

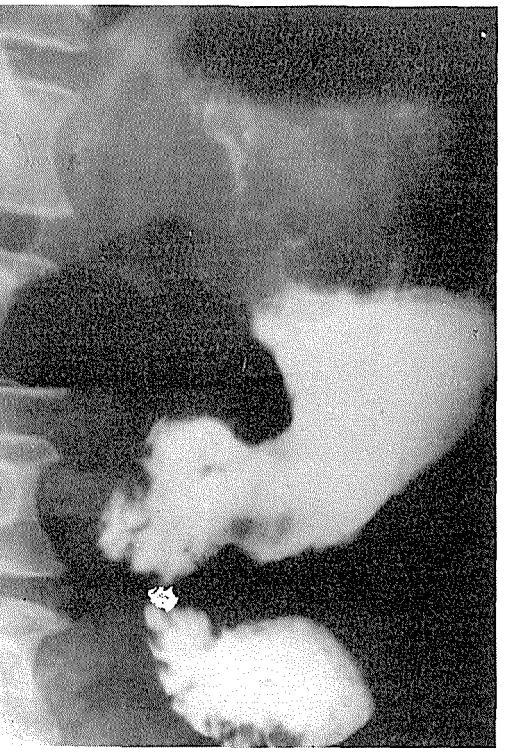

Figure 5. Typical effusion feature in the lesser sac following vagotomy and pyloroplasty (see. Finney).

Discussion

It is surprising that reports on localized effusion in the lesser sac following gastric and duodenal surgery without proved dehiscence of the surgical suture and without special clinical symptoms are so rare. We consider this state to be more frequent than it has been generally believed. The lesser sac effusion of other genesis has been reported far more often. Pancreatitis with a formed pseudocyst or without it, perforation of gastric and duodenal ulcers, traumatic perforation of the small and large intestines and liver abscess take the first place.[1, 2, 3]

Causes for this state can be of various nature. With regard to the course, the surgical traumatism of the adjacent structures and pneumoperitoneum of the same origin as of subphrenic localization, presumably take the first place. Taking into consideration these emergency causes, the term pneumoperitoneum of the lesser sac seems the most appropriate.

Localized effusion in the lesser sac following gastric and duodenal surgery need not be taken as an alarming state unless leaking of contrast medium at the site of the operative suture has been proved. Radiological follow up is necessary till the complete disappearance of effusion one to two months postoperatively. Recognition of this state as well as of other possible simultaneous postoperative complications is of significance, in order not to overemphasize its importance, with respect to differential diagnosis.

Together with characteristic symptoms described, which clearly define this particular radiological entity, and with proper understanding of syntopy in the region of the lesser sac, diagnosis and differential diagnosis are not hard to obtain.

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Aseptic hip necrosis: Early ultrasound diagnosis

Mladen Babić, Slavko Kozić, Damir Matovinović

Specialized Clinical Orthopaedic Hospital, Lovran, Croatia

In its early phase aseptic hip necrosis in adults represents a diagnostic problem. Among other well established diagnostic methods we use ultrasound, a method that already has considerable importance in the diganosis of locomotor system diseases. We began to use ultrasound in the diagnosis of adult aseptic hip necrosis seven years ago, and up to now 51 patients have been examined, their age ranging between 35–55 years. The comparison groups consisted of 30 patients with normal hips and 30 patients with degenerative changes in the hips. The patients were examined on Aloka SSD 500 machine with 3.5 MHz and 5 MHz linear probes. Our own method of examination was introduced. Ultrasound examination findings were compared with findings obtained by other diagnostic methods such as scintigraphy, CT and tomography. In some cases, changes on femur heads were sonographically determined earlier than with other diagnostic methods.

Key words: femur head necrosis-ultrasongraphy

Introduction

Diagnosis of adult aseptic hip necrosis is mostly based on X-ray methods that offer an insight into the degree of necrosis, site of necrosis and surface of affected area. However, X-ray findings are negative in the early phase of the disease in which clinical findings such as pain, limping and reduced hip motions are dominant.

For early diagnosis of this disease other methods may be used, e.g. tomography, scintigraphy, CT and MRI. Since some of these methods have not been available routinely, we were forced to search for new methods of imaging.[1, 2, 3]

Correspondence to: Mladen Babić, MD, DSc, Specialized Clinical Orthopaedic Hospital Lovran, Croatia.

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Ultrasound plays an important role in many clinical fields, including orthopaedics. New ultrasonic machines offer diagnostic possibilities which could not be imagined just a few years ago. Today, soft tissue changes as well as joint diseases are routinely diagnosed, especially in children. Periarticular and intraarticular pathologic changes are also accessible to ultrasonic diagnosis. Intraosseous changes were inaccessible to ultrasound owing to bone acoustic impedance, but with the development of ultrasonic technology it might be possible to overcome this obstacle.[6, 7] Having certain experience in bone tumour ultrasound diagnostics, we speculated about the possibility to visualise by ultrasound pathological changes on the femur head in the early phase of aseptic hip necrosis.[8, 9] In the beginning we studied only the cases with X-ray findings of aseptic hip necrosis. Afterward, we have started to visualise changes

invisible by X-rays in the cases with suspected aseptic hip necrosis.

Materials and methods

In the period from 1985 to 1992, 51 patients with pain in the hip region were examined by ultrasound. The patients included in this study had a painful hip, reduced hip motions and evident or suspected X-ray changes in the acetabulum or femur head. The aim was to visualize changes characteristic for aseptic necrosis. Their age ranged between 35–55 years; there were 29 males and 22 females. The control group comprised 30 healthy persons 20–40 years of age, without a history of pain in the hip, with normal hip motions, and 30 patients with clinical symptoms and X-ray findings of degenerative hip changes (coxarthrosis), in the age of 50–65 years.

There are no data on this problem available in the existing literature. Therefore, we have devised our own method of ultrasonic diagnosis and assessment of the obtained results. An adult hip can be examined only under standardised terms, and femur head should be completely visualised by ultrasound.[10, 11]

We have used Aloka SSD 500 machine with 3.5 MHz and 5 MHz linear probes, and measurements were performed using computer callipers.

The aim of our preliminary work was to establish normal ultrasonic relations in the region of adult hip joints, which differ greatly in comparison with neonatal and infant hips. We have established standards of examinations, since such standards do not exist in the literature, and we have developed our own examination methodology. It is mandatory to investigate the hip in multiple tomographic slices, which is schematically presented in Figure 1. The supine position tenders the anterior and superior part of the femur head and acetabulum accessible to investigation. The probe is positioned in the horizontal plane (Figure 1b), and slowly moved craniocaudally. Afterwards, the probe is turned in vertical plane to locate the great trochanter, and moved lateromedially. In this position the probe should be oriented in the semioblique position, in the direction of the inguinum (Figure 1d). After that, the patient should lie in decubitus position with support of the knees. The leg is thus in the horizontal plane. In this position the hip is examined in horizontal and vertical plane (Figure 1a). In this way, the upper and lateral joint sections as well as the great trochanter can be examined. The examination is completed in prone position (Figure 1c), also in horizontal and vertical planes, which provides an insight into the posterior joint section.

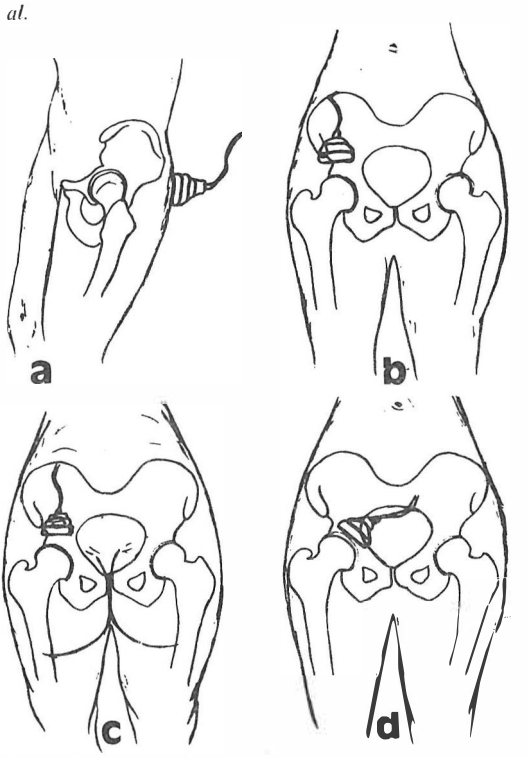

Figure 1. Scheme of standard approaches to adult hip joint means of ultrasound probe (A-probe in the vertical plane, lateral to the hip joint; B-probe in the horizontal plane, anterior to the hip joint; C-probe in the horizontal plane, posterior to the hip joint; D-probe in the semioblique planeinguinum-anterior to the joint).

Results

In healthy individuals, only the narrow bony acetabular part, adjacent to the cartilage, can be visualised. In contact with ultrasonic beam, the superficial segment is imaged on the screen as a semilunar hyperechogenic line. Identically,

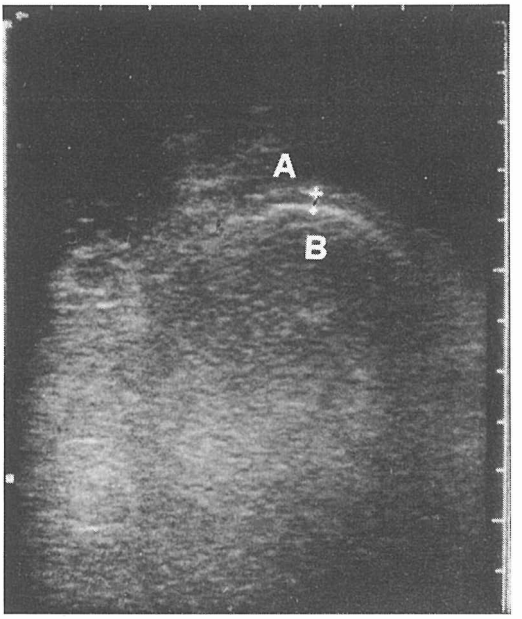

Figure 2. Normal ultrasound finding of adult hip joint. Part of the acetabulum and femur head are shown as two semilunar, hyperechogenic areas (A and B).

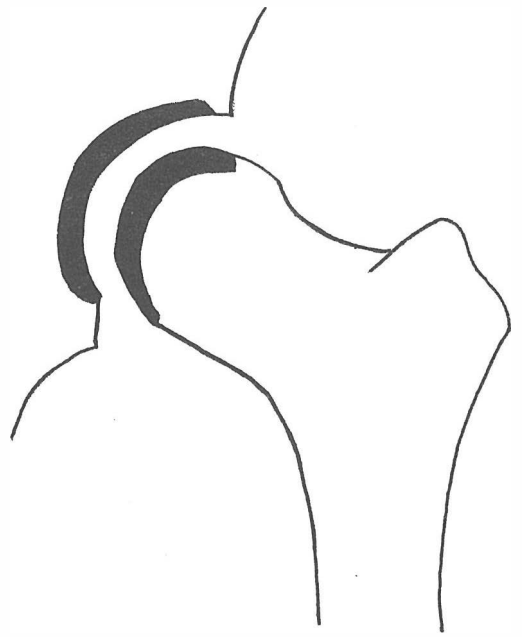

Figure 2a. Scheme of ultrasound finding of normal hip joint. The underlined parts are those visualised sonographically.

only superficial, intracartilaginous bony part of the femur head can be visualised as a hyperechogenic semilunar line (Figure 2, 2a). It is seldom possible to visualize the whole femur head, imaged as a homogeneous hypoechogenic spherical zone below the hyperechogenic line.

When the patient is in supine position, and the probe in the vertical plane, the great and lesser trochanter can be visualised.

In patients with coxarthrosis, a thin hyperechogenic line visible in healthy persons is considerably wider and inhomogeneous, and hyperechogenicity is slowly replaced with normoechogenic area representing non-affected part of the femur head.

The space between the acetabulum and femur head, measured sonographically, is 2–3 mm in healthy subjects.

After having obtained standard images and gained certain experience with healthy hip and coxarthrotic hip examining, we started to carry out the investigations in adults with clear aseptic hip necrosis. These findings were considerably different in comparison with healthy and coxarthrotic hips. In aseptic hip necrosis, the hyperechogenic line is clearly delineated; disrupted and inhomogeneous hyperechogenic zone can be visualised inside the femur head, representing alterations of bony structure in the femur head (Figure 3, 3a, 4, 4b). It is mandatory to examine both hips, and to measure the width of the hyperechogenic zone since it represents the area of aseptic necrosis. It is also necessary to measure the joint fissure width for an indirect assessment of the cartilage condition and eventual existence of intraarticular effusion.

In addition to ultrasound examination, all patients have been examined by other available imaging methods; scintigraphy, X-ray tomography, and in some cases also CT scan.

There were 51 patients examined, and in 29 of them aseptic hip necrosis was confirmed in the course of diagnostic procedure. Aseptic hip necrosis was established by ultrasound in 21 patients. In 16 patients with pain in the hip the findings were negative, and the disease was confirmed using other imaging methods, as well as by clinical follow up. In 8 patients false-ne-

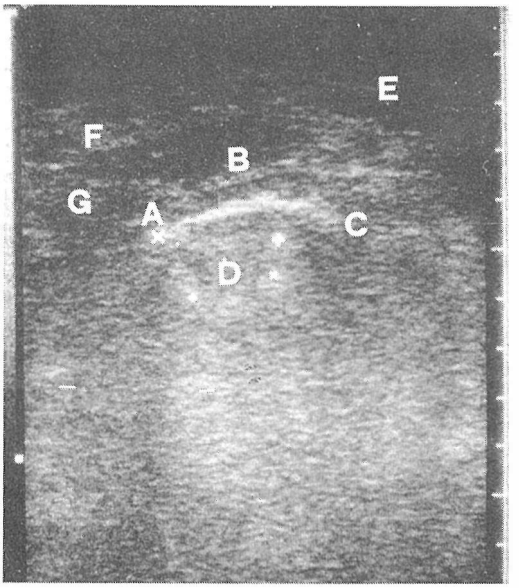

Figure 3. Aseptic hip necrosis in adult-ultrasonic finding. Just beneath the semilunar hyperechogenic zone there is a rhomboid zone of increased echogenicity corresponding to early aseptic necrosis of the hip. A-disrupted continuity of semilunar hyperechogenic zone. B-acetabulum, C-healthy part of the femur head, D-aseptic necrosis zone, E-skin, F-subcutaneous tissue, G-muscle.

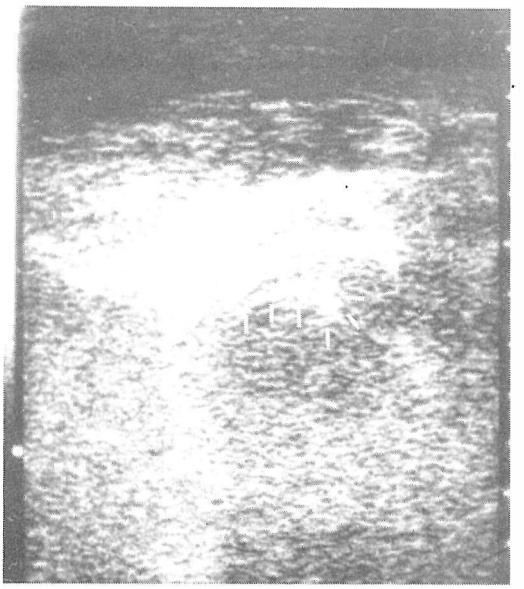

Figure 4. Aseptic hip necrosis in adult – ultrasonic finding.

Figure 3a. Scheme of ultrasonic finding of aceptic hip necrosis. The underlined parts are those visualised sonographically.

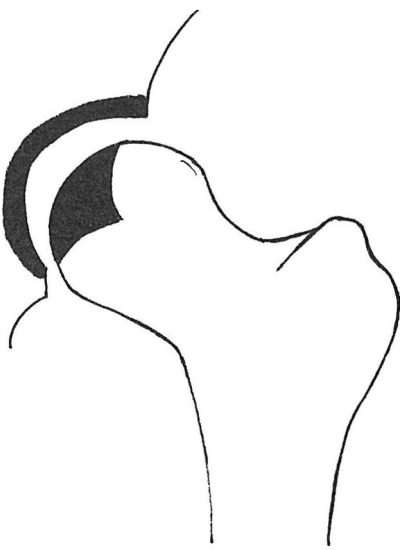

Figure 4a. Scheme of ultrasonic finding of aseptic hip necrosis. The underlined parts are those visualised sonographically.

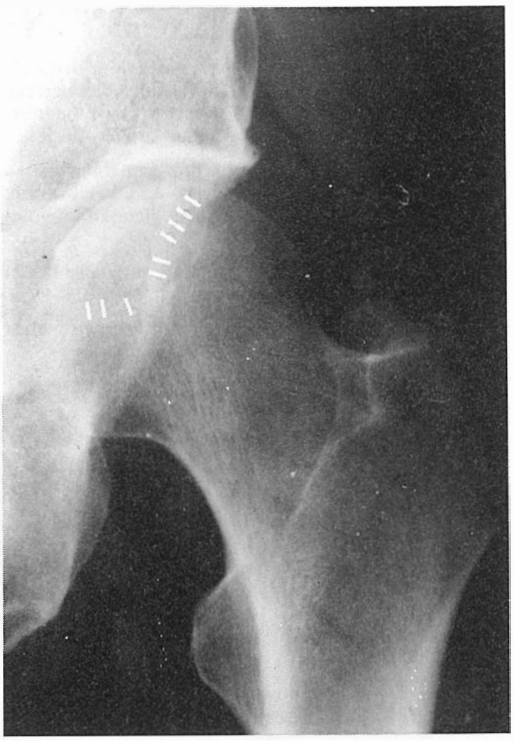

Figure 4b. X-ray finding in the same patient.

gative findings were obtained. False-negative findings occurred mainly in the beginning of our study as we lacked experience; 6 false positive findings were also obtained primarily during the first years of our investigations.

Discussion

So far, etiology of aseptic hip necrosis has not been completely explained. Various pathological conditions, having nothing in common with each other, can cause aseptic hip necrosis. It is usually a consequence of a hip trauma, circulatory disorders in the femur head, as well as of metabolic diseases.[12] It is not seldom found in collagen-disorders, endocrinological disturbances, degenerative diseases and alcoholism. Rarely it can be found in septic infections and venereal diseases. Aseptic hip necrosis in infancy (Perthes' disease) has different features and age of onset.

In its early stage, aseptic hip necrosis represents a substantial diagnostic problem. Classical X-ray diagnosis being insufficient at this stage, we have tried to improve the diagnostic procedure by ultrasound imaging.

In the period of 7 years we have been using probes of 3.5 MHz and 5 MHz. We believe that an 8–10 cm long 5 MHz linear probe is the most convenient. Using such a probe we could obtain a general insight into the analysed structures. While measuring bone structures, it should be kept in mind that ultrasound beam velocity in the bones is cca 25 % higher than soft tissue velocity. Hence, the values obtained in the bones are always somewhat lower than in reality. During the study, mathematical corrections were performed in order to obtain real values.[13, 14]

Altered bone structure due to aseptic necrosis enables us to visualize deeper bony structures of the hip, thus rendering pathological investigation of the altered structures relatively easy. In normal bone very limited quantity of information can be obtained by means of ultrasound,[8, 15] whereas ultrasonic beam in pathologically altered bone has different properties, which enables us to obtain more diagnostic information.[6] Alterations smaller than 1 cm cannot be visualised sonographically in bony structures with presently available ultrasonic machines.[11, 15]

Interventional ultrasonography provides an opportunity for femur head biopsy in certain patients with suspected pathological alterations of the femur head, thus improving the diagnostic procedure.

Ultrasound finding in a healthy person shows a semilunar hyperechogenic line, the feature observed due to properties of ultrasonic beam in junction with healthy bone structure.[7, 15] Conversely, in aseptic hip necrosis ultrasonic finding is much more prominent owing to a large visible hyperechogenic area.[7, 8] Alterations in the bone structure in the course of the disease enable ultrasonic beam penetration inside the bone itself, and the reflected beam provides a substantially bigger amount of information.[9]

A high proportion of false-positive and certain proportion of false-negative findings were recorded in the begining of our study, when we were inexperienced in this imaging method, resulting in the misinterpretation of ultrasonic image. Errors were primarily due to unrecognised phenomenon of reverberation in few cases, and due to misinterpetation of the superposition of shadowing caused by probe malpositioning.

Large degenerative alterations of the femur head with formation of cystic zones represent a significant diagnostic problem versus aseptic hip necrosis. Hyperechogenic area in the femur head is visible in degenerative alterations as well, and special care should be taken to delineate a sharp border between the necrotic bone tissue in aseptic necrosis and normal bone tissue. Hyperechogenic area in degenerative disease merges gradually with the normoechogenic area of normal bone. This is the only difference between the two conditions.

After performed sonographic examination and follow up of patients with aseptic hip necrosis in adults it is possible to draw the following conclusions:

– By means of ultrasound, aseptic necrosis can be diagnosed sooner than with classical diagnostic procedures;

– Examination is harmless and can be often repeated;

– Dynamic visualisation form different directions is possible;

– Ultrasound provides a considerable contribution to resolving these diagnostic problems, especially in an early stage of the disease.

– Ultrasonographically guided biopsy can be performed from specific sites and pathohistological diagnosis can be obtained.

Our observations contribute to broadening the applicability of ultrasound diagnostics.

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A comparative study of ultrasonography and computed tomography in orbital diseases

Miklós Barta, Péter Rácz,[1] Tamás Puskás, Ida Szépe, Judit Ferentzi,[1] Györgyi Munkácsi[1] and Antal Sáfrán[2]

Departments of Radiology, Ophthalmology[1] and Otorhinolaryngology[2], Markusovszky Hospital, Szombathely, Hungary

Examinations were performed in 121 patients suspect of orbital disease. The sensitivity of the echographic method was 2 mm for extraocular intraconal orbital processes. In the majority of endocrine orbitopathies ultrasound examination yields a sufficient amount of information to confirm the clinical diagnosis. CT examination is indispensable before surgery and radiotherapy, and when the disease is extraconal or destroys the orbital wall.

Key words: orbital diseases; ultrasonography; tomography, x-ray computed

Introduction

The diagnostic use of ultrasonography (US) and computed tomography (CT) of orbital disorders is dealt with by a large number of papers;[1-12] however, there are only hints concerning comparison of the two methods.

In this study we tried to establish the diagnostic value of an excellent though not specially ophthalmological US equipment in orbital diseases, and to compare the efficacy of US and CT. Results obtained by Doppler-sonography are not discussed here.

We found that an overwhelming majority of orbital processes can be diagnosed by the use of Picker LSC 7000 real-time equipment, especially if the pathological alteration is adjacent to the bulbus. All orbital disorders are clearly discernible by CT. Computed tomography is indispensable before surgery and radiotherapy.

Correspondence to: Barta Miklós M. D., Markusovszky Kórház, Radiológia, Szombathely, POBox 143, H-9701.

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Materials and methods

Between October 1, 1988 and July 31, 1991, 121 patients with a suspected orbital disorder were examined in Markusovszky Hospital. There were 59 US and 115 CT examinations carried out; in 26 cases both US and CT were done at the same time.

US examinations were performed by Picker LSC real-time equipment, using a 5 MHz linear array transducer and a Kitecko gel-cushion placed to the closed eyelids. The US diagnosis was further confirmed by CT (Somatom DRH-2 Siemens), clinical course and histology.

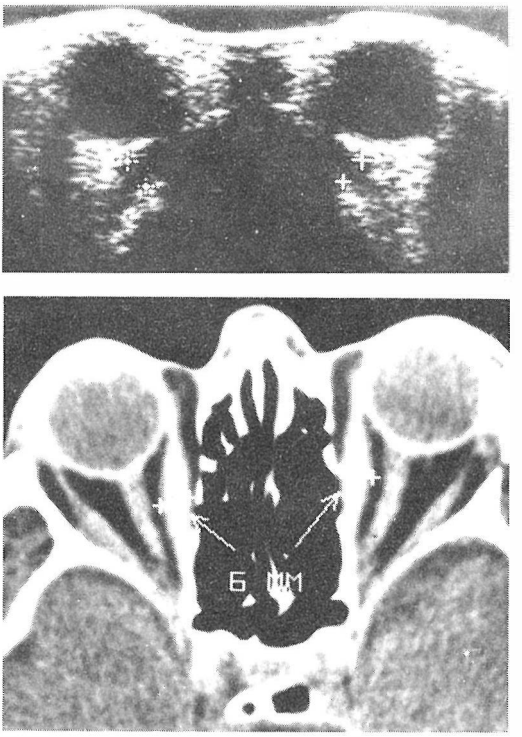


Figure 1. a) Transversal sonogram of the medial rectus muscle in a patient affected by endocrine orbitopathy. b) Axial CT of medial rectus muscle in the same patient. The same finding was obtained by both methods.

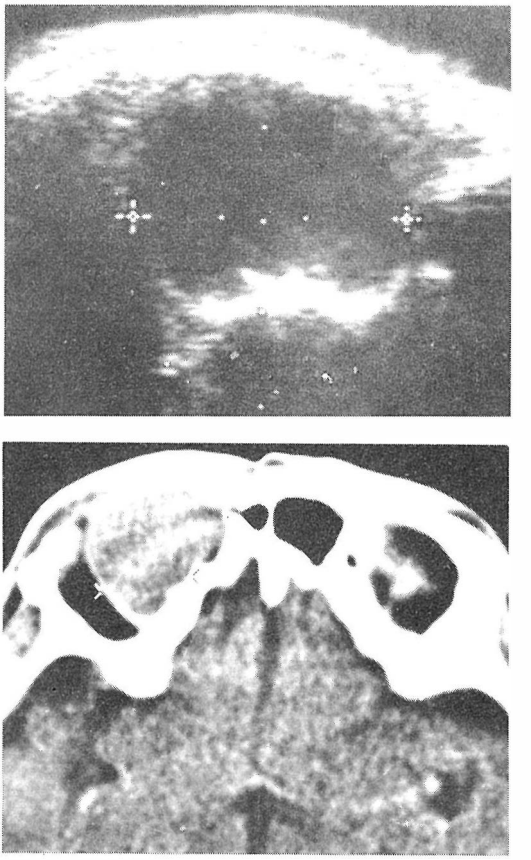


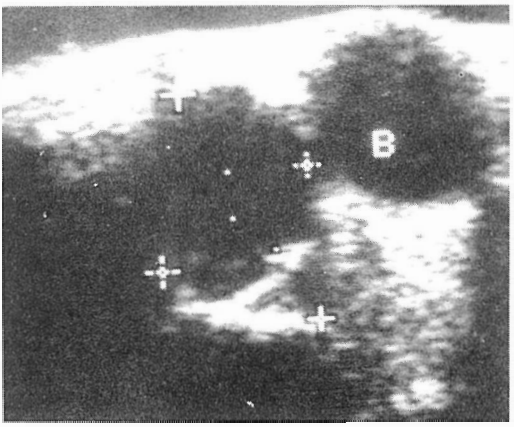
Figure 2. a) Tarnsversal sonogram: cystic lesion in the left orbit. b) Axial CT: the cystic lesion with mural enhancement (arrow→) can be seen on the left of the open frontal sinus.

Results

The evaluation of the method according to diagnosis is shown in Tables 1 and 2. Nine US and 16 CT examinations were repeated. The most frequent indications were endocrine orbitopathies and tumours (Figures 1–3). Endocrine orbitopathies can only be demonstrated by US if the medial rectus muscle is involved; all intraconal processes, however, are discernible by US. US has a restricted diagnostic value in extraconal disorders, their relationship to the osseous orbital wall could not at all, or only hardly, be established by the use of US. E.g., the neurofibromatosis of one of the patients could only be revealed by the positive result of the Valsalva-manoeuvre. In a false negative case an extraconal tumour (dermoid) was not detected by US. In another case enlargement of the lacrimal gland was detected but its exact nature could not be explained because no surgery was performed.

Discussion

For orbital examinations miniaturised 8–10 MHz transducers are used.[6, 10, 13] No sufficiently exact topographic information can be obtained by orbital US, mainly because of lack of imaging in the coronary plane. Its efficacy is limited in posterior processes or disorders adjacent to the osseous orbital wall. The anterior and mid third, however, can be sufficiently evaluated by sonography.[1, 6, 10, 13]



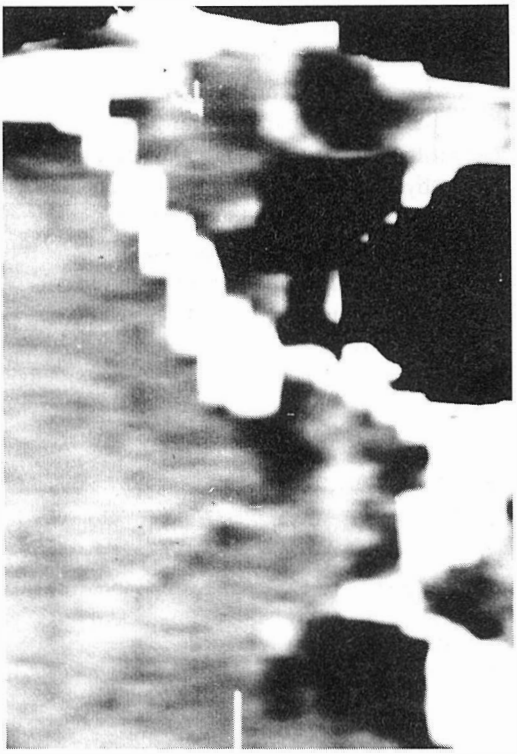


Figure 3. a) Sagittal sonogram: Cystic lesion with septal structure above the left eye. b) Sagittaly reconstructed CT scan: Cystic stenotic process in the left half of the frontal sinus (arrow→), propagating into the orbit. The eyeball is disclocated forward and downward. Diagnosis: Frontal sinus mucocele, verified by surgery.

Here we present the use of US and CT in the evaluation of orbital diseases.

Value of US in the diagnosis of orbital processes

The orbital processes discernible acoustically from their environment can be diagnosed by US.[1, 2, 6, 10, 13, 14] The advantage of the equipment used by us over that intended for special ophthalmological purposes is in its lower frequency securing better penetration and overview of the pathological alteration and its environment. On the other hand, the small transducer with higher frequency produces a more detailed picture. The apex cannot be examined by US, but no diseases with such localisation occurred in our material.

All intraconal processes could be detected. The use of US can be recommended in the diagnosis and follow-up as long as the medial rectus muscle is involved.[5, 15] This muscle is always discernible by our equipment and its width can be measured.

Table 1. Diagnoses based on orbital US and CT.

	US	CT	US and CT
Congenital disorders (neurofibramatosis and Paget's disease)	1	2	1
Inflammation (orbital phlegmone)	5	–	–
Endocrine orbitopathy	11	22	11
Tomours +	23	25	9
Injury + +	–	25	–
Unclarified (enlargement of the lacrimal gland)	1	1	1
Negative radiological finding	18	40	4

+: lymphoma (3), neurinoma (2), glioma (1), meningeoma (1), mucocele (1), dermoid (1), lipoma (3), haemangioma (1), metastatic neuroblastoma (2), retinoblastoma (4), anaplastic carcinoma (3), planocellular carcinoma (3).

+ +: blow-out fracture (8), other orbital fracture (13), orbital foreign body (2), traumatic exophthalmos (2).

+ + +: hyperthyroidism (4), protrusion (2), orbital injury (14), diplopia (3), papillar stasis (7), optic nerve atrophy (10).

The method has a restricted value in extraconal processes because of the shadow of the osseous orbital margin accompanying the use of a rather big linear transducer. In some cases, the infiltrative nature of the lesion can be shown by monitoring the situation during eye movement. Dehiscences of the orbital wall can be shown by the Valsalva manoeuvre. US follow-up may suffice in processes clarified earlier by other imaging or diagnostic methods. Previous US may be helpful in choosing correct CT-technique (e.g. in case of a negative sonogram the examiner must be prepared for viewing the skull as well).

The place of CT in the diagnosis of orbital disorders.

CT is an excellent tool in imaging the exact site and structure of orbital processes. Administration of a contrast medium is hardly necessary, its use may be helpful in intraorbital, intracranial and perisellar disorders. The exact relationship of the lesion to bone and environment can be clarified by CT. Orbital CT is indispensable before surgery and radiotherapy.

Table 2. US and CT findings obtained by parallel examinations.

	Number of patients	US		CT	
		positive	negative	positive	negative
Congenital disorder (neurofibramatosis)	1	1	–	1	–
Endocrine orbitopathy	8	6	5	11	–
Tumours +	9	8	1	9	–
Unclear (lacrimal gland enlargement)	1	1	–	1	–
Negative radiological finding + +	4	–	4	–	4

+ : lymphoma (NHL: 2,HL: 1), neurinoma (2), optic sheet glioma (1), mucocele (1), meningeoma (1), dermoid (1).
+ + : diplopia (4).

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Blunt splenic injuries: A sonographic contribution to indications for conservative or operative treatment

Damir Miletić,[1] Željko Fučkar,[2] Vladimir Mozetič,[3] Alan Šustić[4]

[1] Clinical Institute of Radiology, [2] Clinic for Surgery, [3] Ultrasound Diagnostic Unit, [4] Department of Anesthesiology, Clinical Hospital Center Rijeka, Croatia

In the presented 10 year period altogether 932 patients after blunt abdominal injury were examined, and 110 traumatic lesions of the spleen were sonographically diagnosed, from which 89 were directly visualized whereas in 21 patients only free abdominal fluid was present. We have sonographically detected 26 (29.3 % of directly visualized lesions) subcapsular splenic hematomas, 13 (14.6 %) shallow splenic lacerations, 20 (22.5 %) intraparenchymal hematomas and 30 (33.7 %) deep splenic ruptures. By means of ultrasound we have conservatively treated 88.5 % of subcapsular hematomas, 77 % of shallow spleenic lacerations, 80 % of intraparenchymal hematomas and none of deep splenic ruptures. Ultrasound showed reliable results with respect to sensitivity (97 %), specificity (100 %) and accuracy (99,7 %).

Key words: spleen-ultrasonography; wounds, nonpenetrating

Introduction

The spleen is a parenchymatous organ covered with very thin capsule which is sonographically invisible, but gives clear outline to the spleen. It is surrounded by the perisplenic and left subphrenic space which are, in normal conditions, only virtual peritoneal recesses.[1]

The traumatic rupture of the splenic capsule results in an intraperitoneal bleeding, particulary in the mentioned recesses. Due to interposed stomach air, left subphrenic collections cause diagnostic difficulties.[2] Intracapsular (primary) splenic rupture forms traumatic parenchymal lesion of the spleen with intact capsule. If untouched splenic capsule ruptures under the pressure of blood collection, more severe symptoms of bleeding appear.[3] Namely, when an intralienal blood collection erupts into the peritoneal cavity, a secondary bleeding from the lesion follows. A few hours or even 30 days may pass between the first, subcapsular, and the second, open bleeding. Because of a danger of the secondary splenic rupture, a patient with injury of this organ should be hospitalized at least for 3 weeks with permanent ultrasonographic control.

Splenic tissue have sonographically perfect homogeneity. It means that all reflections in the splenic parenchyma should be considered abnormal, except vascular reflections at the hilus level.[4, 5]

Correspondence to: Mr. sc. dr. Damir Miletić, Klinički zavod za radiologiju, Klinički bolnički centar Rijeka, Krešimirova 42, 51000 Rijeka, Croatia.

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The most frequent mechanism of blunt splenic injuries is deceleration. The spleen is often injured organ in blunt abdominal trauma.[6, 7, 8] Blunt splenic injuries are often concomitant with other abdominal or extraabdominal organ injuries and bone fractures. For example 20 % of injured patients with caudal rib fractures have concomitant rupture of the spleen.[9] Traumatic effect and rupture modality are connected with the perfusion status in the moment of trauma (hydrostatic intraparenchymal pressure increase).

Although sonographic appearance of a blunt splenic injury is well-known, the aim of this study was to determine the role of ultrasound in early indications for the conservative treatment of such injuries whenever possible.

Patients and methods

Between January 1982 and January 1992 altogether 932 patients with blunt abdominal injury were examined at the Ultrasound Diagnostic Unit of the Clinical Hospital Center Rijeka, Croatia.

Left subcostal and intercostal approach were used for the sonographic examination of the spleen. We have also used right prone position of a patient with raised left hand. It is necessary to mention that abdominal pansonographies were always applied due to frequent concomitant lesions, as well as presence of peritoneal recesses, eventually with blood collection.

Ultrasound examinations were performed by means of the following equipment: Fisher Emisonic, Brüel and Kjear 1486, Aloka SSD 260 LS and Hitachi EUB 515 with sector, linear and convex transducers of 3.5 and 5 MHz.

Results

If blunt splenic injury was suspected, we obviously searched for essential sonographic signs, such as:

1) limited fluid collection (hematoma) in the splenic parenchyma,
2) splenic oedema and
3) free peritoneal (especially perisplenic) fluid.

Intralienal hematoma and/or splenic oedema was found in 89 patients after blunt abdominal trauma, which means in 32.1 % from altogether 227 sonographically detected injuries of an abdominal organ. Ultrasound findings of blunt splenic injuries are presented in Table 1.

In Table 1, sonographic appearance of particular splenic injury was noted immediately after the trauma. Patients in which the ultrasound

Table 1. Sonography of blunt splenic injuries.

Type of injury	Sonographic appearance	Number	%
Subcapsular splenic hematoma	Anechoic spindle- or sickle-like formation which elevates a thin capsule, without perisplenic extravasation, homogenous structure of the splenic parenchyma	26	29.2
Shallow splenic laceration	Thin perisplenic hypoechoic liquid »halo«, the spleen sonographically appears intact	13	14.6
Intraparenchymal splenic hematoma	Hypocchoic focal lesion in the splenic parenchyma without perisplenic extravasation	20	22.5
Deep splenic repture	Heterogeneous echoes from the particular parenchymal segment with hypoechoic bleeding foci, perisplenic blood collection filling other peritoneal recesses	30	33.7
Total		89	100.0

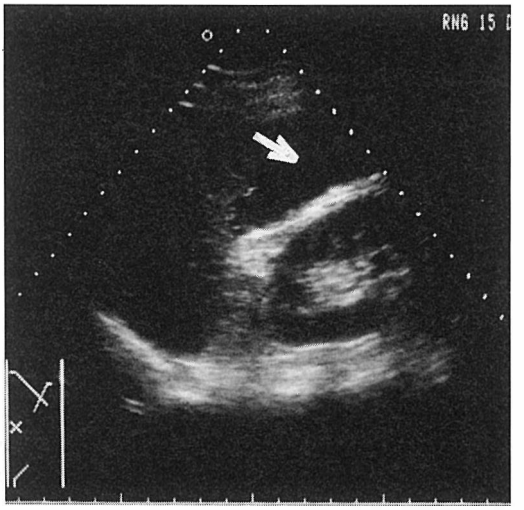

Figure 1. Intercostal sector scan of the subcapsular splenic hematoma (arrow).

finding of blunt splenic injury was diagnostically or therapeutically equivocal were usually followed-up by means of ultrasound several times during the first 24 hours, as well as in following days after the injury. We have also sonographically checked every patient with clinical aggravation.

After initial volume compensation all the patients with subcapsular hematoma (Table 1, Figure 1) were hemodinamically stable. This group of patients was conservatively treated by sonographic follow-up of subcapsular blood resorption. Three patients with a concomitant hemorrhagic lesion of the liver were, on the contrary, operated on (Table 2).

In patients with presumed shallow laceration (Table 1, Figure 2) a free perisplenic fluid was

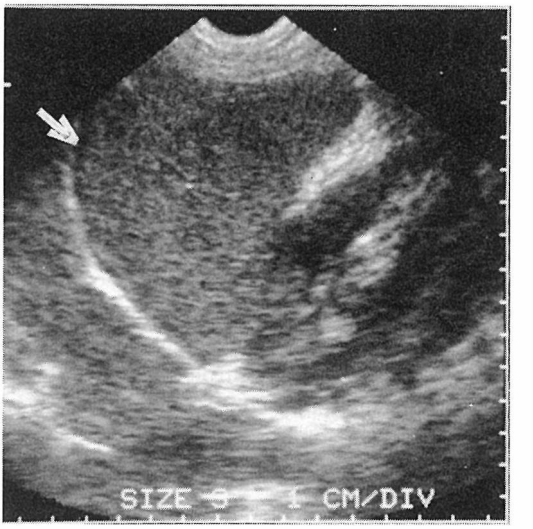

Figure 2. Intercostal sector scan of the minimal perisplenic blood collection (arrow).

Table 2. Treatment of particular sonographic type of splenic injury.

Type of injury	N°	Urgent laparotomy	Secondary splenic rupture	Conservative treatment
Subcapsular hematoma	26	3 (11.5 % due to concomitant injury)	0	23 (88.5 %)
Shallow laceration	13	0	3 (23 %)	10 (77.0 %)
Intraparenchymal hematoma	20	0	4 (20 %)	16 (80.0 %)
Deep rupture	30	30 (100 %)	0	0
Total	89	33 (37 %)	7 (8 %)	49 (55.0 %)

Table 3. Summarized results and parameters of the diagnostic value of ultrasound in blunt splenic injuries.

Results	Number	Parameters	%
True positive	110	Sensitivity	97
True negative	819	Specificy	100
False postivie	0	Accuracy	99.7
False negative	3	Positive predictive value	100
		Negative predictive value	99.6

sonographically detected without presentation of the place of injury. In 11 patients (85 % of this group) a thin layer of minimal blood collection was found exclusively in the perisplenic and left subphrenic space, while Morrison's and Douglas pouch were empty. In 2 patients (15 % of this group) a blood trace was found in the Morrison's pouch. In the first few hours after the injury all the patients were hemodinamically stable, whereas 5–15 hours later hypotension and threatening hemorrhagic shock appeared. In 3 patients (23 % of this gorup) ultrasound follow-up examination evidenced an increased perisplenic collection, but no overflow to the Morrison's and Douglas pouch. Sonographically, it was a secondary splenic rupture (Table 2). These 3 patients underwent explorative laparotomy. The splenic salvage succeeded in two of them whereas in the remaining one splenectomy could not be avoided. In the conservatively treated patients with splenic laceration we have sonographically controled a resorption of the perisplenic blood collection.

Patients with intraparenchymal hematoma (Table 1, Figure 3) were hemodinamically stable at the time of ultrasound examination (i.e. in the first 30–60 minutes after the injury). Free intraperitoneal fluid was not found. In 8 patients (40 % of this group) we have sonographically detected an increase in the hematoma and oedema of the spleen from 12 to 24 hours after the injury. Hematomas remained stable (unchanged size) for another 2–4 days. After that, a regression untill complete resorption was observed. However, 4 (20 %) patients of this group suddenly developed a hypovolemia with hypotension 3–30 hours after injury. On sonography, the splenic structure became inhomogeneous, the hematoma ruptured into the peritoneal cavity with evidence of free fluid. Secondary rupture of the spleen was diagnosed and splenectomy couldn's be avoided.

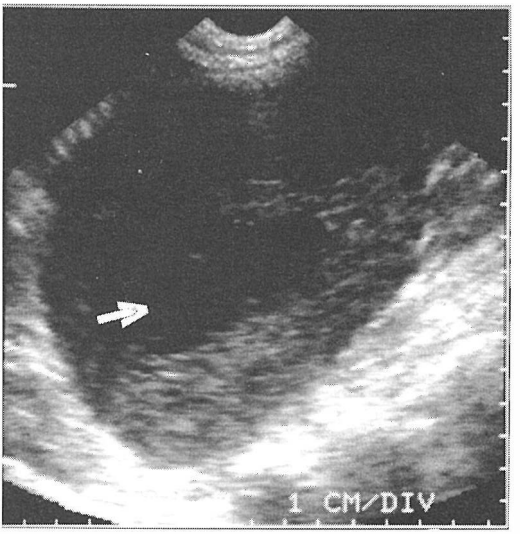

Figure 3. Intercostal sector scan of the intraparenchymal splenic hematoma (arrow).

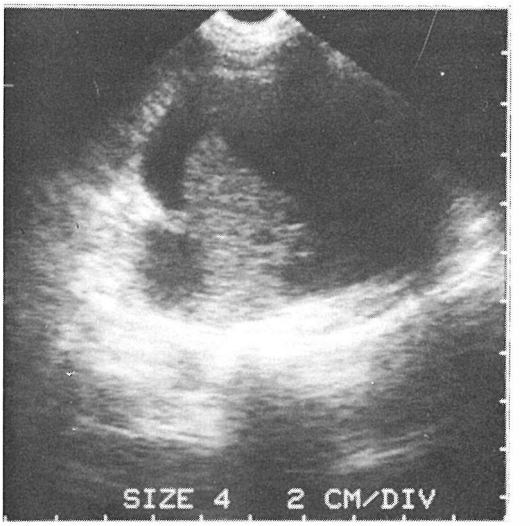

Figure 4. Subcostal sector scan of the splenic rupture.

One-third of all sonographically determinated blunt splenic injuries were deep ruptures of the splenic parenchyma (Table 1, figure 4). All the patients in this group were hemodinamically unstable. Rupture of the spleen was followed by abundant endoabdominal effusion which required urgent laparotomy (Table 2). Splenectomy was done in 26 (87 %), and splenic salvage in 4 (13 %) patients of this group.

In 21 patients (7.6 % of all sonographically detected intraabdominal injuries) a splenic rupture was found intraoperatively, while ultra-

sound detect only free abdominal fluid. It means that sonographer has diagnosed splenic injury only indirectly. Ultrasonographic detection of the hematoperitoneum played an important role in the decision for operative treatment.

Blunt splenic injury was sonographically diagnosed in 110 (39.7 % of total 277 patients with sonographically detected traumatic lesion of an abdominal organ). False negative result (Table 3) represented 3 unrecognized splenic ruptures which were surgically verified.

Abdominal pansonography did not require more than 15 minutes, and it was possible to carry out the compensation of a circulating volume simultaneously.

Discussion and conclusions

Following our results, the spleen is absolutely the most frequently injured organ in blunt abdominal trauma, which corresponds to the results of other authors.[10] We have sonographically examined 932 patients with blunt abdominal injury and detected 277 traumatic intraabdominal organ lesions. Blunt splenic injury was found in 110 patients (39.7 % of altogether 277 intraabdominal injuries) and was the leading cause of hematoperitoneum. In 89 patients the splenic lesion was visualized directly, whereas in 21 patients only free abdominal fluid was detected. According to our results, all the patients with indirect sonographic evidence of splenic trauma required laparotomy. Apart from therapeutic, laparotomy had even diagnostic role in this case. Conservative treatment is possible only with direct sonographic visualization of blunt splenic injury. Such visualization have been achieved in 89 patients, i.e. in 32.1 % of all sonographically evidenced abdominal injuries. We can correlate the sonographic appearance and prognosis of the particular blunt splenic injury.

Subcapsular splenic hematoma included almost one-third, precisely 29.2% (Table 1) of all sonographically detected blunt splenic injuries. According to our experience, subcapsular splenic hematoma usually had a fovourable prognosis and should be treated conservatively (Table 2) by ultrasound follow-up of the hematoma resorption.

Shallow splenic laceration (Table 1) can also be treated conservatively, although, it requires more than just sonographic follow-up, due to possible secondary splenic rupture. In this group even 10 (77 %) patients were conservatively treated despite intrapertioneal hemorrhage.

Intraparenchymal splenic hematoma (Figure 3) was diagnosed in abouth one-fourth (Table 1) of blunt splenic injuries. If no further complications exist, the treatment is conservative (Table 2). This sonographic finding on the first examination restores the diagnosis, but does not provide enough prognostic information. Namely, even 20 % of patients with intrasplenic hematoma underwent surgery due to secondary splenic rupture (Table 2). Consequently, regular ultrasound follow-up is necessary.

Deep splenic rupture represented a frequent sonographic finding in blunt injuries of this organ (Table 1). They are always followed by abundant hematoperitoneum and are regarded as an indication for urgent laparotomy.

Our results point out that ultrasound, in hands of an experienced sonographer, provides a valuable information of posttraumatic status of the spleen. Consequently, ultrasound is one of the basic diagnostic devices in the determination of indications for conservative treatment, and in follow-up of non-surgicall treated patients. The presented results were obtained by close collaboration of a surgeon, anesteziologist and sonographer.

Our results lead to the following conclusions:

1. Subcapsular splenic hematoma usually requires conservative tratment.
2. If vital signs are stable, shallow splenic lacerations and intralienal hematomas require also conservative approach with frequent ultrasound follow-up examinations.
3. Deep splenic rupture as well as secondary rupture of the spleen with massive endoabdominal effusion (Douglas, Morrison) are

indications for urgent laparotomy, regardless the circulatiory condition.

4. Ultrasound is a reliable, quick, cheap and repeatable technique of great value in diagnostics, prognosis and follow-up of a patient with blunt splenic injury.
5. Our results indicate that ultrasound in the hands of an experienced sonographer working in a well organized team can be regarded as the first diagnostic method in approach to the patient with blunt splenic injury.

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Quantitative analysis of blood flow in the estimation of renal transplant function

Dražen Huić,[1] Darko Grošev,[1] Mirjana Poropat,[1] Ljubica Bubić-Filipi,[2] Damir Dodig,[1] Darko Ivančević,[1] Mario Medvedec[1]

[1] Clinical Department of Nuclear Medicine and Radiation Protection, University Hospital Rebro, Medical Faculty, Zagreb, Croatia; [2] Center for Dialysis, Clinic of Urology, University Hospital Rebro, Medical Faculty, Zagreb, Croatia

We performed 74 perfusion studies of renal transplants in 52 patients using 99mTc-pertechnetate. Renal blood flow (RBF) was expressed as a percentage of cardiac output (CO). Mean RBF/CO in patients with creatinine serum level (CSL) < 150 μmol/l was 13.1 % ± 5.6, and for those who had CSL between 150 and 300 μmol/l was 8.1 % ± 3.8. Patients with CSL between 301 and 450 μmol/l had mean RBF/CO 5.6 % ± 2.5, and those with CSL > 450 μmol/l had mean RBF/CO 3.6 % ± 1.1. Differences among all groups and a correlation between CSL and RBF/CO values were statistically significant. Patients with chronic rejection on biopsy had higher RBF/CO values (mean 5.3 % ±2.4) than those with acute rejection (mean 3.9 % ± 0.2) and cyclosporin nephrotoxicity (mean 3.8 % ± 1.6). RBF/CO values are accurate in differentiation of renal transplants regarding their function and they could be helpful in the estimation of trasplant function alteration.

Key words: kidney trasplantation; renal circulation; blood flow velocity

Introduction

Complications responsible for graft failures and finally for graft removing are: surgical complications, acute tubular necrosis, cyclosporin nephrotoxicity (and other complications caused by therapy) and the most often, rejection.[1]

Correspondence to: Dražen Huić, MD, Klinični zavod za nuklearnu medicinu i zaštitu od zračenja Medicinskog fakulteta, KBC Rebro, Kišpatićeva 12, 41000 Zagreb, Croatia. Fax. 38 (41) 23 57 85.

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Perfusion and dynamic renal scintigraphy are approved methods in evaluation of renal transplant function. Allograft perfusion is a qualitative examination. By means of that procedure it is possible to get information about the activity moving through blood vessels of the kidney, but not about the magnitude of the kidney blood flow. That is the reason why many authors have described various perfusion indices, with more or less success.[2-5]

A.M. Peters and colleagues described a method for measuring renal blood flow (RBF) as a percentage of cardiac output (CO). The method determines the count rate that would be

recorded over the organ if the tracer behaved like radiolabelled microspheres and was totally trapped in the vascular bed of the organ on the first pass.[6, 7]

We wanted to evaluate that method in our department, where we have been performing the perfusion and dynamic scintigraphy of renal transplants for more than 10 years.[8]

Patients and methods

From October 1, 1991 to July 1, 1992, 52 patients were studied prospectively in 74 examinations. There were 17 females and 35 males, their age ranging from 12 to 59 (mean age 35). Forty-two cadaveric and 10 living related kidneys were transplanted from 5 to 76 months (median 31) before examination. All patients were cyclosporin treated.

We performed the perfusion and subsequent dynamic graft scintigraphy using 99mTc-pertechnetate and iodine-131 Ortho Iodo Hippuric Acid in patients in whom worsening of transplant function was suspected. We chose creatinine serum level (CSL) as an indicator of the renal transplant function and a relation between RBF/CO values and CSL values was obtained.

In some patients a renal biopsy was performed. We presented only the biopsies done within 30 days of the study in the case of chronic rejection, and within 5 days for others diagnoses. The perfusion scintigraphy was done with 99mTc-pertechnetate (550 MBq) injected rapidly as a compact bolus. A gamma camera with low energy parallel collimator was used for data acquisition. Flow images were collected at a frame rate of 1 per sec for 60 sec, in a 64*64*16 matrix.

Pre and post dose syringe counts were measured on collimated gamma camera's face as a 10 sec static frames for the measuring of the net injected dose. Deadtime correction was performed as described previously.[9]

The distance between an anterior abdominal wall marker and the centre of the transplanted kidney was obtained on a lateral view for depth correction factor measuring. An image was made for 30 sec in a 128*128*8 matrix. The obtained distance (x) was later multiplied with a soft-tissue linear attenuation Tc coefficient ($\mu = 0.153\,cm^{-1}$).

Data analysis was performed by Peters method.[7] One region of interest (ROI) was positioned around the transplanted kidney. Three ROI-s were drawn along the course of the abdominal aorta (Figure 1). There is no need to avoid the iliac artery if there is some overlay with the transplanted kidney because the error obtained by including the artery within the graft ROI is negligible.[7] ROI-s in the course of the abdominal aorta have to be very short (one or two pixel long) because too long ROI-s produce overestimated results.[7] Each aortic curve was corrected for recirculation using a gamma fit, integrated and multiplied by the ratio of the maximum upslope of the renal curve to the maximum upslope of the integrated

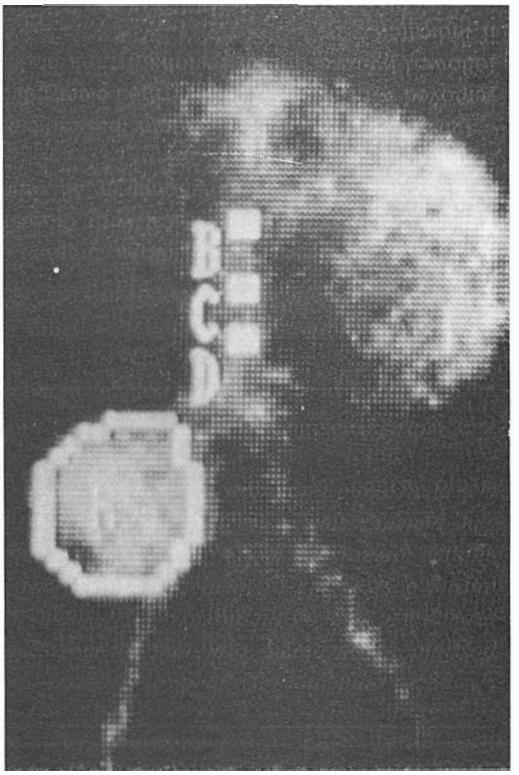

Figure 1. Regions of interest over transplant (A) and aorta (B, C, D).

gamma function aortic curve. The obtained curve represents the renal curve that would have been recorded if the 99mTc pertechnetate had an infinite transit time through the renal vascular bed. If the procedure is accurate, the resultant curve will parallel the renal curve.[6, 7] The procedure with generated curves is presented on Figure 2.

RBF as a fraction of CO was finally calculated from the formula:

$$\text{RBF/CO} = \frac{gk}{ga} \cdot \frac{A}{D} \cdot \text{DCF} \cdot 100 \qquad (1)$$

where RBF/CO = RBF as a percentage of CO; gk = maximum upsloge of renal curve; ga = maximum upslope of integrated aortic curve; A = plateau of integrated aortic curve (cts/sec); D = net patient dose (cts/sec); DCF = depth correction factor ($e^{\mu x}$).

RBF/CO values were obtained for all three aortic curves and the final result was expressed as a mean value.

Statistical analysis was performed by t-test and Student's t-test.

A correlation was measured by standard procedure.

Results

We compared RBF/CO values with CSL values by dividing all patients' examinations into four groups regarding current patients' CSL (Table 1). The mean RBF/CO values of groups were progressively lower with growing CSL. The group with the lowest CSL (< 150 μmol/l) had the highest mean RBF/CO value (13 % ± 5.6) and the opposite (CSL > 450 μmol/l, mean RBF/CO = 3.6 % ± 1.1). Differences among all four groups are statistically significant.

Table 1. RBF/CO values in comparison with creatinine serum levels.

	CSL (μmol/l)			
	<150	150–300	301–450	>450
N	12	39	15	8
X (%)	13.1*	8.1*	5.6*	3.6*
s.d.	5.6	3.8	2.5	1.1
s.e.m.	1.6	0.6	0.6	0.4

CSL – creatinine serum level, N – number of studies, X – mean RBF/CO, s.d. – standard deviation, s.e.m. – standard error of the mean, *$p < 0.01$.

The presumed reciprocal correlation between RBF/CO values and CSL values is presented on Figure 3. The correlation coefficient is 0.58. The coefficient square is 0.34. The correlation is statistically significant ($p < 0.001$).

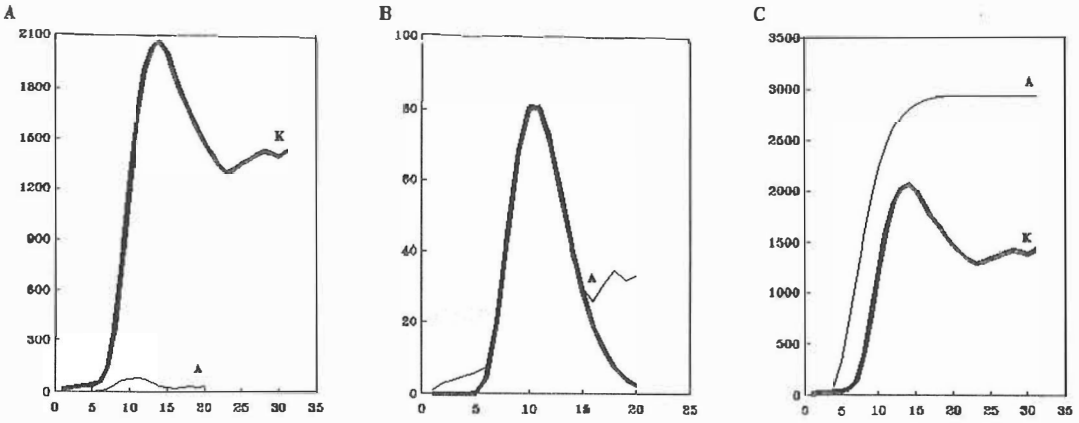

Figure 2. Procedure with generated curves. A) Raw renal (K) and aortic (A) curve. B) Smoothed aortic curve along with fitted gamma-variate curve. C) Integrated and fitted aortic curve (A) multiplied by gK/gA slope's ratio to obtain parallelism with upslope of kidney curve (K).

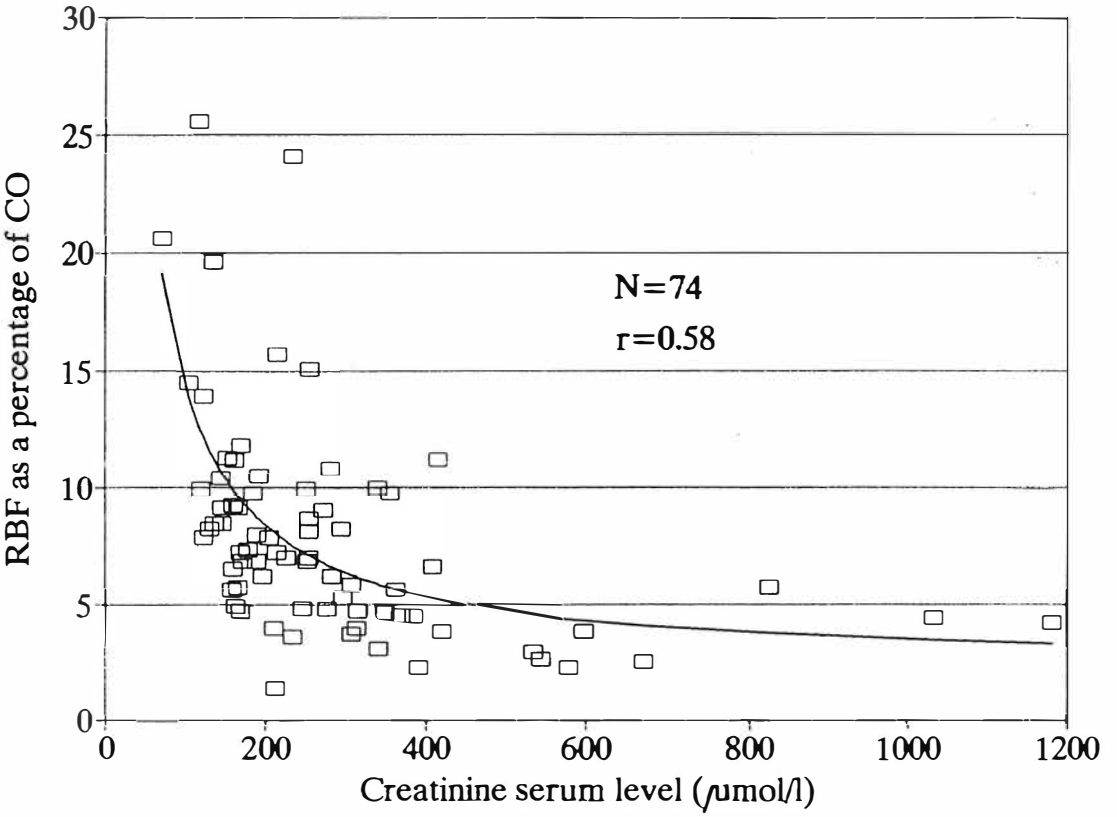

Figure 3. Correlation between RBF/CO values and CSL values.

Two and more examinations were performed in 16 patients. RBF/CO values in almost all cases moved in opposite direction than CSL values. RBF/CO values in comparison with CSL values for all examinations of these patients are presented on Figure 4.

The biopsy diagnosis was obtained in 28 patients. The most often diagnosis was chronic rejection. The mean RBF/CO values are presented for all biopsy diagnoses in Table 2. Differences between the group with chronic rejection and the others are statistically significant.

Table 2. RBF/CO values in patients with transplant biopsy.

	Biopsy diagnosis			
	chronic rejection	acute rejection	MPGNF	cyclosporin nephro-toxicity
N	15	3	7	3
X (%)	5.3	3.9*	8.3**	3.8*
s.d.	2.4	0.2	1.6	0.2
s.e.m.	0.6	0.1	0.6	0.1

MPGNF – membranoproliferative glomerulonephritis, N – number of studies, X – mean RBF/CO, s.d. – standard deviation, – s.e.m. – standard error of the mean, *$p < 0.05$ toward the mean RBF/CO of chronic rejection, **$p <$ toward the mean RBF/CO of chronic rejection.

Discussion

The obtained RBF/CO values were compared with CLS as a not ideal but often employed indicator of renal transplant function. The correlation and differences among all four groups based on the CSL were statistically significant. We have concluded that RBF/CO values are accurate in the differentiation of renal transplants regarding their function.

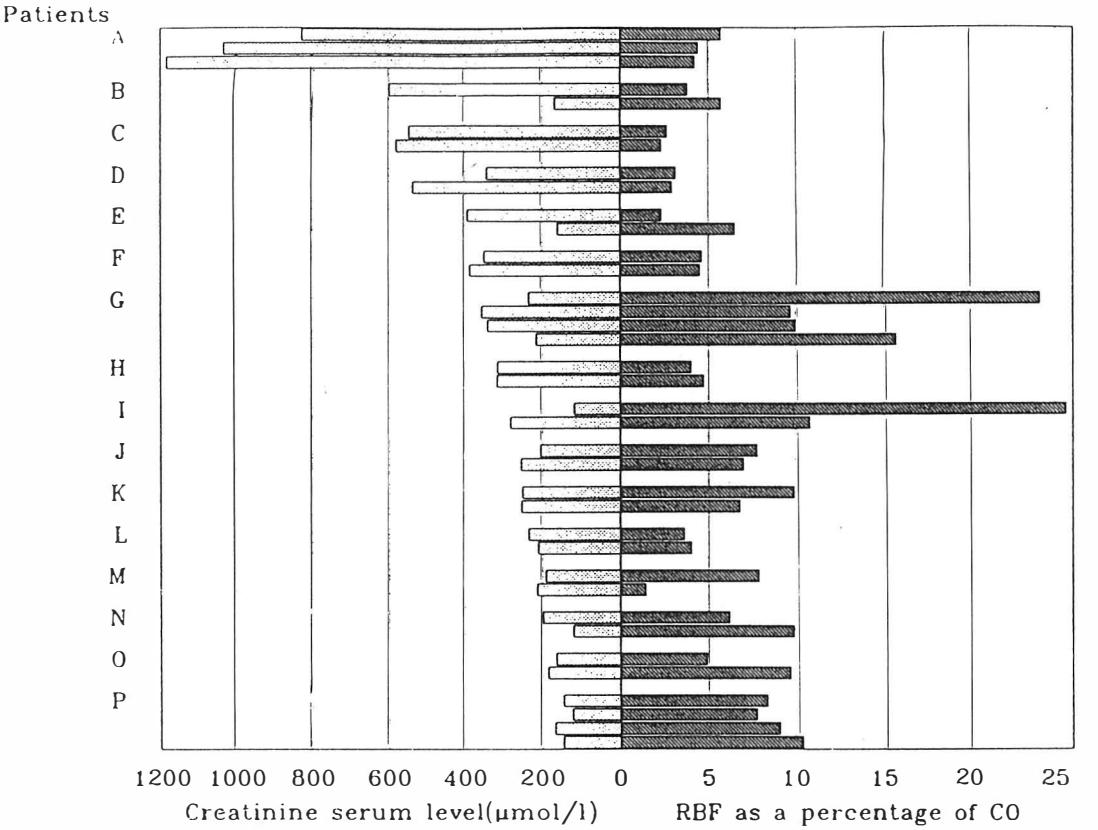

Figure 4. RBF/CO values in comparison with creatinine serum levels in patients with two or more examinations.

In almost all 16 patients with two or more examinations RBF/CO values followed the direction of CSL values changing in keeping with the reciprocal correlation. That suggests a potential role of RBF/CO values as indicators of the alternation of transplant funciton.

The only accurate way to find out what is really happening with the transplanted kidney is to perform a renal biopsy. In our study patients with biopsy proven chronic rejection had a mean RBF/CO 5.3 % (range 3.5–8.0 %). A mean RBF/CO for children in one study was 13.1 %[10] and in another authors concluded that acute rejection could be eliminated if RBF/CO values were higher that 5 %.[7] A mean RBF/CO value for patients with acute rejection in our study (3.9 %; range 3.6–4.0 %) agrees with values obtained for children (3.3 % from the first study,[10] and less than 5 % from the second[7]). Our results suggest that perfusion is the worst in patients with the acute rejection and cyclosporin nephrotoxicity. The main problem is the differentiation of these two conditions and this point should be further evaluated in a larger number of proven cases.

There were no patients with recent kidney transplantation in our investigation. That is the reason why we did not register any patient with acute tubular necrosis and with surgical complications. RBF/CO values could be normal in patients with acute tubular necrosis despite elevated CSL. Such a situation could be easily resolved by dynamic scintigraphy.

This method has many advantages. There is no need for a compact bolus, which is specially important when dealing with pediatric pa-

tients.[10] Values are expressed in physiological units. The technique is independent of the time difference between bolus passing through the artery and the kidney; this is, for example, a problem with Hilson's index.[3]

We completely agree with the conclusion that the major role of nuclear medicine is to determine whether the allograft function has changed, rather than to determine absolute values for various clinical condition.[11] It is possible to avoid wrong estimation based on visual comparison and qualitative analysis only, by using quantitative analysis of transplant blood flow.

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Subjective problems of patients associated with treatment of maxilofacial malignancies

Mirna Juretić,[1] Marijan Car,[1] Zoran Žgaljardić,[1] Alan Šustić[2]

[1] *Department of Maxillo-facial surgery*
[2] *Department of Anesthesiology University Hospital Rijeka, Croatia*

Owing to contemporary medical progress rather extensive surgical interventions have been made possible in oncologic oral and facial surgery in patients who underwent treatment during the progressive stage of the disease. Of 74 operated patients at the Department of Maxillo-facial surgery during 5 years, 43 of them filled in the test containing 7 questions in order to show the patient's attitude towards his severe dissease and the satisfaction with life quality after the surgical intervention. The patient's statements about the appearance and function of swallowing and speech, the family acceptance and habitual community were taken as the basic parameters.

Key words: maxillary neoplasms-surgery: facial neoplasms-surgery; quality of life

Introduction

The principles of surgical oncologic therapy of the head and neck are identical with those in surgical treatment of malignoma in all other regions.

Obviously, the tumor should be radically removed with histologically verified clear edges followed by resection of regional lymph nodes, if indicated.[1, 2]

In malignomas of the head and neck the tumor extirpation as a role does not present any problem, while the reconstruction of post-operative defect due to great aesthetic and functional importance often does.[3, 4]

Owing to the development of surgical technique the cases with advanced disease can be treated with much more success. The patient is informed about the gravity of the disease, about the duration of therapy i.e., eventual surgery with subsequent irradiation, which certainly reflects on psychological conditions.[5]

A number of factors have great influence on patient's behavior and reactions the physician in confronted with, as for example:

a. Concern about possible mutilation (aesthetic aspect)

b. Questions about definite curability

c. Anxiety associated with prolonged hospitalization

d. Comparison with prolonged hospitalization

e. Character and education-level of the patient

f. Family relationship

g. Age, social status, etc.

With various and complex reconstructive methods large postoperaive defects have been

Correspondence to: Marijan Car MD. Klinički bolnički centar Rijeka, Krešimirova 42, 51000 Rijeka, Croatia.

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repaired, after removing advanced tumors of the head and neck.

The aim and concern of this study is to investigate the reaction of patients to the new situation and the quality of their life after the therapy.

Materials and methods

At the Department of maxillo-facial surgery (University Hospital, Rijeka, Croatia) 74 patients with oral cavity tumors were operated upon in the period from January 1987 to January 1992.

In all cases (T3, T3-4, T4) large postoperative defects were present as a consequence of advanced disease, and consequently repaired with microvascular free flaps; depending on sacrificed tissue, simple (skin and fascia) or complex (skin, fascia, bone) flaps were used. The flaps with corresponding vessels were taken from distant parts of the body (forearm, dorsal part of the foot, fibula, metatarsal bone), and anastomosed to neck blood vessels.[6] Fourty-three patients (58 % of all surgically treated cases have been regularly followed up. The examines were predominantly males (42 or 98 %) with only 2 % females, all aged from 35 to 78 year, respectively.

In the test-group 22 (or 81 %) of cases were patients who consumed alcohol to excess (over 1,5l of wine and other intoxicating liquors) with 12 % treated alcoholics. 8 patients (37 %) daily drank minor quantities of alcohol (up to 1l of wine). Particular attention was paid to the educational level which could influence the patient's answers (seriousness of the disease, the need for surgical intervention, etc.) as well as the subsequent reintegration in habitual environment, especially in older members. In the test-group, 2 examiners (5 %) had university degree, 1 (2 %) professional high-school degree whereas 12 (44 %) had secondary vocational school diploma. The rest were manual workers of various profiles – 18 (42 %) 10 were farm-laborers (23 %) with low-school education from 2 to 8 classes of elementary school. Until the onset of the disease 14 (33 %) of the examines, hade been in active employment whereas the rest 29 (67 %) were retired or unemployed persons or social cases. On the basic of given answers certain conclusions can be reached.

Seven questions have been posed in relation to the disease, to reaction and to the new situation after surgical treatment. Standard test-questionnaire had the following items:

1. What was your acquaintance with the disease before surgical intervention?
   a. not informed
   b. minimally informed
   c. adequately informed
2. Was the information about your operation satisfactory?
   a. yes
   b. no
3. Did the relationship in your family undergo a change?
   a. no change
   b. improvement in relations
   c. deterioration of relations
4. Did the relation between you and friends, neighbors, associates or business colleagues show any difference?
   a. no change
   b. better relation
   c. worse relation
5. Are you content with the aesthetic aspect of your surgery?
   a. yes
   b. partly
   c. no
6. Are you satisfied with function (speech, swallowing)?
   a. yes
   b. partly
   c. no
7. Would you undergo another surgical intervention if necessary?
   a. yes
   b. no

Results

The following figures (1, 2, 3, 4, 5/A/B) present the results obtained by testing 43 patients after surgical intervention for tumors of the oral cavity and neck.

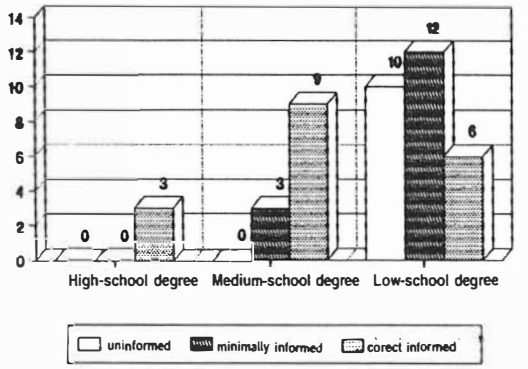

Figure 1. Information of the patients about the disease severity.

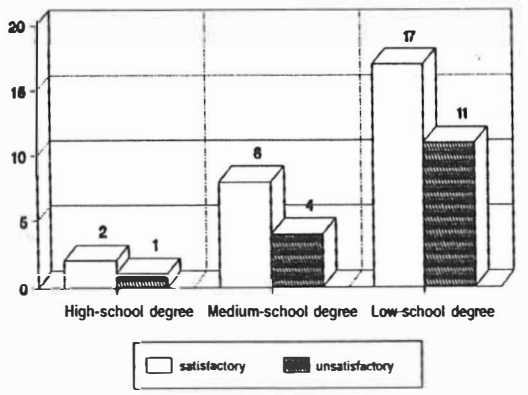

Figure 2. Explanation of the patient about the operation and the disease severity.

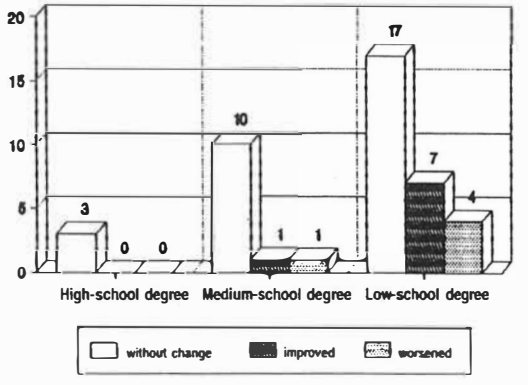

Figure 3. Family relationship after the operation.

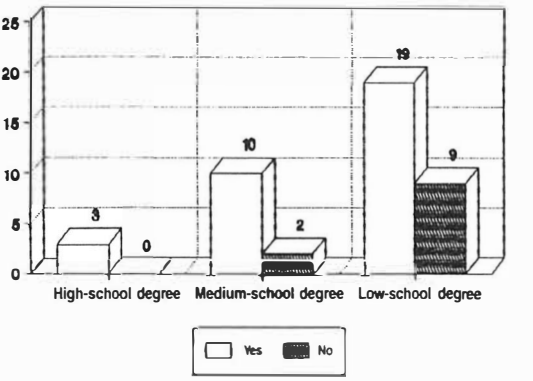

Figure 4. Repeated consent to operation if needed.

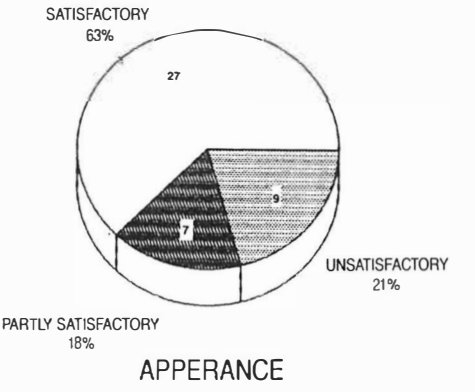

Figure 5. Apperance after the surgical treatment.

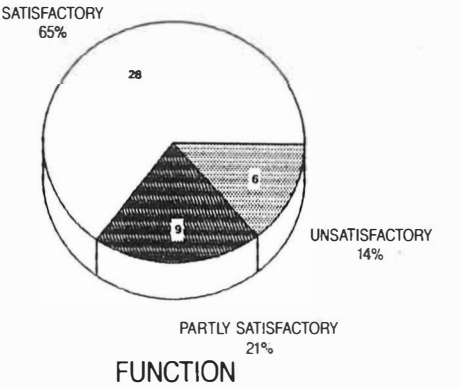

Figure 6. Function after the surgical treatment.

Discussion

The patients who previously underwent surgery (1–5 years ago) were examined. All have been treated in advanced stage of the disease, although the oral cavity is accessible to inspection and to early detection of the disease. This could be due to the fact that the majority of patients were either alcoholics, chain-smokers of social cases with low education. Although they "carried" the disease for a long time, after the onset of symptoms (pain, hemorrhage, difficulties on swallowing), they readily accepted even very complex surgical procedures.

Therapist's explanations about the disease, its consequences, the possibility of reconstruction, etc., are of great importance especially if they give assurance for future quality life. From the answers to the questionnaire the authors could conclude that some patients believe they have been inadequately informed (23 %) or only partly so (55 %). Besides that, some "blame" may be ascribed to the low education level and to alcohol, damage in many cases. However, the majority were satisfied with surgical results; absolutely satisfied were 25 (58 %), and with speech and swallowing function 21 (49 %), respectively. Partial discontent with function was present in 17 (39 %), particularly regarding speech disorders. These may be expected owing to a great loss of fine anatomic structures of the oral cavity caused by extensive surgery. As a significantly favorable result, the authors regard successful reintegration in the family (88 %), working milieu and among friends, where their aesthetic aspetc will not cause feelings of compassion or repulsion.

Conslusion

It is of utmost importance to examine all emotional, social and medical factors in the cases of patients treated in advanced stage of malignant disease, with various subjective distresses. With selective questionnaire 43 surgically treated cases in the last 5 years were tested at the Department for Maxillo-facial Surgery (University Hospital, Rijeka, Croatia).

All had undergone highly complex reconstructive surgery 1 to 5 years previously. There were no recurrences or metastases observed, and all in all patients were content with life quality.

Reintegration in the family and society was quite satisfactory. The authors advocate better information about the disease, and possible consequences of treatment, particularly speech or swallowing function disorders, as this could reduce malcontent present in some cases. The way of exposing all problems perhaps should be adapted to the intellectual level of patients.

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Invasive cervical adenocarcinoma: An analysis of 67 treated cases vs squamous carcinoma

Vida Stržinar

Insitute of Oncology, Ljubljana, Slovenia

Adenocarcinoma (AC) of the cervix uteri has become an important clinical entity owing to its increasing incidence, high malignant potential, and relative radioresistance. The treatment results of 67 patients treated at the Institute of Oncology, and University Department of Gynecology in Ljubljana between 1973–1978 are presented in correlation with the results of 835 patients with squamous cell carcinoma (SC) treated in the same period. The rate of adenocarcinoma among all cervical cancers is 7%. Five-year survival was analysed according to the mode of treatment and stage of the disease. The survival in stage I was not influenced by treatment modality. There was also no difference as to the histologic type; in both studied types the survival was 79.3%. However, in advanced stages the mortality rate was alarmingly high: only 7.9% of patients with adenocarcinoma in stages II, III and IV survived 5 years, whereas the corresponding survival rate in patients with squamous cell carcinoma was 37.8%. Radioresistence of adenocarcinoma was evident in the group treated by irradiation alone: their 5-year survival was 9.1% vs 36% observed in squamous carcinoma. The overall 5-year survival of patients with adenocarcinoma was 38.8% vs 54.6% in squamous carcinoma.

Key words: cervix neoplasms-therapy; adenocarcinoma; squamous cell carcinoma; survival rate

Introduction

Adenocarcinoma (AC) of the uterine cervix is a relatively rare form of cancer. Its epidemiologic characteristics are similar to those observed in squamous type. During the past decades the incidence has been increasing.

Carcinoma shows prevailingly infiltrative growth (barrel shaped cervix), and it is relatively radioresistant. This renders the prognosis extremely unfavourable, particularly in the advanced stages of disease and poorly differentiated types.

The presented report analyses 5-year survival of patients with adenocarcinoma of the cervix with respect to the stage and treatment approach. The results are compared with those obtained in patients treated for squamous carcinoma (SC) in the appointed period.

Correspondence to: Vida Stržinar, MD, MSc, Institute of Oncology, Zaloška 2, 61105 Ljubljana, Slovenia.

UDC: 618.146-006.6-08-036

Patients and methods

The presented analysis was carried out in patients with carcinoma of the uterine cervix treated at the University Department of Gynecology and/

or the Institute of Oncology in Ljubljana from 1973 to 1978. The total number of treated patients was 979; 29 patients were excluded from the analysis because they had been lost to follow up or had died of unknown causes. In the group of 950 patients there were 67 (7.1%) with adenocarcinoma.

Distribution by stages and comparison with squamous cell carcinoma are presented in Table 1 (staging according to FIGO classification

Table 1. Distribution of patients according to histologic type of carcinoma by stage.

Histologic type	Stage					
	I.	II	III	IV	All	
	No.	No.	No.	No.	No.	%
SC	338	218	234	45	835	87.9
AC	29	14	17	7	67	7.1
Other ca	21	5	18	4	48	5.0
Total	388	237	269	56	950	100.0

1972, confirmed 1978). Thus the rate of Stage I is 43,3% vs 40,4% for sqauamous cell carcinoma. There is no difference in age distribution between both histologic types. Median age of patients wiht AC was 54 years, and of those with SC 56 years.

Histological typization of AC was not performed, and there were no data on tumor differentiation or grade (G) available.

The treatment aproach was as follows (Table 2):

Table 2. Five-year survival of patients by treatment method and stage of adenocarcinoma.

Therapy Stage	Surg.		Surg + RT		RT		All	
	No.	%	No.	%	No.	%	No.	%
I	18/21	79.9	3/5	–	2/3	–	23/79	79.3
II	0/2	–	2/3	–	0/9	–	2/14	14.3
III	–	–	0/2	–	1/15	–	1/17	5.9
IV	–	–	0/1	–	0/6	–	0/7	–
Total	18/23	78.3	5/11	–	3/33	9.1	26/67	38.8

* percentages are not given when the number of patients is below 20.

– 23 patients underwent Wertheim-Meigs surgical procedure (radical or extended hysterectomy with pelvic lymphadenectomy);

– 5 patients preoperatively received intracavitary ^{226}Ra applications using Manchester technique; TD 40 Gy was delivered to point A prior to Wertheim-Meigs operation.

– 3 patients were postoperatively treated by external irradiation; TD 40–56 Gy (2 Gy daily) were delivered to the whole pelvis;

– 33 patients received a combined tele- and brachyradiotherapy in the following order: external irradiation – TD 40 Gy to the whole pelvis, followed by brachytherapy – TD 40 Gy to the point A, ending with additional irradiation to the parametrium and lymph nodes – TD 20 Gy with shielding of the center.

– 3 patients were hysterectomized because of local recurrence after radical irradiation.

The data were processed at the Institute of Biomedical Information of the Medical Faculty, University of Ljubljana, using their own software program STAT installed in a DEC 10 computer system.

The following two types of analysis were used:

1) basic statistic description of variables

2) analysis of variables with distribution of cases into subgroups

Crude five-year survival rate was calculated by direct method. All patients were followed for 5 years; those lost to follow up were not included in the analysis.

Results

In the investigated group of 67 patients 26 (38.8%) survived 5 years. Table 3 presents a comparison with SC where 5-year survival was 54.6%. Graphic comparison of the survival results in both histologic types is shown in Figure 1. The same rate of survival in both histologic types, i.e. 79.3%, was achieved in stage I patients only. In more advanced stages 5-year survival for SC was 37.8%, whereas in AC it was only 7.9%. The difference was statistically significant ($p<0.001$).

Table 3. Five-year survival by histologic type and stage of the disease.

Histologic type	Stage									
	I		II		III		IV		All	
	No.	%	No.	%	No.	%	No.	%	No.	%
SC	266/388	79.3	117/218	53.2	69/234	29.5	3/45	6.7	456/835	54
AC	23/29	79.3	2/14	–*	1/17	–	0/7	–	26/67	38
Other ca	18/21	85.7	3/5	–	4/18	–	0/4	–	25/48	52
Total	310/388	79.9	122/237	51.5	74/269	27.5	3/56	5.4	409/950	53

* percentages are not given when the number of patients is below 20.

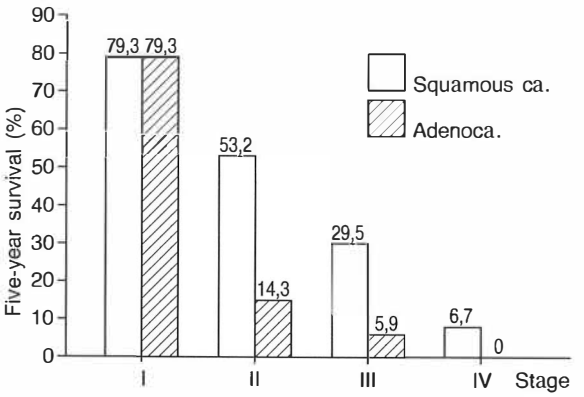

Figure 1. Five-year survival of 902 patients with cancer of the uterine cervix by histological type and stage of carcinoma.

Table 2 presents the survival with respect to treatment approach and stage. Thus, surgery alone proved effective in 78.3%, whereas a combination of surgery and radiotherapy was successful in 5 of 11 patients (45.5%), and radiotherapy alone in 3 of 33 (9.1%) patients only.

There was no difference between AC and SC patients treated by surgery alone. The difference is, however, evident in irradiated group where 182 of 513 (36%) SC patients survived 5 years. In the group of 141 SC patients treated with a combination of surgery and radiotherapy there were 102 (72%) 5-year survivors vs 45.5% in AC group; the difference is statistically significant.

Discussion

Recently, the rate of AC among cancers of the uterine cervix has been showing tendency to increase. Thus the rate of about 5% reported fot the past few decades has increased to almost 10% (9%, according to the data from Ann Rep No 21).[1] Some authors even report rates as high as up to 35%.[2] There are two possible interpretations of these values:

1) the incidence of invasive SC has been decreasing owing to successful screening using Papanicolaou test, whereas in AC this test fails to detect the disease in 25–50% of cases,[3, 4]

2) the number of AC cases is absolutely on increase.

Epidemiologic characteristics are the same as in SC, whereas possible influence of obesity, diabetes and hormonal treatment are still subbject to investigation, likewise in endometrial carcinoma.[4]

The clinical picture is similar as in SC, though AC often starts endocervically and therefore remains concealed. Barrel-shaped cervix is a typical result of its infiltrative growth.

Prognosis mainly depends on the stage of disease, being extremely poor in advanced carcinomas (Figures 2, 3).[1] There are no significant differences in the survival between Stage I AC and SC patients when our results (approximately 80% 5-year survival) are compared with those reported by other authors. On the other side, in advanced stages the mortality rates for AC are significantly higher. This difference is most apparent in patients treated by radiotherapy alone. The survival in our patients was only 9.1%, according to Ann Rep 20%, the mortality therefore being 2–5 times higher than in SC. With the use of combined surgical and

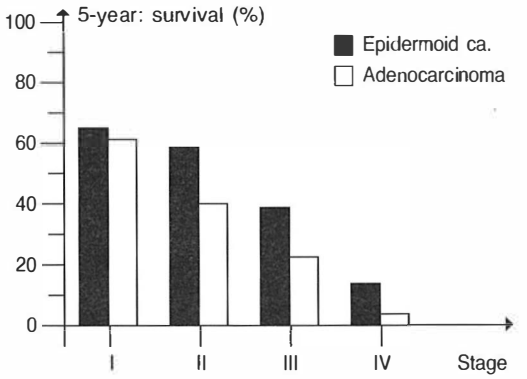

Figure 2. Carcinoma of the uterine cervix, 1982–1986. Five-year survival by histological type and stage for patients treated by radiation alone.

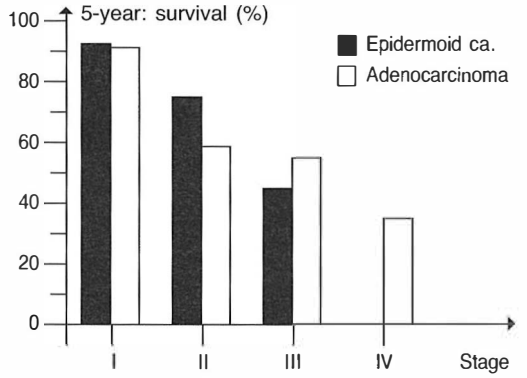

Figure 3. Carcinoma of the uterine cervix, 1982–1986. Five-year survival by histological type and stage treated by surgery alone.

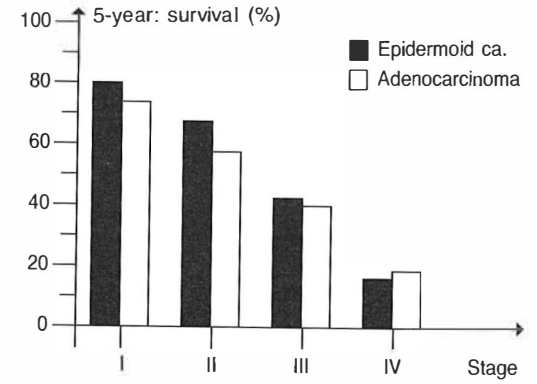

Figure 4. Carcinoma of the uterine cervix, 1982–1986. Five-year survival by histological type and stage for patients treated by surgery and postoperataive radiation.

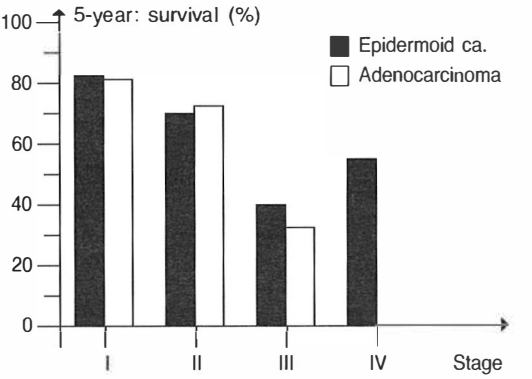

Figure 5. Carcinoma of the uterine cervix, 1982–1986. Five-year survival by histological type and stage for patients treated by preoperative radiation and surgery.

radiation treatment these differences are not so marked (Figures 4,5).[1]

Obviously, AC is a relatively radioresistant tumor, which is particularly the case with bulky tumors. The treatment of choice is therefore surgery which is indicated even in the cases of borderline operability. When radical surgery is not feasible, the therapy is completed with additional irradation. A signaficantly better survival is reported in patients with Stage II of the disease who have had histerectomy and irradiation than in those treated by radical hysterectomy or irradiation alone.[2] In primarily inoperable patients residuum after radiotherapy should be surgically removed (histerectomy after irradiation).

In our patients with AC the data on tumor type and differentiation were missing. According to the data from literature, the worst prognosis is associated with mucoepithelial and mucinous type of AC (Ferenczy's classification),[5] and the best with endometroid type. Poorly differentiated AC metastasizes faster, and the mortality in G3 is three times higher than in G1.[3] The survival in SC is not significantly influenced by tumor type and grade.

In clinically operable tumors, as in SC, lymph node status is the most relevant prognostic factor, though in AC the survival is two times

lower (approximately 30% vs 60%), which corresponds to the systemic nature of the disease[3]. Chemotherapy is not effective.

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Viral tumor inhibition

Anton Cerar

Institute of Pathology, Medical Faculty, Korytkova 2, Ljubljana, Slovenia

Clinical and experimental observations of viral tumor inhibition (VTI) are reviewed. A list of viruses with VTI, and diverse terminology used in the field are given. The modalities how these viruses were obtained, principles for their use and different mechanisms of VTI are described. Further studies are needed to improve the therapeutic effect of VTI.

Key words: viruses; tumor inhibition; immunostimulation

Viral tumor inhibition (VTI) after natural infection

First reports on tumor regression after natural viral infection date back to the verge of the 19th century. Thus in 1893 Kovacs drew attention to clinical improvement in leukemic patients after various infections,[1] whereas in 1912 de Pace described the case of a patient with carcinoma of the cervix uteri which regressed after the patient had been vaccinated against rabies, probably with attenuated viable virus.[2] More recent reports associate previous measles infection with a remission of Hodgkin's disease,[3] a regression of Burkitt's lymphoma,[4] and again a regression of Hodgkin's disease.[5] Csatary reports on the regression of advanced and metastatic gastric carcinoma associated with an epidemics of fowl plague, or infection with the Newcastle disease virus (NDV).[6] Pasquinucci in his report mentions remission of acute lymphoblastic leukemia in children after measles.[7] Either natural infection or artificial inoculation with varicella virus was often reported to have induced a partial remission of acute leukemia.[8] Other reports on similar cases have been collected and reviewed by Sinkovics.[9]

Correspondence to: Asist. Prof. Anton Cerar, MD, PhD, Institute of Pathology, Medical Faculty, Korytkova 2, 61000 Ljubljana, Slovenia.

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Experimental studies of VTI

Published as well as unpublished clinical observations on the viral tumor inhibition rose interest of clinicians as well as experimental oncologists. Growing interest of the latter in this field was noted in the 20's when French investigators studied the growth of viruses in animal tumor models and discovered that some viruses had the potential of inhibiting tumor growth.[10]

Renewed interest in this field was apparent in the 50's when the studies centred on the detection of new viruses with tumor growth inhibition potentials gave way to the studies exploring the mechanisms of VTI. A review of the research in this field was presented in the late 50's with a report on 50 different viruses

tested.[11] The viruses were mostly tested in vivo in experimental animals, but partly also in vitro and in clinical experiments. Many of these experiments proved the existence of VTI, at that time called viral oncolysis.

Viruses with VTI properties were obtained in the following three ways:

1) by testing in a number of experimental tumors,

2) by adaptation of viruses without initially apparent oncolytic properties to tumors through several passages,

3) by isolation of the so-called "passenger viruses" which have contaminated experimental tumors and thus caused a sudden decrease in their growth potential.

In the beginning of experimenting with oncolytic viruses their pathogenic effect on the experimental animals represented a major problem. It also turned out that the most effective viruses were at the same time highly neurotropic. However, further research helped to detect viruses which were practically devoid of any pathogenic effect on the host despite their preserved tumor inhibitory activity. One of such viruses was the neurotropic influenza virus extensively studied in the 70's by Lindenmann and Klein.[12] The results of these studies threw a new light on the immunologic aspect of VTI. The finding that some viruses with VTI properties change the immunogeneity of the infected tumors by inducing new antigens in the cell membranes became widely recognised. Accordingly, a new term viral xenogenization of tumor cells was introduced by Hiroshi Kobayashi, based on the fact that the viral activity renders the tumor tissue alien to the host.[13]

In order to avoid possible virus related danger to the host, in the 70's many investigators began to use the so-called oncolysates, i.e. tumor homogenates infected by virus in vitro, which applied particularly to clinical trials. [14, 15, 16]

Recently, there have been attempts to transfect individual viral genes into the tumor cells with the aim to enhance the immunogeneitly of tumor cells, and to avoid adverse effects of viable viruses.[17]

With reference to the use of viruses for VTI, the following principles have been established:[18]

1) Virus should maturate by budding through the plasma membrane of the tumor cell;

2) The host must be capable of immune response against the budding viral antigens;

3) Virus should be fully adapted to a complete tumor cell division cycle;

4) Virus should not be oncogenous to the tumor host.

The above principles, which partly restrict the applicability of VTI, have been based on the experiences with viruses which have a specific mechanism of activity. A comprehensive overview of the scope of VTI application and its perspectives has been presented by Sinkovics.[19]

Viruses with VTI potential

VTI inducing viruses can be found in almost all families of viruses (Table 1); some of them are pathogenic for humans, and others for animals. Most viruses with VTI potential, discovered till 1973, were neurotropic.[20]

The analysis of quotation frequency of individual viruses with VTI, including viral oncolysates, shows which viruses have been studied most thoroughly, and which might be regarded as most promising for clinical application. Thus, after 1960, among the most frequently quoted have been retroviruses, NDV, influenza and vaccinia virus, which come far before all others. Among other frequently investigated viruses are also adenoviruses, virus of lymphocytic choriomeningitis, as well as viruses of vesicular stomatitis, measles, mumps, herpes simplex, and bovine enterovirus type 1. As a family, paramyxoviruses play by far the most important role both in studies and in natural viral infections associated with VTI. Paramyxoviruses are followed by the group of retroviruses which are mainly responsible for opportunistic infections in experimental animals and tissue cultures.

Mechanism of VTI

In the beginning, investigators of VTI believed that the effect of viruses on tumor cells was

Table 1. Classification of viruses with VTI by viral families.

Virus family	Nucl. acid type	Virus
Poxviridae	DNA	vaccinia, neurovaccinia, ectromelia
Adenoviridae	DNA	different types of adenoviruses, cow mammillitis
Herpesviridae	DNA	herpes simplex, varicella-zoster
Papovaviridae	DNA	polioma
Retroviridae	RNA	mouse leukemia and sarcoma (Gross, Friend, Moloney, Rauscher)
Paramyxoviridae	RNA	NDV, Sendai, mumps, measles
Ortomyxoviridae	RNA	influenza
Picornaviridae	RNA	coxsackie, Mengo, hepatitis A, encephalomyocarditis
Arenaviridae	RNA	lymphocytic choriomeningitis, Junin, Pichinde, Tacaribe
Rhabdoviridae	RNA	vesicular stomatitis
Bunyaviridae	RNA	Bunyamwera
Togaviridae	RNA	West Nile, dengue, Kyasanur forest disease, St. Louis, Ilheus, Sindbis.

mainly attributable to lytic infection. Therefore, viruses exhibiting VTI properties were called oncolytic viruses.[11] However, it soon became apparent that the immune response of the host should be regarded as an important factor in this process. It has been proved that a change in the antigen structure of the tumor cell membranes occurs due to viral infection.[21, 22, 23] Such antigens can be seen particularly in the viruses which leave cells by budding. Thus, tumor cells acquire antigens extrinsic to the organism, which trigger humoral and cellular immune response. Some authors call this viral effect immune cytolysis.[24] The appearance of virus-specific antigens on tumor cells was extensively investigated in retroviruses[25–28]

On the other hand, many authors describe a direct effect of viruses on the immune system. Thus, Byrne and co-workers report a significantly decreased NK cell activity in malignant melanome bearing animals;[29] the infection with vaccinia virus induced the NK cell activity to reach the level seen in animals without tumor. Molomut and co-workers point out the importance of interferon induction by means of Pichinde virus which on the other side stimulates the activity of NK cells.[18] Virus also prolongs the virus- and tumor – specific responce of cytotoxic leukocytes. Vaccinia virus infection was associated with the appearance of activated macrophages which exerted cytostatic and cytotoxic effect on malignant melanoma cells,[30] as well as with an increased sensitivity of human tumor cells to homologous complement.[31]

Apart from its activity on the immune system, viruses may also exert other effects. Steeg et al. have found that the transfection of adenovirus 2 Ela into tumor cells influences the expression of gene responsible for metastasising, thus inhibiting the metastatic process of the tumor.[32] Fearon and co-workers also reported on transfection of the gene coding hemagglutinin antigen of influenza virus into the undifferentiated cells of murine colon cancer.[33] Thus, a strongly immunogenic tumor was obtained, which did not grow in the singeneic mouse but rather protected the animal against transplantation of unaltered tumor cells. Toolan and co-workers noted a decreased incidence of dimethylbenzanthracene induced tumors in new-born animals which were inoculated with parvo virus H1.[34] As a possible explanation of this phenomenon, Guetta et al developed the theory that carcinogens activated viral proliferation thus causing VTI with tumor cell lysis.[35]

The reported cases of VTI mechanisms have been selected only to illustrate the large spec-

trum of possible mechanisms and their variability from one virus to another.

Conclusion

In spite of extensive research on VTI there are only few encouraging results for its application in tumor therapy in men. To improve the latter, much work is still needed to clarify the mechanisms of VTI and factors influencing the effect of VTI.

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Incidence of structural chromosomal aberrations and sister chromatid exchanges among medical personnel handling antineoplastic drugs

Vlatka Brumen

Institute for Medical Research and Occupational Health, University of Zagreb, Laboratory for Mutagenesis, Zagreb, Croatia

The aim of the study was to evaluate the genotoxicity risk of professional exposure to antineoplastic drugs in a selected occupationally exposed group by means of standard mutagenetic methods. The study comprised 17 nurses handling cytostatics and the equal number of matched controls. The methods applied were: structural chromosomal aberration analysis and sister chromatid exchange (SCE) method. The exposed group showed a significant increase of SCE frequencies, and, although insignificant, an increased total number of induced chromosomal aberrations. Such results confirm the suspected genotoxic effect of professional exposure to antineoplastics.

Key words: antineoplastic agents-toxicity; sister chromatid exchange; chromosome aberrations; occupational exposure

Introduction

Early detection and adequate therapy of malignant diseases are still a major medical problem despite the high level of development and progress of modern medicine. Whenever possible, radical surgery should be the first step in the treatment of a malignoma. However, in most cases an additional supportive radiotherapy and chemotherapy are required in the postoperative course, those therapeutical procedures remaining the only possible choice in the case of inoperable tumors.

Correspondence to: Vlatka Brumen, M.D., Ph.D., Institute for Medical Research and Occupational Health, University of Zagreb, Laboratory for Mutagenesis, Trg I. Meštrovića 16, 41020 Zagreb, Croatia.

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Side-effects of antineoplastic therapy have been rather well and long established and can be summarized by the following three keywords: mutagenesis, teratogenesis and carcinogenesis,[1, 2, 3] However, it was only recently that the problem of cytostatic therapy has been approached from the point of view of noxious effects it may have on the medical personnel in charge of preparation and application of cytostatic drugs. Consequently, nowdays a systematic health surveillance of the forementioned personnel is considered necessary. Nevertheless, direct genotoxicity of cytostatic drugs on the professionally exposed personnel is still a point of dispute among various authors.[4, 5, 6]

The aim of this study was to assess the real direct genotoxicity risk in the personnel professionnally exposed to cytostatic drugs by means of standard mutagenetic methods, respecting

the conditions found in the workplaces of the examinees.

Subjects and methods

The exposed group consisted of 17 nurses, their mean age being 32.2 (± 9.9 years), in charge of preparation and application of cytostatic therapy at a pediatric department of a university hospital. Their daily professional contact with antineoplastic drugs had lasted 12.5 years (± 9.4) on the average. The most commonly used cytostatics were oncovin, methotrexate, cisplatinum, adriablastin, CCNU and endoxan.

An equal number of age and sex compatible non-medical personnel of the same hospital served as controls. The selected examinees had never either professional or therapeutical contact with antineoplastic drugs.

A detailed case history, comprising data on personal, family and professional background preceeded mutagenetic testing of each examinee. During the interview, a special attention was paid to the interfering factors which are known to modify the mutagenetic test results. The data on the most commonly used antineoplastic drugs, as well as on the safe handling practices, were also collected.

Mutagenetic testing procedures included conventional, internationally verified methods such as structural chromosomal aberration analysis[7] and sister chromatid exchange method – SCE.[8] In vitro cultures of peripheral blood lymphocytes served as cellular material. During the preparation, F-10 (HAM medium) GIBCO enriched with 20 % of calf serum was used, while phytohaemaglutinine FITO KRKA served as a mytotic stimulator.

During the SCE procedure 10 micrograms/ml of bromodeoxyuridine – BrdU (SIGMA) were added into the culture.

The results of conventional structural chromosomal aberration analysis are presented as the total number of a particular type of chromosomal aberration detected in the first two hundred well spread in vitro metaphases.

Within SCE test 50 clearly visible metaphases were analysed for each examinee. The results are given in form of the mean value of SCE frequencies scored in those 50 metaphases. Besides that, the lowest and the highest value of the SCE incidence were also recorded. The normal value of 7 sister chromatid exchanges per cell, established by the Laboratory for Mutagenesis, was taken as the superior borderline value in the interpretation of the obtained results.

All the results obtained by both methods were evaluated statistically by means of Student t-test and chi-square test.[9, 10]

Results

The type of detected structural chromosomal aberrations and their numerical distribution per cell are given for both groups of examinees in Table 1. As can be seen from the table, owing to one or as many as two dicentrics, aberrant findings of structural chromosomal aberration analysis were recorded in four of the exposed subjects, while no such findings were encountered in the control group.

Although the total incidence of structural chromosomal aberrations does not show a statistically significant difference between the exposed and the control group ($p = 0.8$), almost every type of recorder chromosomal aberrations was more frequent in the exposed than in the control group, as presented in Table 1.

The same table shows an average SCE-frequency for both groups of examinees. Statistical evaluation by means of the t-test revealed a significant SCE-value increase in the exposed group, as compared with the controls ($p>0.001$). Out of the ten exposed subjects with SCE-values beyond normal, three had accompanying aberrant findings of structural chromosomal aberration analysis. All the corresponding findings in the control group were below the laboratory normal.

Even though the mean SCE value is considered to be representative for the results obtained by this method, it would be of relevance to present the SCE-frequency ranges for each subject in both groups. Table 1 shows the upper

limits of those ranges to be often far beyond the laboratory normal, while no such case has been recorded among the control subject ranges.

Discussion

Besides numerous problems connected with therapeutical application of antineoplastic drugs, the contemporary medicine is also faced with the problem of potentially noxious effects of cytostatics on the ocupationally exposed personnel. One of the problems still pending is a direct genotoxicity of cytostatic agents in medical personnel handling them. However extensive, the results of cytogenetic studies are often controversial, although using the same methodological approaches of detection and analysis of chromosomal damages, which are still considered the best bioindicator of mutagene exposure. Detecting changes in the peripheral blood lymphocyte cell genome of the exposed personnel, a number of authors try either to prove or reject the suspicious genotoxic effect of cytostatic drugs. The techniques most commonly used are: conventional structural chromosomal aberration analysis and, more suitable still in chemical mutagen exposure, the sister chromatid exchange (SCE) method.

The cytogenetic research results in the selected professional groups are often controversial. A majority of authors report a significant SCE-value increase among the exposed subjects,[2, 11, 12] while some do not find any significant difference in comparison to the controls.[5, 13, 14]. However, the results of this study show the SCE-frequency to be statistically significantly higher in the exposed than in the control group ($p>0.001$).

Several factors have to be taken into account in presentation and interpretation of the results obtained by the SCE-method. The common procedure is to analyse at least 50 clearly visible metaphases, and then present the SCE frequency per cell in form of a mean rate encountered therein. The mean rate is then compared either with the normal laboratory value or with the literature normals. Hovewer, we consider such an interpretation insufficient, and believe that the SCE ranges obtained both in the exposed and in the control group should also be reported. Namely, our previous experience shows the highest single SCE rate obtained in the exposed subjects to be far above the normal value in a majority, or even in all cases, even though the mean SCE frequency rate may be bellow normal.[15, 16]

Besides professional exposure, there is a number of interfering factors which may affect the SCE frequency. The most commonly encountered in literature are smoking, viral diseases, vaccines, oral contraceptives, radiodiagnostics and/or radiotherapy in the referent period from 6 months up to a year before sampling.[13] Subjects with a positive history of some of the foregoing interfering factors may either be automatically excluded from the investigation, or included in the proportion which does not exceed the statistically significant difference between the exposed and the control group. The latter has been applied in this paper, and confirmed by the Chi-square test.

The structural chromosomal aberration analysis is the method of choice in physical mutagen exposures, but it is also valuable in chemical mutagen exposures and particularly in simultaneous mixed exposures.[16] Several authors report a significant increase of the chromosomal aberration incidence among medical personnel handling cytostatics.[12, 17, 18] However, the incidence of structural chromosomal aberrations among our examinees was not found to be statistically singificantly higher in the exposed group ($p = 0.8$), though the tendency of their increase was evident, as compared with the controls.

Since a number of data from literature point out a positive correlation between changes in the somatic cell genome occurring among persons exposed to cytostatic agents and neoplasia, the results of such cytogenetic studies should be considered from the carcinogenesis point of view.

Establishing a teratogenic risk due to a particular type of professional exposure by a direct detection of sex cells chromosomal damage is

Table 1. Changes in the peripheral blood lymphocyte cell genome among both medical personnel handling cytostatic drugs and control persons.

EXPOSED GROUP

Subject	Age (years)	Duration of exposure (years)	Smoking (cig per day) (years)	ABERRATION YIELD Chromatid break	Chromo-somal break	Accentric	Dicentric	Tetra-ploidy	Total % of aber-rations	Mean SCE-rate	SCE-range
1.	56	37	40/20	1	2	2	-	1	2.5	8.4	4–18
2.	20	2	-	2	1	-	-	1	1.5	6.0	4–9
3.	21	2.5	-	3	-	3	1	-	3.5	8.4	3–13
4.	30	11	-	2	2	-	-	-	2	6.2	3–11
5.	29	8	6/10	2	2	1	-	-	2.5	8.8	4–17
6.	32	13	10/12	2	-	3	2	-	3.5	9,1	5–14
7.	53	27	15/30	5	1	2	-	-	4	9.9	5–16
8.	20	1.5	20/2	-	1	1	1	-	1.5	7.7	3–12
9.	32	12	15/5	-	2	-	-	-	2	6.7	4–12
10.	28	8	10/6	2	1	-	-	-	1.5	8.0	4–16
11.	35	15	-	2	1	2	-	1	2.5	6.2	4–11
12.	21	1.5	15/3	1	-	1	-	2	1	7.4	3–13
13.	21	1.5	15/3	1	-	1	-	2	1	7.4	3–13
14.	32	13	20/13	1	1	1	-	-	1.5	11.1	6–20
15.	44	25	-	3	1	-	-	-	2	6.4	4–9
16.	35	14.5	-	-	1	-	-	-	0.5	7.6	3–10
17.	32	12.5	10/4	-	1	2	1	1	2	6.3	4–10
Mean value	32.2	12.5		1.6	1.1	1.1	0.3	0.4	2.1	7.8	
± SD	9.9	9.4		1.02	0.44	0.78	0.50	0.49	0.92	1.4	
	p = 0.7								p = 0.8	p = 0.001	

CONTROL GROUP

Subject	Age (year)	Smoking (cig per day) (years)	ABERRATION YIELD Chromatid break	Chromo-somal break	Accentric	Tetraploidy	Total % of aberrations	Mean SCE-rate	SCE-range
1.	28	20/10	2	3	-	-	2.5	4.6	2–5
2.	30	-	1	2	1	-	2	4.8	0–5
3.	24	-	3	2	-	-	2.5	4.2	1–6
4.	21	10/10	2	2	1	-	2.5	5.8	2–6
5.	30	-	1	-	-	-	0.5	6.2	1–7
6.	31	-	1	1	-	-	1	6.4	3–7
7.	26	15/8	2	-	-	-	1	5.3	2–6
8.	40	-	1	1	1	1	1.5	4.3	2–5
9.	28	10/5	2	2	1	1	2.5	4.5	3–6
10.	34	-	-	1	-	-	0.5	4.8	2–5
11.	20	20/4	2	2	1	-	2.5	4.6	3–6
12.	42	-	3	1	-	-	2	4.8	2–5
13.	41	15/5	3	1	1	-	2.5	4.3	0–6
14.	29	-	3	2	1	1	3	4.8	0–5
15.	34	20/5	2	1	2	-	2.5	4.3	1–5
16.	24	-	3	1	-	-	2	4.8	2–6
17.	30	-	3	1	1	1	2.5	6.5	3–8
Mean value	30.1		2.0	1.4	0.58	0.24	1.97	5.0	
± SD	6.5						0.48	0.5	

a very complex and practically hardly applicable routine approach, the conclusions of which could be reached only by the follow-up of filial generations.[19] Therefore, indirect approaches are used, with a great attention being paid to the history data of the examinees. Selevan and co-workers indicate the fetal loss among nurses handling cytostatics to be 2 to 3 times higher than in the general population.[20] One of our examinees had a miscarriage in the first trimester of pregnancy, and another one reported psychosomatic abnormalities in both of her two children.

Workplace conditions, exposure regimens and the use of all the personal protective equipment available can considerably modify the primary noxious factor impact.[21] The work place conditions of the nurses comprised by this study were extremely inadequate (no flow hood available, minimal personal protection comprising only masks and gloves). Cytostatics were prepared in the room also used for other daily activities, including coffee breaks. Cytostatic storage and waste disposal did not meet the regulations. Though genotoxic effect of professional exposure to cytostatic drugs could not be entirely excluded in any of our previously studied risk groups, the results of investigation carried out in better equiped workplaces were significantly less indicative.[15, 16]

Conclusion

The results of this study confirm the suspected genotoxic effect of the professional exposure to cytostatic agents and advocate the need of a systematic health surveillance of the exposed occupational groups, as well as a regular application of all the safe handling practices in their workplaces.

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Etiology and primary cancer prevention

Maja Primic Žakelj

Institute of Oncology, Ljubljana, Slovenia

Cancer is a common name for a group of approximately 180 different diseases of more or less known etiology, and accordingly also of different possibilities of their prevention. Development of a particular type of cancer depends on a range of different factors from the environment, lifestyle, genetic makeup, and chance. Primary prevention involves changing lifestyle and environmental factors by health education and legislation. Several factors associated with an increased cancer risk as smoking, alcohol beverages, diet, reproductive and sexual behaviour, occupation, environmental pollution, certain drugs, ionising and nonionising radiation, biologic and psychological factors are discussed along with the possible preventive measures.

Key words: cancer, neoplasms-etiology; primary prevention

Introduction

Cancer is a common name for a group of approximately 180 different diseases of more or less known etiology, and accordingly also of different possibilities of their prevention. Carcinogenesis is a complex multistage process characterized by an irreversible change of the cell; in its further course the process results in an uncontrolled tumor growth and, if untreated, it invariably ends with a lethal outcome. The natural course of the disease is long, the period from the initial cell change to the clinical evidence of disease – i.e. latent period being 10 to 15 years or even more for a majority of cancers. Development of a particular type of cancer depends on a range or different factors from the environment, lifestyle, genetic makeup, and chance.[1]

Carcinogens associated with the environment and lifestyle, chemical, physical and biological agents, act as initiators, promoters or cocarcinogens. The initiators are genotoxic substances which cause irreversible cell change, mutation. Nevertheless, a tumor will develop only if after mutation the cell has been exposed also to the activity of promoters. In view of the primary prevention it is important to note that the effect of promoters is dose dependent and also reversible.[2] Cocarcinogens alone cannot initiate or promote malignant growth but they increase the metabolic activation of other carcinogens.

Neoplasms are ultimately the result of interplay between hereditary and environmental factors. The hereditary predisposition manifests itself in different ways. There can be mutation of individual genes present in rare hereditary syndromes, decreased ability for deoxyribonuc-

Correspondence to: Maja Primic Žakelj, MD, MSc, Institute of Oncology, Zaloška 2, 61105 Ljubljana, Slovenia.

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leic acid repair and the associated predisposition for somatic mutations, variability in the metabolism of chemical carcinogens, and hereditary disorders in the immune response.[3]

Carcinogens are investigated in laboratory and epidemiologic studies. The former comprise short-time tests on cell cultures and bacteria, as well as long-term animal experiments. Analytical epidemiological studies, both cohort and case-control are used to give direct answers to the question on carcinogenicity for humans.[4]

From the historical point of view, the first carcinogens discovered were those associated with a particular occupation, e.g. scrotal cancer in chimney sweeps and cancer of the urinary bladder in workers involved in aromatic amine production.[5] This fact is also responsible for the generally prevailing opinion that a majority of cancers can be attributed to the environmental pollution with chemicals. The results of various studies show, however, that pollution of both working and living environment play only a minor role in the total cancer burden.[1] Most of it is ascribed to carcinogens associated with lifestyle, smoking, excessive alcohol drinking, diet, excessive exposure to the sun.

In 1981 Doll and Peto estimated the proportion of cancer-related deaths in the United States that could be ascribed to the known risk factors (Table 1):[1]

Table 1. Proportion of cancer deaths attributed to various different factors.

Factor	Percent of all cancer deaths	
	best estimate %	range of acceptable estimates %
tobacco	30	25–40
alcohol	3	2–4
diet	35	10–70
food additives	<1	–5*–2
reproductive and sexual behaviour	7	1–13
occupation	4	2–8
pollution	4	<1–5
industrial products	<1	<1–2
medicines and medical procedures	1	0.5–3
geophysical factors	3	2–4
infection	10?	1–?
unknown	?	?

* Some factors are protective, thus negative value.

Here it should be pointed out that these data refer to mortality. UV radiation, on the other hand, causes skin cancer which practically never appears among causes of death, and therefore the proportion of this cancer in incidence is greater.

The measures of primary prevention aimed to completely eliminate or diminish as far as possible the exposure to carcinogens are on one hand considered a task of general public interest; legislation and surveillance should be implemented to ensure suitable living and working conditions. On the other hand, health education should be directed into increasing the awareness of the fact that cancer prevention can be most effectively realised by changes of lifestyle. This does not mean, however, that despite a large proportion of environment-related cancers, pri-

mary prevention could result in a cancer incidence decrease to the same extent. Namely, we still do not know all risk factors associated with the most frequent cancers (e.g. colorectal and prostate cancer in males and breast cancer in females), and on the other hand, fixed life habits such as smoking and diet are difficult to change. A decrease of lung cancer incidence in male population of the U.S.A., where smoking is on the decline, indicates, however, a certain success of primary prevention.[4]

What can we do to reduce cancer incidence at this time?

Smoking

Though the causative association between smoking and lung cancer was established as late as in the 50's of this century,[6, 7] today we can already conclude that approximately 85 % of all lung cancers in males and 75 % in females are attributable to smoking. Thus, smokers consuming two or more packs of cigarettes daily are 15–25-times more likely to die of lung cancer than nonsmokers.[8, 9] Tobacco smoke represents a combination of initiators and promoters. It contains at least 3600 ingredients. The main carcinogens are found in its solid part, i.e. tar. Particularly its polycyclic aromatic hydrocarbons act as contact carcinogens e.g. in the lung, larynx and pharynx, whereas remote organs are affected by substances such as *nitrosamines* and *aromatic amines* that are absorbed and activated. Cigarette smoking is associated also with cancers of other sites such as oral cavity, esophagus, urinary bladder, renal pelvis, pancreas, uterine cervix, and possibly also the liver.[10, 11, 12] The magnitude of cancer risk depends on age at start of smoking, duration of smoking, tar content in the tobacco smoke and intensity of inhalation (depth and rate of inhalation and duration of smoke detention in the lung). Nonsmokers exposed to environmental tobacco smoke are also at higher risk of cancer.[13] Pipe smoking increases the risk of cancer of the lip; pipe and cigar smoking are associated with an increased risk of cancer of the oral cavity, pharynx, esophagus and lung whereas the associated risk of bladder cancer is lower than in cigarette smoking. Chewing and snuffing of tobacco is associated with cancer of the oral cavity.[4]

The fact that lung cancer is difficult to detect in an early stage when it is still curable renders the prevention of this disease all the more important. In as many as two thirds of the patients the disease is detected only when advanced well beyond the possibility of cure. Therefore, the most effective measure for diminishing the incidence of tobacco-related cancers is never to smoke at all, or to give up smoking. It has been shown that the risk of cancer for ex-smokers decreases with length of time since stopping smoking, almost reaching the nonsmokers' level 10–15 years after the cessation of smoking.[14] Though the decrease of lung cancer incidence, observed in the male population of some West-European countries and North America, could be ascribed not only to an actual decrease in the rate of smokers, but partially also to the use of cigarettes with low tar content and filters, it is still true that a safe cigarette does not exist, and there will probably never be one.[4] Therefore, a proper health education encompassing the youngest population group, supported by corresponding legislation should be most effective.

Alcohol

Alcoholic beverages increase the risk of cancer of the oral cavity, larynx, pharynx and esophagus. There is a multiplicative interaction between alcohol and tobacco in inducing cancers of all these sites.[4] Different studies have shown that health hazard is associated with all types of alcoholic beverages and not only with strong spirits.[15] In studies in many countries, associations have been observed between the cancer of the rectum and beer consumption.[4] Though alcohol itself is not a carcinogen but rather a modulator of carcinogenesis which is induced by a chemical procarcinogen, it also can function as a tumor promoter and/or cocarcinogen. But *acetaldehyde,* a metabolite of ethanol, is

carcinogenic, and most probably increases the risk of esophageal cancer in non-smoking alcoholics.[16] Primary liver cancer is frequent in alcoholics who also suffer from liver cirrhosis. The role of alcohol in the etiology of breast cancer is not clear yet. A substantial number of case-control studies and cohort studies pointed out an association between alcohol intake and breast cancer. When such an association has been observed, the relative risks have generally been between 1.5 and 2 for intakes of alcohol that varied, by study, from 1 g/day to over 40 g/day.[17] The modest elevation in relative risk is potentially important because of the high incidence of breast cancer in many countries, and so attributable risk may be substantial.

As a possible prevention measure, reducing of daily intake of alcoholic beverages is by far the most important. It is recommended not to drink more than the equivalent of two small drinks per day.[18]

Nutrition

Through nutrition people are exposed to the greatest variety of different agents. The risk of cancer can be influenced either by foods and nutrients in their natural form, or by substances generated during the course of their storing, processing or digestion. Subject to investigation are also various additives used in order to preserve the food or change its color and taste, as well as unintentionally added substances such as pesticides, artificial fertilizers and industrial pollutants. On the other side, there are some dietary factors, which are known to play a protective role in the etiology of cancer. Further, cancer risk is also indirectly associated with hypernutrition, as well as with malnutrition, devoid of biologically valuable ingredients.[1]

Among the dietary factors implicated in the etiology of certain cancer sites are *heterocyclic aromatic amines* which are produced during frying and broiling of meat and fish, *salt* and salted foods, smoked food, *nitrozamines* produced from nitrates and nitrites and excessive fat consumption. Food storing gives rise to carcinogens such as *mycotoxins* (e.g. alfatoxins) which are associated with liver cancer. Fruit and vegetables are protective for most epithelial cancers, owing to their content of fibres, vitamins and minerals.[4]

During the last 50 years, the incidence of stomach cancer has been generally decreasing. The risk of this cancer is increased by excessive salt intake, smoked food and nitrozamines. Gastric cancer is presumably preceded by chronic atrophic gastritis caused among other things also by excessive salt intake and previous Helicobacter pylori infection.[19] Fruit and vegetables are protective for stomach cancer because of the vitamins A, C and E.

While the results of descriptive epidemiologic studies and animal experiments support an association between increased dietary fat intake and increased risk of breast cancer, evidence from analytic epidemiological studies is less consistent. Although few are significant, several of the retrospective studies of dietary fat indicate a small increase in risk, but prospective studies to date provide no support to the dietary fat hypothesis in breast cancer.[20, 21, 22] For colon cancer, accruing data from case-control and cohort studies tend to support an etiologic association.[23, 24, 25] Information on associations of fat intake with incidence of rectal, prostate and endometrial cancer is still limited.[25]

High consumption of fruit and vegetables is associated with decreased risk of cancer of most sites. The association is most marked for epithelial cancers of the respiratory and alimentary tracts and less convincing for hormone-dependent cancers. The consumption of vegetables and fruit in the raw form appears especially beneficial.[26] A large number of potentially anticarcinogenic agents are found in these food sources, including carotenoids, vitamins C and E, selenium, dietary fibre, dithiolthiones, glucosinolates, indoles etc. They induce detoxification enzymes, inhibit nitrosamine formation, provide a substrate for formation of antineoplastic agents, dilute and bind carcinogens in the digestive tract, alter hormone metabolism, have an antioxidant effect and inhibit carcinogenesis by quenching free radicals or singlet oxygen.[27]

It is presumed that calcium contained in dairy products, vegetables and fish also exerts a protective effect on colonic cancer.[28]

The protective effect of fibres for colon cancer has not been fully explained yet; thus it is not clear whether it should be ascribed to fibres *per se* or rather to other ingredients of fruit and vegetables. Likewise, also the protective role of fibres contained in cereals remains to be clarified.[29] Their protective action against breast cancer, which has been revealed by some epidemiological studies, is attributable to an increased estrogen secretion in feces, but plant antiestrogens may be involved also.[27]

In comparison with other risk factors, the impact of various additives in food (e.g. colors, preservatives, substances aimed to change color, consistency or taste of the food) is believed to be of minor importance.[1] It should be stressed, however, that the use of these chemicals should be controlled by legislation.

Based on the present knowledge, a balanced diet is recommended, whereas with respect to cancer prevention, the following guidelines should be followed:[18]

1. Reduce fat intake to less than 30 % of total calories with no more than 10 % of total calories from saturated fats, 6–8 % as polyunsaturated fats, and the remainder as monounsaturated fats. Appropriate dietary changes involve choosing leaner meats, fish, eating poultry without skin, choosing low-fat diary products and avoiding the use of added fat such as butter. Increased fish consumption is recommended in substitution for meats containing high levels of saturated fatty acids. With the reduction of dietary fat the calories missing should be substituted by whole grain and cereal products rather than by sugars.

2. Consume a variety of vegetables and fruits.

According to the World Health Organisation, 400 g/day of fruits and vegetables is recommended.[30] A major part of the ingested fibres should be derived from foods, particularly vegetable, rather than foods artificially enriched with fibre during manufacture.

3. Adjust exercise and food intake to maintain healthy body weight.

The key to this recommendation is balance of energy intake to match energy expenditure. The balance of exercise and food intake is particularly important in controlling obesity, and hence should be recommended to lower the risk of obesity associated cancers.

4. Avoid use of dietary supplements.

With a balanced diet according to these recommendations, there will be adequate consumption of all vitamins, other essential micronutrients and minerals, so there is no need for dietary supplementation. There is a belief widely held by the public that if something is good, more is better. The fallacy of this belief is found in the risk of toxic effects from megadoses of some substances, such as vitamin A and selenium. Taking a supplement but failing to reduce fat or consume adequate fruits and vegetables may place an individual at an unnecessarily increased risk of disease, overwhelming any possible benefits that the supplement may have brought.

5. Limit the use of salt and the consumption of salty, saltpreserved food and nitrites.

A suitable target is in the order of 6 g/day. It is an action especially to be stressed in the countries, where the incidence of stomach cancer is still high, such as in Slovenia.

These recommendations are directed to children from the age of 2, as well as adults of all ages. The applicability to children is important as for some cancers, particularly stomach and breast cancer, the effect of dietary risk factors may commence at an early age, i.e. in childhood and adolescence. Parents should therefore ensure that a correct dietary pattern is established early in life.

Reproductive and sexual behaviour

Reproductive and sexual behaviour is associated with cancers of the genital organs. Thus, breast cancer is more frequent in females with an early menarche, late menopause, who have never given birth or had their first child after the age of 35 years.[31] This is indicative of an

influence of sexual hormones though the exact mechanism of this action has not been explained yet.[32] An advanced age at first birth also increases the risk of endometrial and ovarian cancers.[4] It has also been found that cancer of the uterine cervix is more common in women with a history of early sexual life and who had multiple sexual partners.[33] Viral transmission has been suggested as the most probable reason for that; among the suspected viruses, those belonging to papilloma group have been studied most extensively.[34]

As to breast cancer prevention, apart from the recommendations for greater physical activity balanced nutrition, maintenance of normal body weight and earlier age at first birth, no other preventive measure have been suggested so far. Since recently, several trials are carried out on preventive use of tamoxifen in women at high risk. The opinions on these investigations are controversial, as it has not been clarified yet whether the benefit of such a treatment outweighs its potential hazard for healthy women.[35, 36] Beginning of sexual life at a later age and not changing sexual partners are suggested as preventive measures against cervical cancer; probably, condom and diaphragm can also be regarded as a useful protection.

Occupation

Occupational cancer represents a minor part of the total cancer burden (approximately 4 % of all cancers), though these are the cancers in which primary prevention is most effective. The group 1 of agents classified as carcinogenic to humans by International Agency for Research on Cancer[37] includes among others asbestos, some aromatic amines, arsenic, chromium (VI) compounds, vinyl chloride, solar radiation, mixtures as soots, coal-tars, coal-tar pitches, mineral oils as well as some complex exposures such as boot and shoe manufacture, furniture and cabinet making etc. The most common cancers due to occupation are those of the lung, paranasal sinuses, skin, urinary bladder and leukemias.

In studying all types of cancer, thus also occupational ones, it should be kept in mind that the latent period, i.e. a period from the beginning of exposure to carcinogen to clinical onset of the disease, is generally 10–30 years long. Thus, it is possible that the causative agent is a substance which is no longer in use. On the other hand, the possibility exists that some substances, having come into use recently, may exert their carcinogenic effect some time in the future. Considering the latent period, and the recent increase in the production and use of numerous chemicals, it can be expected that the present incidence of occupational cancers does not yet reflect the effect of these substances.

Preventive measures are effective only when supported by corresponding legislation; in this way, the production and use of certain substances can be effectively banned, or adequate measures can be enforced to prevent or diminish the possibility that workers get in direct contact with the carcinogenic substance, depending on the risk involved and on the possibility to have the agent replaced by a less dangerous one.[38] The use of protective equipment always comes last in the row of available measures. Equal attention should be paid to proper health education of industrial technologists, managers and workers.

Environmental pollution

American scientists believe that environmental pollution is not as important in etiology of cancer as it is often believed.[1] The association between air pollution and lung cancer is being studied, but apart from that, there are no other similar investigations carried out on possible relations with cancers of other sites. Polluted air contains several organic (e.g. policyclic hydrocarbons, soots etc.) and inorganic (e.g. asbestos) agents considered to be carcinogenic for humans or certain animal species. As the risk of lung cancer is significantly influenced by other carcinogens such as active and passive smoking, occupational carcinogens and radon, it is very difficult to assess quantitatively the impact of air pollution on the risk of lung

cancer. It is presumed that 1% of all lung cancers in the U.S.A. can be attributed to the polluted air in more dense urbane areas.[1]

Drinking water was also found to contain a large variety of known and suspected carcinogens, e.g. heavy metals, halogenated hydrocarbons and asbestos. It is difficult to evaluate to what extent this pollution contributes to cancer incidence.[4]

In view of the primary prevention, we should aim to reduce as far as possible the air and water pollution, and to monitor the quality of these natural resources with respect to accepted standards.

Drugs

Some drugs, particularly antineoplastic agents and combinations of agents (e.g. cyclophosphamide, MOPP), are also implicated in the etiology of cancer.[37] Considering their relevance for cancer treatment, the use of at least some of these drugs cannot be completely avoided. Therefore, combinations of more effective though less dangerous drugs are searched for.

As far as exogenous sex hormones are concerned, the estrogen replacement therapy, given to relieve symptoms of the climacteric, is associated with endometrial cancer.[4] Present evidence indicates no increased risk of breast cancer associated with prior use of oral contraceptives in women over 45 years of age.[39] There is a weak association between long term use of oral contraceptives and breast cancer diagnosed before the age of 36, and perhaps up to the age of 45,[39] especially if they were used before 25th year of age, or before first pregnancy.[40] On the other hand, oral contraceptives protect against cancers of the ovary and endometrium.[36]

Ionizing radiation

Among the physical factors, ionizing radiation is certainly one of the most thoroughly studied carcinogens; besides, the standards and regulations referring to radiation protection are most complete. The consequences of medium dose radiation were studied on survivors of the atomic bombs in Hiroshima and Nagasaki, on patients irradiated for medical reasons, as in persons occupationally exposed to ionizing radiation.[4] This radiation can cause all types of cancer, with the exception of chronic lymphatic leukemia and possibly Hodgkin's disease.[41] The influence of ionizing radiation depends on the type of rays (X or gamma, electrons, alpha particles and neutrons), the susceptibility of individual organs to radiation, the age at onset of exposure, and on sex. Also, the latent period differs with respect to different organs. Less is known about the consequences of low dose radiation.

In the last years, the presence of radon in dwelling places is a subject of great public concern. It has been known for a long time that the inhalation of radon from the uranium-radium decay chain, and particularly of its daughters bound to dust particles, causes lung cancer in uranium miners who have been for many years occupationally exposed to high concentrations of this gas.[41] The lung is affected by alpha particles that are emitted by the polonium daughters and damage only a thin layer of the exposed tissue. Radon in the environment originates from the earth surface, soil and minerals which contain a lot of radium. Radon emission from the surface of the continents represents four fifths of the total radon content (in the world). Underground and geothermal waters contain another 20% of dissolved radon, whereas all the oceans together contribute 1%. A very small proportion of radon in the environment can be ascribed to man's activity: 0.1% is due to uranium mines and deposits, and phosphate mining for artificial fertilizer production, whereas 0.002% result from fossil fuels, coal and earth gas burning. High concentrations of radon are not likely to occur in the outside environment since the air rich with radon mixes with the air from higher layers, whereas concentrations inside some buildings can be much higher owing to insufficient ventilation. Permeation through floor surfaces represents the most substantial source of radon in buildings, depending on the geological structure

of the ground. The highest concentrations can be found in the houses with wooden floors which are usually placed directly on the bare ground, whereas a thick concrete floor represents a considerable protection from radon permeation. A less important source is construction material, though it depends on the source of this material. In comparison with standard materials, the walls made of granite minerals, bricks from electrofilter ashes and walls of phosphate plaster contain higher quantities of radium and therefore represent a substantial source of radon in buildings.[42] It has been estimated that in the U.S.A. 10% of all lung cancers can be ascribed to radon in conjunction with smoking, whereas in Great Britain this proportion is 6%.[43] Namely, smoking and radon are supposed to act synergistically, but the two agents interact less than multiplicatively.[43, 44, 45] Excessive concentrations of radon in the homes can be avoided by respecting the accepted regulations for house-building and by regular ventilation.

The impact of too frequent, but above all unnecessary diagnostic radiographies should not be ignored either.[46] It has been pointed out that in up-to-date mammographies after the age of 50 the possible risk due to low dose radiation is outweighed by the benefit of early breast cancer detection.[47]

Nonionising radiation

Ultraviolet radiation is associated with the appearance of cancers of the skin and lip. Excessive sunbathing is also believed to increase the incidence of malignant melanoma.[48] Therefore, people are explicitly warned not to sunbathe between 11 a.m. and 3 p.m., and advised to use adequate protection equipment and creams.

Recently, possible harmfull effects of *low-frequency electromagnetic (EM) fields* have been frequently mentioned among physical factors. These appear in the vicinity of electric installations, transformations and electric appliances. It is still not clear to what extent an increased risk of leukemias in electro-industry workers can be ascribed to the effect of electromagnetic fields and what proportion of these conditions is due to other carcinogens. It has also not been explained yet to what extent the EM fields influence the incidence of childhood leukemias.[49, 50, 51] The relevant radiation emitted by computer and TV screens decreases by distance so rapidly that a prolonged sitting in front of these sources in comparison with the risk of cancer is a much greater danger for eye or backbone damage.

In view of primary prevention, however, exposure to all types of radiation should be avoided whenever possible.

Biological factors

As to biological factors, hepatitis B virus is associated with liver cancer, whereas Epstein-Barr virus plays a role in the etiology of Burkitt's lymphoma, Hodgkin's disease, B-lymphomas and nasopharyngeal carcinoma. Human T-lymphotrophic virus-type 1 is a suspected cause of certain leukemias (particularly in Japan and Africa). Patients with AIDS are prone to developing Kaposi's sarcoma and non-Hodgkin lymphoma; these patients were also found to be more frequently affected by some other cancers such as Hodgkin's disease, cancers of the oral cavity, colon, testis and pancreas.[4] An increased risk of certain cancers in persons with HIV infection is attributed to immunosuppression, though the HIV seropositive indivuduals are at a greater risk of developing non-Hodgkin lymphomas or Kaposi's sarcoma even without measurable immune deficiency.

Among parasitic diseases, schistosomiasis is associated with cancer of the urinary bladder, whereas infection with liver flukes contributes to the etiology of cholangiocarcinoma.[4] On the whole, however, these etiological factors are of minor importance, at least in Europe.

Vaccination against hepatitis is suggested as a preventive measure to decrease the risk of liver cancer.[52]

Psychological factors

Psychological factors arouse great public interest though their role in the etiology of cancer

is far from clear. Though the theory that certain personality types are more prone to cancer dates back in the 18th century, scientific research on the influence of personality characteristics is scarce.[4] This is partly attributable to the unexplained biologic mechanisms responsible for possible influence of these factors; investigations are centred on the influence on hormonal and immune systems. On the other hand, such studies are associated with several methodological problems.

The results of studies aimed to explain a correlation between different personality types and cancer incidence are controversial. Some investigators have established an increased risk of cancer in depressive persons,[53] whereas others claim just the opposite: in their opinion, less depressive people are more prone to cancer.[54] Another group of investigators is trying to establish possible correlation between a previous exposure to stressful events and cancer. According to some of these reports, such events (e.g. loss of a relative, marital partner or friend) before the onset of disease were not associated with breast cancer, whereas such a correlation was confirmed for some other sites such as lung, stomach and childhood cancers.[55] Should psychological factors become a more relevant subject of future epidemiologic investigations, adequate and standardized methods for their evaluation would have to be searched for, and all other possible risk factors considered. It is not known yet to what extent it is possible to change personality characteristics, but certainly, the adverse effects of stressful life events can be successfully diminished by adequate education and support. The question whether, and to what extent, this contributes to cancer prevention, remains to be answered.

Conclusion

In its program "Health for all by the year 2000", the World Health Organization has set the aim to reduce cancer mortality for 15% in the population under 65 years of age by the year 2000. This goal has been adopted also by the European Community in its program »Europe against Cancer«. For the purposes of health education, European Code with 10 commandments for primary and secondary cancer prevention has been prepared. In view of primary prevention, measures such as smoking cessation and moderation of alcohol consumption, diet rich with fruit and vegetables, maintenance of ideal body weight, avoidance of excessive exposure to the sun and following health and safety instructions at work have been suggested.[56] With our program "Slovenia 2000 and Cancer" under way since 1990 we are following the one from European Community.[57] Besides health education, legislation and surveillance are equally important in primary cancer prevention.[58]

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The twelfth biennial meeting of the EACR

April 4–7, 1993, Brussels

The twelfth biennial meeting of the **European Association for Cancer Research** (EACR) was attended by more than 350 participants, mostly from Europe. The program involved plenary lectures and satellite symposia along with a poster exhibition and selected oral presentations.

In plenary lectures distinguished researchers covered a wide field of cancer investigations. Some of the titles are as follows: *D. Bootsma* (Mülbock Memorial Lecture), The genetic defect in DNA repair deficiency syndromes; *F. Rilke*, Modern trends in pathological diagnosis of cancer; *D.P. Lane*, The p53 supperssor gene; *P. Boyle*, Epidemiology: critical assessment of cancer risk with special attention to passive smoking; *W. Birchmeier*, Cell adhesion molecules and motility factors in the regulation of tumor cell invasion, and *H. Rochefort*, Hormones and breast cancer.

During the three days of the meeting also 15 satellite symposia were held: Molecular aspects of cancer diagnosis, New trends in cancer chemotherapy, Viruses and cancer, Molecular epidemiology of cancer, Cell cycle regulation and cencer, Antibodies and cancer treatment, Tumor suppressor genes, Environmental carcinogenesis: exposure and mechanisms, Mechanisms of drug resistance, Growth factors, Molecular aspects of invasion and metastasis, T-cell responses against cancer cells, Colon cancer: molecular and clinical aspects, Oncogenes and Gene terapy in cancer.

New techniques in molecular biology enabled rapid development of basic science and found application in the clinics. Since it was impossible to attend all the lectures and symposia, only some of them will be pointed out. Basic facts of the presentations will be outlined and those important for clinical application mentioned.

The meeting was opened by D. Bootsma with an excellent lecture about genetic defects and DNA deficiency syndrome. He was the first to isolate and sequence a human gene involved in the DNA repair (ERCC1 gene). The integrity of DNA is crucial for cellular functions such as DNA replication and transcription. The lesions in DNA give rise to mutations, leading to genetic defects, carcinogenesis and cell death. During evolution complex DNA repair systems have been generated to cope with these lesions. The importance of repair mechanisms is obvious since a number of genetic diseases involve defective DNA repair. The best known is Xeroderma pigmentosum (XP). Patients with XP are very sensitive to ultraviolet light and are cancer prone. XP reveals the complexity of the DNA repair mechanisms in human cells which is reflected in extensive heterogeneity; so far, seven complementation groups (A–G) have been described. Besides XP two other genetic diseases have been found: Cockayne syndrome and Trichotiodystrophy. The patients with either of the two diseases are sensitive to UV light, but in contrary to XP, are not cancer prone. The first human gene thar corrects defect in XP has been cloned. It is ERCC3 gene that corrects defect in XPB group. Comparison of the coding sequence of this gene with sequences of the cloned (repair) genes of lower organisms, like yeast and Drosophylla, provides information of ther function. The broad function of the Drosophylla gene indicates its involvment in transcription. Similaray, ERCC3 gene is involved in the transcription in human genes. It has important role

in DNA unwinding. Its function as helicase is essential also in the repair of DNA damage. Therefore, about eight years after the first gene involved in DNA damage repair was discovered, its function has been recognized.

Increasing evidence indicates that deregulation of the cycle machinery may contribute directly to carcinogenesis. A better understanding of the cell cycle machinery is essential for functional determination of many oncogene and suppressor gene products. Therefore, cell cycle regulation is in the focus of interest of many research groups. The best picture how rapidly developing is this field was given by E.A. Nigg in his lecture. He commented a slide he was showing and was made in 1991 with the following words: "This is history". Similarly, like interest in the eighties was focused on growth factors, oncogenes and tumor suppressor genes, to resolve mechanisms involved in the cell cycle regulation, the interest in the nineties has been focused on cyclins. The identification of cell cycle regulatory molecules, which are activated in response to growth stimulation in G1 phase of cell cycle and are responsible for entry of the cells into S-phase is particularly important. In the last few years a pivotal role of protein phosphorylation in the transduction of growth regulatory signals was recognized. More recently, protein kinases and phosphatases have been shown to be the key components of the cell cycle progression. Specifically, cyclin kinases (cdks) were shown to control this process in all eucaryotes. These kinases are inactive as monomers, and require the association with cyclin regulatory subunits for activity. Cyclins control both, the activation and the substrate specificity of the catalytic unit as well as the initiation of the DNA replication and the onset of mitosis. So far, seven cdk's and ten cyclins are known that have the function in cell cycle progression. The first member of the cdk family identified was 34kD product of the cdc2/cdc28 gene ($P34^{cdc2}$). It controls the entry into mitosis, and its activity is regulated through cyclin-binding and phosphorilation and dephosphorilation. The exit from mitosis depends on cyclin destruction and concomitant inactivation of the $p34^{cdc2}$/cyclin B complex. Though not fully understood, several lines of evidence indicate that $p34^{cdc2}$ may trigger entry into mitosis not only by initiating regulatory pathways, but also by direct phosphorilation of lamin proteins, leading to the mitotic disassembly of the nuclear lamina

The importance of adhesion molecules and motifor entry into the S-phase. Cyclins A and E associate with cdk2 kinase, forming complexes that are active during late G1 (cyclin E) and during S-phase (both cyclins). Micro injection of antibodies or antisense cDNA to either cyclin A or cdk2 prevents cell from entering S-phase. D1 cyclin, expressed in the late G1 phase in response to growth stimulation of mouse macrophages with CSF-1, has been found to be overexpressed in a large fraction of breast carcinomas, esophageal carcinomas, in centrocytic lymphomas and other malignancies. Identified as PRAD1, it was overexpressed in parathyroid adenomas (G. Draetta) .

The suppressor gene p53 was the subject of several presentations, including a plenary lecture. This gene appears to be a negative regulation of cell cycle progression. Due to mutations that are found at high frequency in most human cancers, it turns from tumor suppressor gene to oncogene. There is a great interest in the role of p53 in hereditary cancers. The Li-Fraumeni syndrome, which includes breast cancer among a spectrum of malignancies, is associated with germ line mutation in the p53 gene, and overexpression of p53 protein is seen in malignant tissue. The normal p53 protein is sequence specific DNA binding protein that has many properties of transcription factor. The model presented by D.P. Lane suggests that p53 is a "guardian of the genome", acting as a protector of cells from genetic damage by inducing the cell cycle arrest. The normal protein has a very short half life, but DNA damage stabilizes it. In normal cells DNA damage induces, due to posttranscriptional modifications the accumulation of p53 protein in cell nucleus, and arrest of cells in the G1-phase of the cell cycle. During this arrest the cell can repair the damage before it enters into the S-phase. Alternatively, in damaged cells apoptosis will occur (apoptosis

is a particular form of active cell death that is extremely rapid and characterized by auto destruction of chromatin, cellular blebbing and condensation, and vesicularization of internal components). Cells that have mutated p53 (usually with high level of this protein) do not show G1 arrest following DNA damage. Therefore DNA damage will be present through subsequent phases of the cell cycle, resulting in mutations, aneuploidy etc. Normal p53 protein plays an essential role in apoptosis, but cells with mutated p53 cannot enter apoptosis. D.P. Lane's group recently determined that DNA binding function of p53 and its growth suppression activity is negatively regulated by the last 30 amino acids of the protein. Phosphorilation of this domain by casein kinase II can activate the p53 protein and this may represent a key regulator of p53 function.

The importance of adhesion molecules and motility factors was presented by W. Birchmeier. In the cell to cell contacts adhesion molecules are important and seem to be important also in cancer cell invasiveness. Invasiveness of tumor cells can be promoted by up- or down-regulation of the expression of different classes of molecules. For instance, down-regulation of the expression of epithelium specific cell adhesion molecule E-cahderin leads to increased motility and invasiveness of carcinoma cells in the culture. In fact, expression of E-cadherin molecule in squamous cell carcinoma (SCC) of the head and neck was found to be inversely correlated by both the loss of tumor differentiation and lymph node metastasis. Among other important adhesion factors are integrins. They bind to fibronectin in the cells, and their perturbed regulation is also associated with tumorogenicity. In the group of motility factors, scatter factor (SF) is important. It promotes the motility and invasiveness of a variety of epithelial and human carcinoma cells. Molecular and functional analysis revealed that SF and the liver specific mitogen Hepatocyte Growth Factor (HGF) are identical proteins, encoded by a single gene. Thus a novel signal cascade has been discovered, mediating both, cell motility and cell proliferation. The aberrant expression of these factors might be involved in the progression of carcinomas to a more malignant type.

P. Borts held a lecture about the mechanisms of multidrug resistance (MDR). MDR, which is the major cause of chemotherapy failure, is characterized by crossresistance of drugs with different structures and cellular targets (*Vinca* alkaloid, epipodophyllotoxins and anthracyclins). The classical MDR phenotype is caused by increased activity of plasma P-glycoprotein (Pgp), an efflux pump that reduces intracellular drug accumulation. The atypical MDR is also characterized by crossresistance phenotype, but in contrast to classical MDR, this cross-resistance does not involve *Vinca* alkaloids. The cause for atypical MDR is the alteration in the activity of topoizomerase II enzyme. The third non-typical MDR exhibits classical MDR phenotype, but is not mediated through P-glycoprotein. The gene responsible for this MDR is called MRP (MDR-Related Protein) and was described last year. It is thought to encode a protein of 1522 amino acids, belonging to super family of membrane transport genes, as well as *mdr* gene. Although the time from its discovery is short, it has been found that product of MRP has normal function in most human tissues. The konwledge of the presence of another transport protein involved in MDR phenotype has a very important clinical application: from the diagnosis to the modification of cancer treatment.

Several presentations were centered on new trends in cancer therapy. The growth autonomy, a typical feature of transformed cells, is achieved through autocrine production of growth factors (GF), expression of constitutively active GF receptors or a persistent stumulation of mitogenic signaling pathways. Therefore, strategies for the development of new anticancer agents involve growth factor antagonists, growth factor blockers or inhibitors of various enzymes participating in the transmission of mitogenic signals. H.H. Grunicke gave a condensed survey of presently available compounds directed against these target structures, from suramine and erbstatin to the inhibitors of protein kinase C.

An inert pro-drug can be converted to a highly toxic drug. In cancer therapy the obvious aim would be to convert the drug inside the tumor and nowhere else. T.A. Connors talked about pro-drug activation through (tumor) antibody enzyme conjugates. He presented the experimentally obtained results and the response of one clinical trial.

Antibodies have a very large application, all from basic research to clinical diagnosis and treatment. P. Pack presented a new system to obtain »mini« antibodies (with only variable part of the antibody) that can be multiplied in bacteria. Besides experimental data there were also clinical experiences in treatment of B lymphoid origin malignancies presented. Several approaches with different monoclonal antibodies were discussed. These malignancies were selected because they express a number of well characterized antigens that can be manipulated. The data presented indicate that this therapy is still at an experimental level, but in combination with biological therapy might yield promising results.

A very interesting symposia was dedicated to gene therapy in cancer. Presented were several approaches how to manipulate cells with genetic engineering and stimulate antitumor response. One of them is to produce inactive tumor cell vaccines which are constitutevely producing different cytokines or other molecules to enhance immunogenicity of tumor cells. It was reported that irradiated tumor cells expressing murine granulocyte-macrophage colony stimulating factor (muGM-CSF) stimulate potent, and specific anti-tumor immunity. These results may have important implications for the clinical use of genetically modified tumor cells as therapeutic cancer vaccines. The second approach is to restore or augment immunity by the adoptive transfer of T cell clones modifield by gene insertion. The results of reconstruction of viral immunity have been presented, and are encouraging. But the problem is to produce T-cell clones that survive long term *in vivo* without exogenous IL-2. This problem has been approached by a genetic construct of chimeric cytokine receptors that provide an autocrine loop for cell stimulation.

In this report only some of numerous presentations given at the Meeting are mentioned. As there were three satellite symposia held at once, it was impossible to follow all of them. But due to excellent organization, there was enough time for poster viewing (posters were on schedule all the day long) and for discussions with other participants at the Meeting. The overall impression about the meeting is, that it showed a very high scientific level covering a wide range of cancer research investigations, offering participants the possibility to learn about advances in cancer research from the most prominent investigators.

Maja Osmak, Ph.D.
Ruđer Bošković Institute, Zagreb
Gregor Serša, Ph.D.
Institute of Oncology, Ljubljana

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The twentyfifth annual meeting of the European Society for Radiation Biology

June 10–14, 1993, Stockholm

The 25th Annual Meeting of the European Society for Radiation Biology (ESRB) assembled more than 250 participants, maily from Europe, but also some from the USA and Japan. For the first time at such meetings, many scientists came from Eastern European countries.

Durnig the five days of the Meeting, two or three parallel sessions were held. They included Microdosimetry and radiation quality factors, Radiosensitivity and predictive assays, Epidemiology, DNA damage and repair, Radiation and combined treatments, Free radicals in biology, Targeted radiobiology and boron neutron capture therapy, Modifiers of radiation response, Mutagenesis and carcinogenesis, Biological dosimetry, Apoptosis, Radiecology and causes on man of nuclear accidents. It is obvious from the titles that ESRB Meeting covered a wide range of radiobiology – related topics: from basic investigations to patient treatment. In this report I point out the most interesting presentations.

The cell cycle arrest in the G2 phase that occurs after irradiation has been known for years. This arrest allows the cells to repair the damage before entering mitosis. Premature release from arrest occurs in irradiated cells after treatment with caffein. However, mechanisms involved in this processes and not understood. The recent discovery of proteins and protein complexes that control cell cycle progression shed some light on this subject. The studies performed with several embryonic systems and in mammalian somatic cells have demostrated that entry of cells in mitosis is conditioned by the level of cyclin (one of two components of MPF synthesized during interphase), and by a complex cycle of phosphorylation/dephosphorylation of the $p34^{cdc2}$-cyclin dimer. In Chinese hamster cells irradiated with x-rays the level of protein that repress chromosome condensation, the level of the hamster homologues of yeast gene product of the phosphatase cdc25, cyclins A and B appear constant after irradiation and subsequent caffein release. However, the subunits composition of the $p34^{cdc2}$ complex seems to change after irradiation and caffein release, mainly through the altered phosphorylation (J. Hain). Similar results were obtained with mouse zygotes of the BALB/c strain. Namely, in irradiated embryos caffein could induce MPF activation by acting at a step located upstream of $p34^{cdc2}$ dephosphoryation (P. Jacquet).

The role of oncogene expression in radioresistance has been studied for several years. The contradictory data published in the literature, especially about expression of the *ras* oncogene and radioresistance, were presented also at the ESRB Meeting. The radioresistance was found in NIH3T3 cells transformed with *ras* oncogene. This resistance correlated with the level of glutathione (GSH), while the addition of GSH-synthesis inhibitor butathione sulfoximine resulted in drug dose and drug exposure time – dependent decrease in the *ras* transcript (A.C. Miller). Opposite results were also shown. The relation between c-Ha-*ras* and c-*mos* oncogenes and the radioresistance of clinical biopsies from human carcinomas of the uterine cervix was examined. Rearrangements of the *ras* oncogene were found in 9 biopsies, and in 5 of them tumors were characterized as radiosensitive (B. Zhivotovsky). Therefore, it was demonstrated

again that expression of the *ras* oncogene can not be unambiguously correlated with radioresistance.

Also in radiobiology the apoptosis is one of the "hot spots" of investigation. Soon after x-rays were discovered, their lethal effect on biological systems became apparent. The mechanisms involved in cell death of irradiated cells are still of interest. Radiation induces death of various cells. The mode of death (apoptosis or necrosis) seems to depend on the dose of irradiation. For example, low-dose iradiation activates apoptosis in lymphoid cells, whereas at high doses these cells will die of necrosis. Therefore, the susceptibility of different cell types to undergo apoptosis correlates with their radiosensitivity. It is not quite clear what triggers apoptosis. That could be a) DNA damage with excessive formation of DNA strand breaks or b) glucocorticoids, with intracellular Ca^{2+} signal (calcium is involved in early chromatin changes and together with Mg^{2+} activates endonuclease responsible for the genome fragmentation typical for apoptosis). However, the importance of calcium in apoptosis depends on the cell line examined: it is important for irradiated rat thymocytes, but not for irradiated splenocytes. Apoptosis can be triggered also by the depletion of growth factors, that leads to a disbalance of the expression of oncogenes. The direct involvement of oncogene, and that p53 supressor oncogene in apoptosis, was shown in transgenic mice transfected with mutated p53. The thymocytes of these animals exhibited increased radioresistance. Increasing evidence suggests that imbalance of several signalling systems, rather than the dysfunction of a single one, may decide whether a cell is entering apoptotic program or not (L. Szumiel; B. Zhovotovsky).

Cancer is, and will remain a major human and economic problem for a long time to come. In the future, most patients will be treated by radiotherapy, with or without surgery. Two important lines of development may lead to a more efficient treatment and higher quality of life: reduction of the total mass of malignant cells through improved local treatment of macroscopic tumors ("macrotumor therapy") and by regional or systemic treatment of remaining infiltrating or disseminated microscopic growth through cell-seeking and cell-killing substances ("micromolecular therapy"). Both these types of treatment modalities have great potential of development (especially through application of molecular biology) for specific modification of radiation damage or in the search for new principles in systemic therapy (B. Larsson). In such investigations targeted radiotherapy which involves selective tumor cell kill by delivery of radionuclides, preferentially to malignant cells, takes an important place. Molecular delivery vehicles in use at present are monoclonal antibodies (M. Essand) and molecules which are selectively taken up or connected with tumor cells (L. Gedda). Factors which determine the effectiveness of targeted radiotherapy and the absolute and relative uptake of targeting agent by tumor cells, the range of emitted nuclear particles, and the uniformity of radionuclide depsition within solid tumors. The most important radiobiological variables are the intrinsic radiosensitivity of tumor cells and the dose rate of irradiation (T.W. Wheldon). Targeted therapy using ß–emitters such as ^{131}I is most effective in sterilization of large micrometastases which are likely to escape sterilization by other means.

Radiological principles and microdosimetric considerations have been applied in the treatment of advanced neuroblastoma. Five children so far have been treated with ^{131}-meta-iodobenzyl-guanidine, followed by a single infusion of melphalan, and with 7×1.8 Gy total body irradiation (M.N. Gaze).

The inherent radiosensitivity of tumor cells is recognised as an important determinant of the outcome of radiotherapy. Cell lines derrived from human tumors exhibit considerable differences in radiosensitivity, and are greater at low dose rates (1 Gy/h) than at high. Current models of radiation cell killing envisage a linear component that involves non-recoverable damage, dominating the cell killing at a low dose rate. The individualisation of clinical radiotherapy requires the measurement of cellular radio-

sensitivity, which provides useful information on radiosensitivity of both tumor cells and also of normal-tissue cells the response of which limits radiation dose. Besides cell survival assays which are usually too slow for routine use, studies are under way to indentify assays based on DNA damage, either its initial level or the extent of damage remaining after a repair interval. These assays are rapid, but their predicitve power is yet to be fully evaluated (G. Steel).

A direct correlation was obtained (for the first time) between cellular and tissue sensitivity in a group of fibroblasts from cancer patients, using low levels of irradiation and low dose rates. As significant individual differences in normal-tissue radiosensitivity were observed, such information about radiosensitivity of normal tissues obtained by *in vitro* systems should be included as an integral part of radiotherapy scheduling (J.H. Peacock).

My presentation in this Meeting was aimed to show, that cells preirradiated with multiple fractions of gamma ray doses, change their sensitivity to subsequent treatment with cytostatics. The possible mechanisms involved in this phenomenon were pointed out.

The ESRB Meeting was organized so, that each session started with a plenary lecture(s), followed by poster session, and ended with a workshop. The posters were displayed during the whole meeting, thus enabling the participants to see and discuss them all. It can be concluded, that the Annual Meeting of ESRB held this year in Stockholm showed a very high scientific level. It covered a wide range of radiobiology investigations, giving the participants the opportunity to get acquainted with the latest data from the research in radiobiology.

Maja Osmak, Ph.D.
Ruđer Bošković Institute, Zagreb

Notices

Notices submitted for publication should contain a mailing address and phone number of a contact person or department.

Ultrasound

The 8th international congress on the ultrasonic examination of the breast will take place in Hiedelberg, Germany, *July 1–4, 1993.*

Contact Mrs. Renate Meier, CIS Congress & Incoming Service GmbH, P.O.Box 10 46 23, D-6900 Heidelberg, Germany; or call + 49 6221 166 097. Fax: + 49 6221 12 112.

Vascular intervention

The 4th international course on peripheral vascular intervention will be held in Nancy, France, *October 20–23, 1993.*

Contact M. Henry M.D., 80, rue Raymond Poincare, 54000 Nancy, France; or call + 33 83 27 61 08. Fax: + 33 83 28 75 26.

Gynecological oncology

The Latin-America ESO course will take place in Caracas, Venezuela, *November 22–23, 1993.*

Contact A. Rancati, Av. Pueyrredon 1461, 1118 Buenos Aires, Argentina; or call + 55 51 33 62 221. Fax: + 55 51 33 62 221.

Gynecological oncology

The Latin-America ESO course will take place in Mexico (DF), Mexico, *November 25–26, 1993.*

Contact A. Rancati, Av. Pueyrredon 1461, 1118 Buenos Aires, Argentina; or call + 55 51 33 62 221. Fax: + 55 51 33 62 221.

Cancer registration, creation and use of data

The ESO residential course will be offered in Denmark, *December 3–6, 1993.*

Contact ESO Copenhagen Office, c/o Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen; or call + 45 35 268 866. Fax: + 45 35 264 560.

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Researchers, clinicians, engineers and manufacturers working or interested in the field of bioelectromagnetics are invited to participate in the Congress.

For more information please do not hesitate to contact

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IMPORTANT DATES

Submission of abstracts: 15th July 1993
Notification of acceptance: 15th September 1993
Early registration: 15th October 1993

ICR'94

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18th INTERNATIONAL CONGRESS OF RADIOLOGY

23–28 JANUARY 1994

The Congress is organised by the Singapore Radiological Society under the auspices of the International Society of Radiology. It is co-sponsored by the World Health Organisation, Radiological Society of North America, Ministry of Health, Singapore, National University of Singapore and Academy of Medicine, Singapore. The scientific sessions will include a comprehensive theaching programme, free paper and poster sessions. The teaching programme will feature some of the fremost experts in the various aspects of Radiology. There will be ten simultaneous sessions. The teaching courses include the following topics:

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Deadline for Advance Registration: 31 Avgust 1993
Deadline for Submission of Abstracts: 31 May 1993

Registration Fees: S$ 800 (approx. US$ 500)

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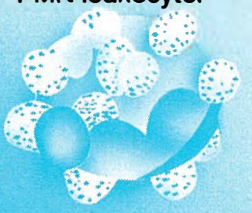

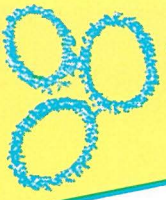

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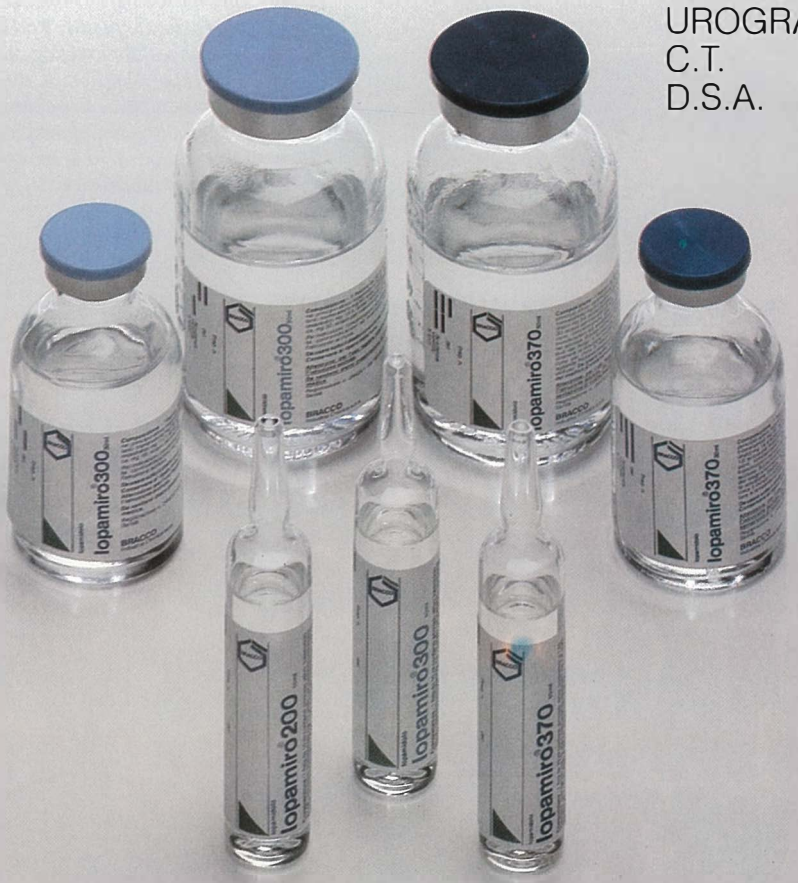

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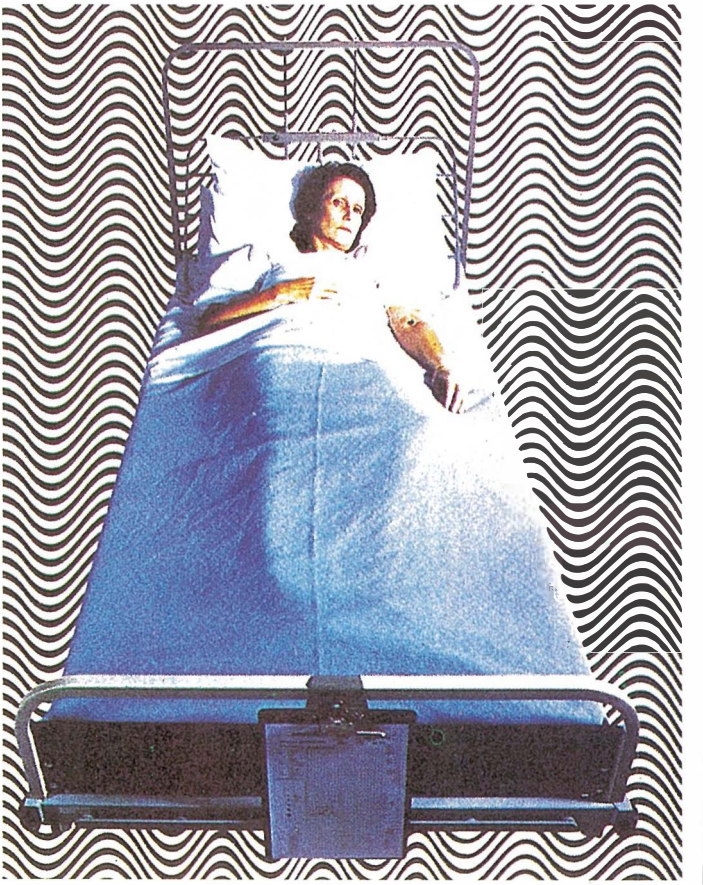

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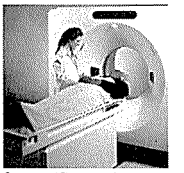

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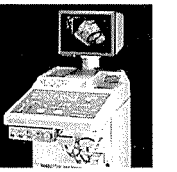

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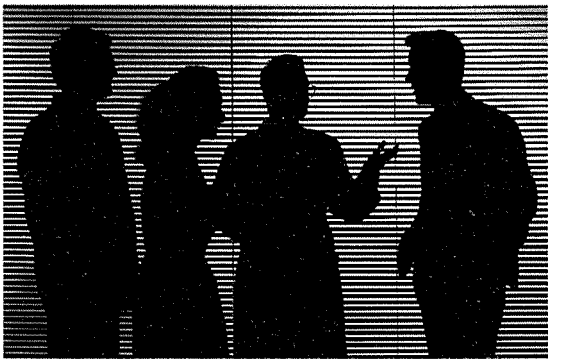

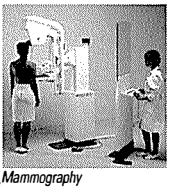

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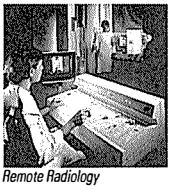

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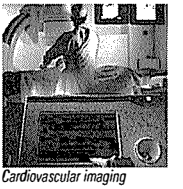

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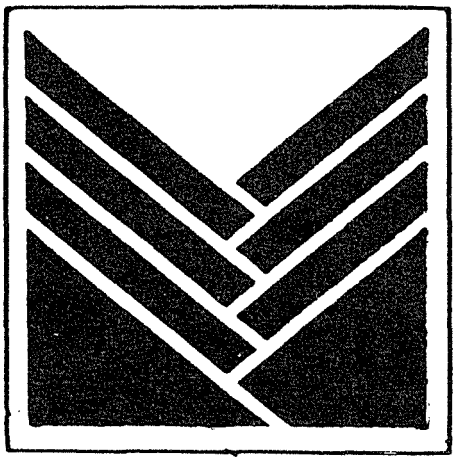

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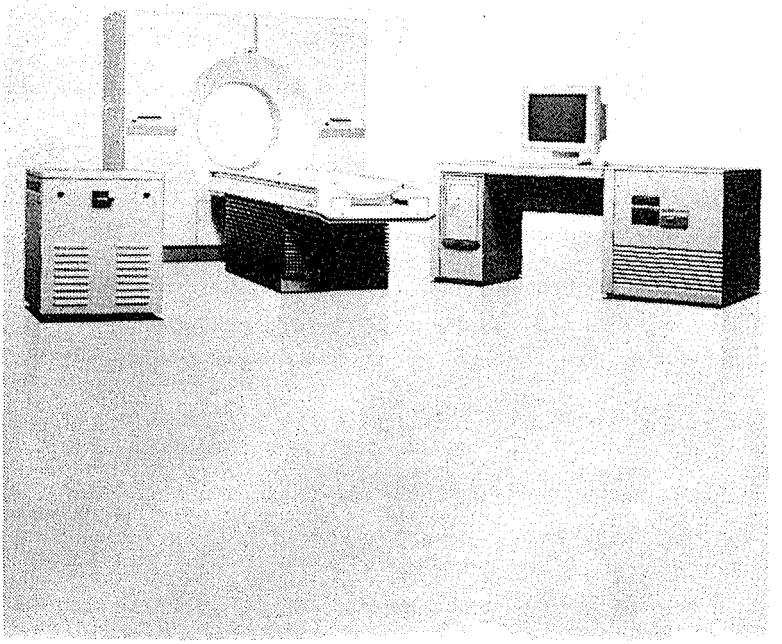

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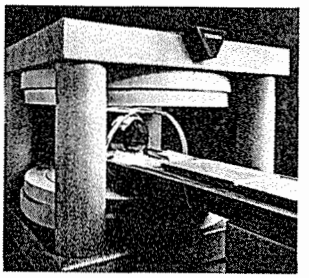

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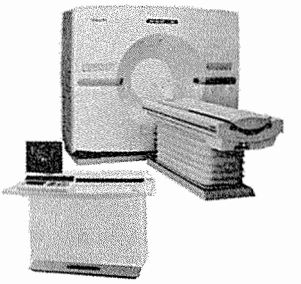

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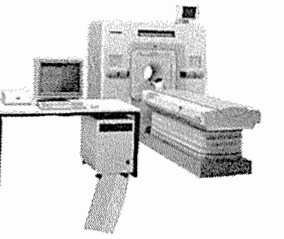

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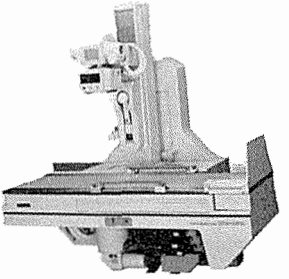

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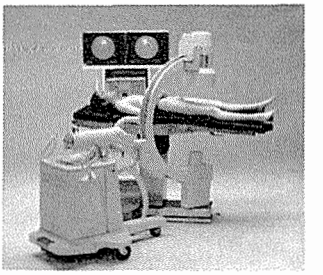

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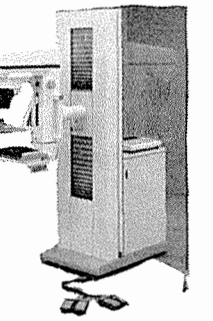

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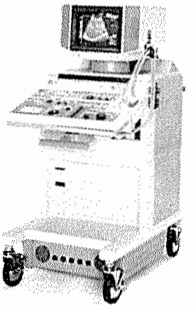

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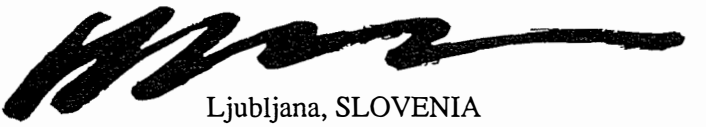

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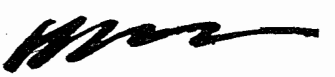

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