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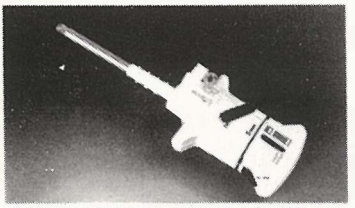

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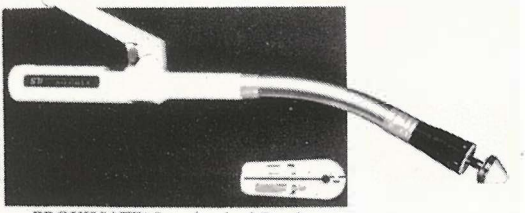

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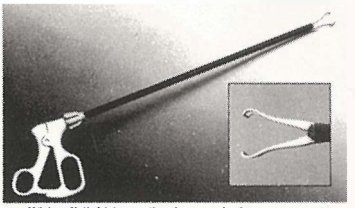

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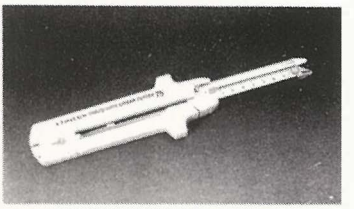

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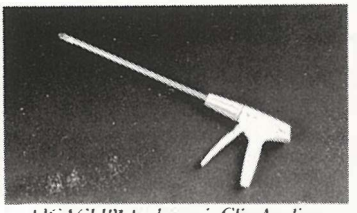

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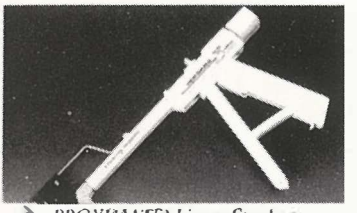

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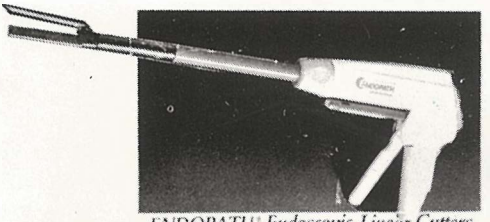

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INTERVENTIONAL RADIOLOGY

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REPORT

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Transcatheter balloon valvuloplasty

Dušan Pavčnik,[1] Andrej Cijan,[2] Vlado Bricelj[3]

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Authors describe percutaneous balloon valvuloplasty in congenital and acquired heart disease. In pulmonary, mitral and aortic stenotic valve, balloon valvuloplasty splits fused commissures and fractures calcific deposits. Since 1987 we performed 13 pulmonary, 26 mitral and 5 aortic valve dilatation. The method is recently used as a method of choice in isolated pulmonary valve stenosis, and as an alternative to surgical commissurotomy in mitral valve stenosis. Aortic valvuloplasty is performed in patients who are not candidates for surgery or for whom surgery carries a very high risk.

Key words: heart valve diseases-therapy; angioplasty, balloon; percutaneous balloon valvuloplasty; pulmonary, mitral and aortic valve

Introduction

The idea that catheter could be used to treat pulmonary valve stenosis was first proposed by Limon Larson in 1960, but Dotter and Judkins first described a catheter technique to dilate peripleural arteries stenosis in 1964.[1] In 1974, Andreas Gruntzig developed a noncompliant balloon and performed the first coronary angioplasty in 1977.[2] Kan et al., in 1982 performed fist balloon valvuloplasty for pulmonary stenosis,[3] Inoue et al. for mitral valve stenosis[4] and Lababidi et al. for aortic valve stenosis.[5] In our institution percutaneous valvuloplasty has been performed since 1987.[6, 7]

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UDC: 616.126.4-089.819.5

Material and methods

Pulmonary valve

Between 1987 and April 1993 balloon valvuloplasty was used to treat congenital pulmonary valve stenosis (PS) in 13 patients. Their age ranged from 10 days to 18 years. All patients had isolated pulmonary valve stenosis with no associated cardiac defects. PS diagnosed by sector scan, pulsed, continuous and colour Doppler echocardiography underwent cardiac catheterisation and angiography. A pullback pressure recording across the pulmonary valve was performed. The mean peak systolic pulmonary valve gradient was 75 ± 26 mm Hg.

The right sided 5-French catheter through the pulmonary valve was then replaced over 0.035 inch guide wire with balloon catheter (Meditech, Schnider or Balt). The balloons

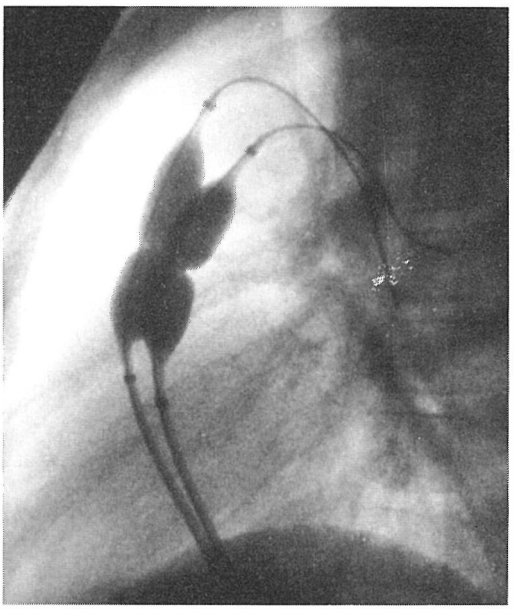

Figure 1. Two balloons of 8 mm in diameter centred across the stenotic pulmonary valve in an early phase of inflation – lateral view.

were from 6 mm to 18 mm in diameter. Balloon diameters were approximately 10 % larger than the diameter of the pulmonary valve annulus. It can be used as single or double balloon technique (Figure 1).

Mitral valve

Between 1988 and May 1993, we undertook balloon dilatation of mitral stenosis in 16 female and 10 male patients. In this group of 26 patients the mean age was 46 years (range: 31–75 years), left atrium diameter (echo) was 4.5 ± 6.7 mm × 7.5 ± 5.5 mm. Patients presented with severe symptoms: 3 patients were in NYHA class II, 19 patients in class III and 4 patients in class IV.

Echocardiographic evaluation showed mild regurgitation (n = 6, Sellers grade 1).

Fluoroscopy documented evidence of valve calcification in 6 patients. Babič's retrograde transarterial approach with double balloon technique[8] was performed in 11 patients and Inoue single balloon technique[4] with transeptal approach in 15 patients.

The Inoue technique is simple and takes the shortest time in comparison with all other techniques. A curved guide wire of 0.025 inch is inserted in the left atrium after transseptal puncture. The septum is then dilated by a 14-French dilator. A single balloon (Toray Medical Co., Tokyo) which fits well into the annulus is inflated until waist disappears.

Haemodynamic parameters (PCW, MG, PT and CO) and echocardiography (MVA) were compared before and after procedure. Statistical analysis was made. The long term observation of clinical state and measurement were performed in 15 patients.

Aortic valve

Percutaneous balloon valvuloplasty was performed between 1989 and 1993 in 5 patients. One patient, 22 years of age, had congenital aortic valve stenosis and 4 patients (mean age 81 years) had severe calcified aortic stenosis, and were not candidates for surgery. The technique of dilatation is grossly similar to that mentioned above. Left heart catheterisation is done by the femoral route, the aortic orifice is crossed with standard 0.038 inch or 0.035 inch guide wire. Over the wire a standard 7-French catheter is introduced into the left ventricle and left ventricular and aortic pressures are recorded to measure the transvalvular systolic gradient. Then 300 m long 0.038 inch guide wire is positioned through the 7-French catheter into the left ventricle, the catheter is removed and the balloon catheter (Meditech or Balt) is introduced over the wire across the aortic valve. Balloons are 40 mm long and inflated diameter is up to 30 mm. The balloon is inflated with diluted contrast medium for a few seconds.

Results

Pulmonary valve

Technically successful dilatation was achieved in 12 of the 13 patients. In one case we were

not able to cross the critical stenosis with a guide wire, and the patient later underwent surgery. In 12 patients dilatation was successful. Transvalvular gradient was reduced from 75 ± 26 mm Hg to 29 ± 16 mm Hg after valvuloplasty ($p < 0.001$).

We had one complication – perforation of the right ventricle outflow tract with a 0.021 inch e 1982, the efficacy and safety of this pulmonary valve stenosis in an attempt to perform balloon dilatation of the pulmonary valve. The complication was diagnosed by contrast injection into the pericardium. The infant was followed by sector scan echocardiography and recovered completely from the injury. The dilatation was successfully repeated a few days later with a soft tipped wire to cross the pulmonary valve.

Mitral valve

Successful dilatation produced a functional improvement in 24 of the 26 patients. In those cases valvuloplasty resulted in significant decrease in PCW from 24.3 ± 5.2 mm Hg to 14.5 ± 4.2 mm Hg ($p < 0.0001$), mitral gradient from 15.7 ± 4.1 mm Hg to 6.9 ± 3.1 mm Hg ($p < 0.0001$). Mitral valve area increased from 1.00 ± 0.002 cm^2 to 1.8 ± 0.03 cm^2 ($p < 0.0001$).

Follow up of 15 patients revealed slight reduction of MVA in all patients. In 3 patients replacement of mitral valve after 12–16 months was done. Twelve patients are still in good haemodynamic and clinical state (36 months).

At the end of the hospital stay 18 patients were in NYHA clas I or II, 6 in class III and two in class IV.

We had some mild complications as menshened bellow, but no death or embolic phenomena occurred in this serie. Four patients had insignificant left to right shunt of atrial septum.

There were two unsuccessful procedures. Mitral regurgitation developed in one patient with calcified valve and in another pulmonary oedema developed. Mitral valve replacement was necessary.

Aortic valve

In all five patients dilatation of the valve was successful, transvalvular gradient was reduced. In patients with congenital aortic valve stenosis the transvalvular pressure gradient was reduced from 75 to 30 mm Hg. In this case a mild aortic regurgitatation increased from I to stage II after procedure. One additional aortic regurgitation was noted in the remaining 4 patients. No further complications occurred. Redilatation was performed in one patient with residual stenosis.

Discussion

Pulmonary valve

Pathology that occurs in congenital pulmonary valve stenosis is characterized by commissural fusion of the cusps. In cases with central or lateral perforation a tipical dome shaped deformity is recognizable. In such valve deformity, balloon dilatation can be successfully applied with low risk.[9] Significant reductions of pulmonary valve pressure gradients immediately after percutaneous balloon valvuloplasty and at follow-up studies indicate that the relief of pulmonary stenosis from commissural splitting or cusp teating is almost permanent.[10] When infundibular stenosis accompanied pulmonary stenosis the procedure was less efficient.[9]

Since 1982, the efficacy and safety of this technique has been fully established and more than 1000 cases have been reported. It is considered a procedure of choice for the pulmony valve stenosis. It is the most common interventional procedure performed on cardiac catherizations in children.[10]

Mitral valve

Mitral valve stenosis remains the commonest of all cardiac valve disorders as a result of rheumatic heart disease in the developing countries.

Since 1983 three technique have been developed. Antegrade double balloon technique, re-

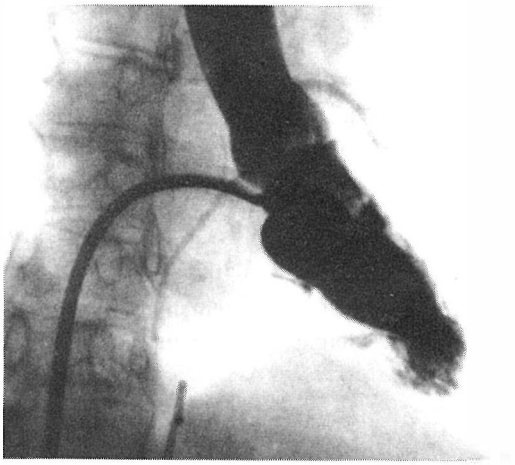

Figure 2. Inoue balloon mitral valvuloplasty. Inflated balloon across the narrow mitral valve.

trograde double balloon technique and Inoue balloon technique.[4, 8, 9] *Antegrade double balloon technique* was in the past the most widely used technique. Besides complications resulting from transseptal puncture, embolic phenomenon or mitral regurgitation which can happen in all the techniques, left to right shunting is frequent in this technique as the atrial septum has to be dilated to insert dilation balloon catheters. During follow-up period, most of the shunts disappear. A well conducted study has shown that about 10 % of all the patients who underwent this technique, had a significant shunt after a period of 6 months.[11, 12] We never used this technique in our hospital.

Retrograde double balloon technique. In this technique, the balloons are inserted through the femoral arteries over long guide wires which are inserted in the femoral vein and brough into the aorta through a transseptal puncture and exteriorised through femoral arteries by the help of a snare. This procedure has the advantage of not producing any left to right shunt. This technique is relatively complex. Local complications at the site of femoral arteries are more frequent.[13] This technique was used in our hospital in 11 patients.

Inoue balloon technique. Inoue who has performed more than 1000 cases of mitral balloon valvuloplasties has named this procedure as percutaneous transluminal mitral commissurotomy (PTMC). This technique has a lot of advantages over other techniques, however, the major drawback has been the short time available for the procedure in order to minimize the complications rate[14] (Figure 2).

Closed mitral commissurotomy was for a long time the only effective treatment for mitral stenosis.[15] Balloon mitral valvuloplasty is undoubtedly an attractive alternative to surgical commissurotomy. Initially, it was limited to young patients with pliable non-calcified valves. Mitral valvuloplasty has now been extended to calcified valves and in patients with moderate involvement of the subvalvular apparatus. The commissural splitting is a mechanism in successful balloon technique. A good haemodynamic stability was achieved in 70 % of patients for five years if one commissure was split and in 89 % of patients if both commissures were split. In patients with calcified valves dilatation improves valve area through commissural opening and fracturing the nodular depozit.[16, 17]

Its use in recurrent mitral stenosis is safe and effective.

The main contraindications for this technique is presence of fresh thrombus and significant mitral regurgitation.

Aortic valve

The clinical improvement of dilated patients is often dramatic, but restenosis note is considerably high.[18] It is unknown which patients will receive long term benefits from balloon dilatations.[19]

It appears to be a technique of choice in patients who are not surgical candidates or for whom surgery carries a very high risk, i.e. mainly in elderly patients. It is also considered as an effective and less invasive alternative to surgical valvotomy in infants and children particularly in the cases of restenosis after surgical valvotomy where the need for the implantation of a prosthetic valve is otherwise mandatory.

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Radiol Oncol 1993; 27: 180-5.

Percutaneous removal and replacement of occluded biliary endoprostheses

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Percutaneous removal and replacement of occluded biliary endoprostheses performed five times in three patients with highly located malignant biliary stenoses are presented. Percutaneous manipulation and its difficulties are discussed in detail. The methods available for treating obstructed endoprostheses are also described with special regard to percutaneous approach. Percutaneous stent exchange was performed once in one patient, and twice in two other patients. With all these interventions a survival of 25, 60 and 89 weeks, respectively, could be achieved. The authors emphasize that percutaneous method is indicated only if endoscopic attempts are excluded or have failed. Despite its invasiveness percutaneous stent replacement in skilled hands is considered a relatively simple and safe procedure which is able to improve greatly the patient's quality of life.

Key words: bile ducts, interventional procedure, bile ducts neoplasms-surgery, stents, endoprosthesis – transhepatic removal of stents, biliary endoprosthesis; complications, prosthesis failure

Introduction

Insertion of a percutaneous transhepatic endoprosthesis is an accepted option for the palliative treatment of inoperable malignant strictures of the bile duct mainly if there is no chance for an endoscopic stent placement. One of the major arguments against percutaneously placed endoprostheses, however, is the difficulty of replacing or exchanging them percutaneously when they become occluded. The fact that hilar, intrahepatic and/or multiple lesions can only be treated by percutaneous precedures including insertion of double/multiple endoprostheses further complicates this problem. For this reason, some interventional radiologists reserve endoprosthesis for patients with a short life expectancy.[1] An increasing number of radiologists consider that the drawbacks of external/internal drainage render the use of this system for the relief of biliary obstruction in appropriate for most patients with malignant disease, including those with a relatively long life expectancy.[2,3,4]

In our institution the patients who are not surgical candidates or not suitable for endoscopic stent placement receive one or more percutaneously placed endoprostheses instead of one or more external/internal catheters. For this reason, we are ready to treat the occluded endoprostheses either endoscopically or percutaneously.

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We present here our experience gained in 3 patients with exchanging endoprostheses 5 times by percutaneous approach.

Patients and methods

All three patients had malignant bile duct obstruction, where tumorous lesions were highly located and/or intrahepatic (No 1: gallbladder carcinoma, No 2: cholangiocarcinoma, No 3: gastric carcinoma – shigellocellular type). In two patients a 14 French Carey-Coons endoprosthesis (Meditech, U.S.A.), while in one a 12 French Lammer endoprosthesis (COOK) had been inserted using a several-step technique. In patient No 3 another Allison-Gibson spiral shaped stent (COOK) had also been placed to create and maintain communication between the two lobes of the liver.

All patients presented with recurrent jaundice (19, 26 an 48 weeks after the initial stent placement). In patient No 3, two successful endoscopic removals and replacements of the occluded prostheses in the common bile duct had been carried out in a period of 48 weeks.

Ultrasound examination confirmed the suspected occlusion. In patient No 3 an attempt for endoscopic exchange failed at that time.

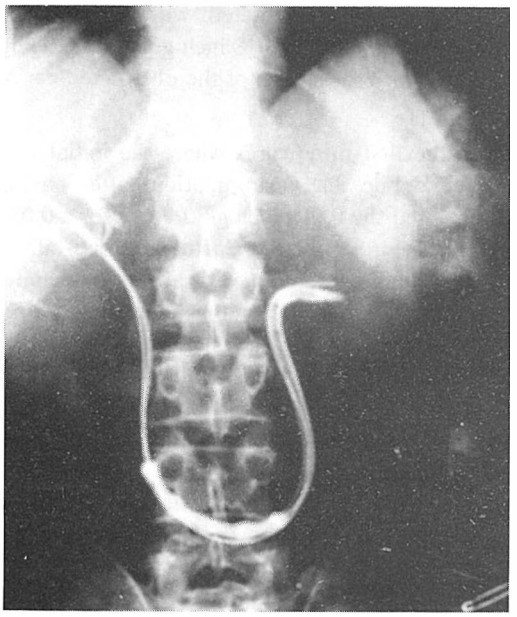
Transhepatic cholangiography (PTC) was then performed and an appropriate segmental bile duct leading directly to the proximal end hole of the occluded endoprosthesis was chosen for another fine needle puncture. In all of three cases after a successful puncture of the right bile duct a 0.018 inch superglide guide wire with excellent torque control (Radiofocus^{R}, Terumo, Japan) was inserted through the lumen of a Chiba needle.

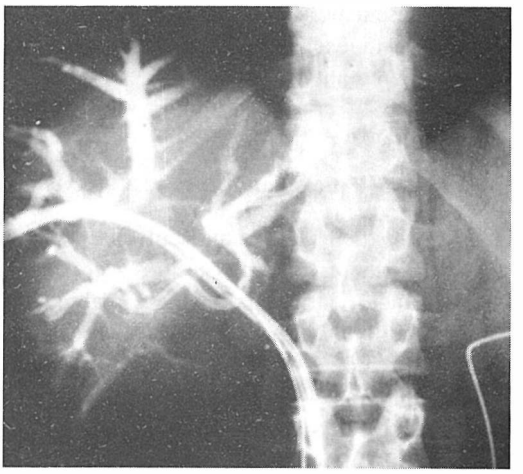
In patients No 2 and No 3 (21 and 22 weeks later) further attempts were made to exchange the existing endoprosthesis for another one. In these cases, the proximal extension of the tumor did not leave enough room for sufficient manipulation from the right bile duct leading to the proximal end of the endoprosthesis. Therefore, the proximal end hole of the stent was directly punctured and cannulated with a 22 gauge Chiba needle and a 0.018 inch guide wire being inserted into the lumen of the obstructed endoprosthesis.

In the first three cases where the initial step included bile duct manipulation, after having exchanged the 0.018 inch guide wire for a 0.038 inch wire, a 9.3 French Portner-Koolpe biliary biopsy device (COOK) with a double channel was inserted over the 0.038 inch guide wire. This wire served later as a "safety" guide, while another 0.032 inch superglide wire with excellent steerability was also placed into the common bile duct for cannulating the clogged lumen of the stent. After withdrawal of the double channeled device two guide wires were in their place and one of them was applied for entering the incrusted lumen while the "safety" guide ensured the already achieved position in the bile duct and made the manipulation safer.

Once the guide wire was positioned into the stent's lumen a 5 French straight angiographic catheter was advanced into the stent over the 0.032 inch wire (or over the 0.018 inch guide wire when the occluded lumen was punctured directly) which was then exchanged for a 0.038 inch superglide or Lunderquist (COOK) wire.

The parenchymal tract was dilated for 14 or 16 French using progressively larger dilators. A 6 or 7 French balloon catheter (balloon length 3–4 cm, inflation diameter 4–5 mm) (Meditech) was inserted over the guide wire into the proximal part of the stent. The balloon was inflated and the catheter and endoprosthesis as a unit were withdrawn together. In three cases the removal and exchanging were performed in the same session (2 Carey-Coons, 1 Miller double mushroom endoprostheses). In two cases the new prosthesis was placed after a few days' external/internal drainage (2 Carey-Coons prostheses). In the lumen of the new endoprosthesis a 5 French straight "safety" catheter was left for one or two days. If the control contrast filling did not reveal any dysfunction of the stent, the catheter was withdrawn and the parenchymal tract was then embolized with Gelfoam to prevent bile leakage.





Figures 1a, b. Patient No 3 with highly located multiple malignant stenoses originating from recurrent gastric carcinoma (shigellocellular type). A spiral-shaped endoprosthesis had been placed connecting the two lobes of the liver. After puncturing the right sided bile duct leading to the proximal end of the occluded 14F Carey-Coons endoprosthesis, a double channeled device was used for inserting two guide wires. One of them served as a "safety" guide while the other was manipulated into the stent lumen. After appropriate dilatation of the parenchymal tract over the latter guide wire a balloon catheter was then advanced in the proximal part of the stent. After balloon inflation the stent moved downward first, but mainly because of its size we decided to withdraw it percutaneously instead of pushing it into the duodenum. The inflated balloon catheter together with the stent was pulled out with careful traction.

Results

In our three patients the initial endoprosthesis patency lasted 19, 26 and 48 weeks, respectively. In patient No 3 the 48-week patency could be achieved by two additional endoscopic stent removals and changings (Figures 1a, b).

Second stents remained patent for 16, 21 and 22 weeks, respectively. Patient No 1 died of tumor dissemination without recurrence of jaundice. In patients No 2 and 3 a third endoprosthesis was implanted after successful percutaneous removal of the occluded stent. These patients survived additional 13 and 19 weeks, respectively (Figures 2a, b, c).

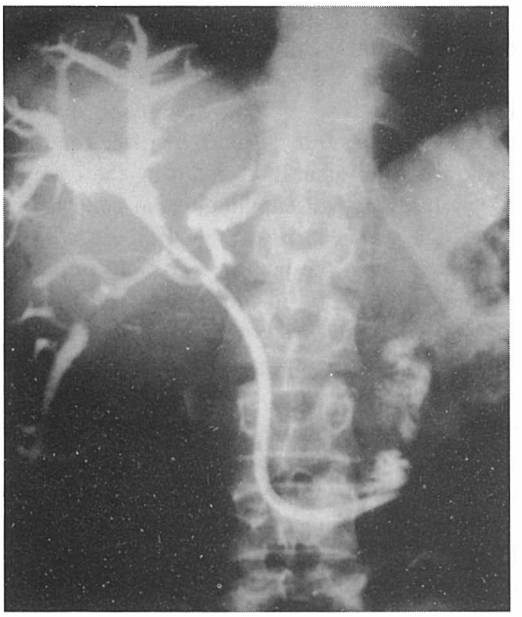
Discussion

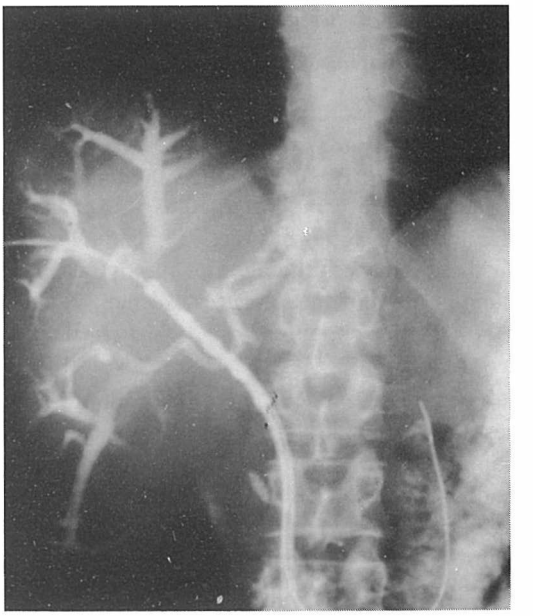
There are several possibilities for treating occluded endoprostheses:

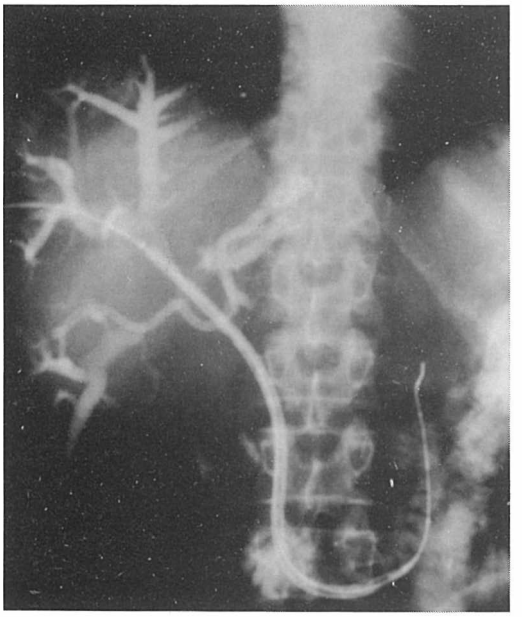
1. Endoscopic extraction and exchanging. Stent replacement is undoubtedly more easily achieved endoscopically than percutaneously, and its complication rate is lower; the patient's discomfort is significantly less serious.[5] Anatomical situation caused by the bulk of the tumor and/or some forms of previous surgery may prevent the passage of the endoscope or cannulation of the papilla.

2. Deocclusion by unclogging the lumen. The deocclusion can be accomplished by using a brush biopsy wire inserted percutaneously through a suitable biliary radicle.[4] After thorough washing a "safety" catheter is left in the lumen for one or two days to ensure the patency of the stent. The main disadvantage of the method is that it requires time consuming percutaneous manipulation, and despite successful deocclusion the incrusted endoprosthesis as a source of potential incrustation remains in its place.

3. Pushing the stent into the duodenum with new prosthesis replacement. From a suitable







Figures 2a, b, c. 3 months later a partial occlusion occurred due to incrustation of the stent. This time the proximal end hole of the endoprosthesis was punctured directly by a 22 gauge Chiba needle. A 0.018 inch superglide guide wire was inserted into the lumen of the fine needle, which was exchanged for a 0.038 inch Lunderquist wire. Over this guide a balloon catheter was inserted and by means of that the stent was successfully withdrawn.

percutaneous approach the occluded prosthesis can be pushed downward into the duodenum by a pusher (which is a part of the introduction set) or by using a balloon catheter.[3, 6] Although this method is less traumatic to the liver parenchyma than the percutaneous removal, yet it may also need a lengthy manipulation for cannulation of the clogged lumen.[6]

4. Percutaneous transhepatic extraction and exchanging. The use of angioplasty balloon catheters for the repositioning or transhepatic removal of biliary endoprostheses has been reported previously.[3, 4, 7] In these reports access to the endoprosthesis was obtained by catheterisation of a suitable biliary duct and manipulation of either an angiographic catheter or a guide wire into the endoprosthesis.

This method has several disadvantages: manipulation of the guide wire or catheter into the stent is sometimes rather difficult, the catheter, or guide wire may fail to enter the stent, and all this may result in repeated punctures of the biliary system.[2]

In three of our five cases the endoprosthesis cannulation was successful, but the time needed for this was relatively long (15–25 minutes fluoroscopy time) even with the use of a guide wire with excellent torque control. Therefore, on

the last two occasions we punctured the proximal end-hole of the occluded endoprosthesis with the Chiba needle directly according to Adam.[2] We were also forced to choose this kind of procedure by the fact that the proximal progression of the tumor made the anatomical situation more complicated, thus further limiting the possibilities of necessary manipulation. In these instances the absence of contrast medium in the bile ducts ensures excellent visualisation of the endoprosthesis, which facilitates its cannulation.[2]

The way of removal of occluded endoprostheses is greatly influenced by their shape and configuration. Percutaneous distraction of an endoprosthesis with special end-configuration (Miller double mushroom tipped or Allison-Gibson spiral shaped endoprostheses) may be much more difficult than that of a larger bore stent (Carey-Coons type) and may need special devices[2, 3, 6, 8, 9] After successful cannulation of the endoprostheses' lumen we had no further technical difficulties with their distraction (4 Carey-Coons type and 1 Lammer endoprostheses). Using percutaneous removal, one must take into account that this procedure requires a significant parenchymal tract to be create, but this disadvantage can be turned into advantage as another endoprosthesis should otherwise be implanted. Gelfoam embolization of the tract prevented bile leakage in all of our cases.

Indwelling biliary stents should be used routinely in patients requiring non-surgical relief of obstructive jaundice. The availability of a simple and effective method of replacement of malfunctioning endoprostheses will encourage their application in preference to external/internal drainage, thereby improving the quality of the patient's remaining life.

More recently the presence and availability of self-expandable metallic stents have given a breakthrough also in the treatment of malignant biliary stenoses. These devices can be inserted by a 5–10 French balloon catheter, therefore, it does not require significant dilatation of the parenchymal tract. Furthermore, there is no need for a multi-stage procedure and since the metallic stents provide a lumen of 1 cm the potential for occlusion is much less than that or other plastic endoprostheses.[10, 11, 12]

The use of self-expandable metallic stents increases the cost of biliary drainage due to their high price. But they can be placed in one session, thereby markedly reducing the cost of hospitalisation, and eliminating the need for a multi-stage procedure with all the cost as well as discomfort to the patient involved. The cost of treatment can be further diminished by decreasing the rate of potential complications. The total fluoroscopy time needed for lengthy manipulation can also be decreased significantly, thus keeping the amount of scattered radiation, which both the personnel and the patient are exposed to, within acceptable limits.[13]

All these advantages can effectively counterbalance the high price, the only major drawback of self-expandable metallic stents. We are strongly confirmed that the use of these promising devices will be the tratment of choice in selected patients with highly located, intrahepatic and/or multiple malignant stenoses who can expect a relative long survival.

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Computed tomography guided percutaneous drainage of hepatic abscessus

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The indications, technique and results of percutaneous drainage in 60 patients with 64 hepatic abscesses are presented. The procedure was guided by computed tomography (CT). Evacuation of the cavity was achieved in 59 (92.2%) abscesses and surgery treatment was not necessary in 55 (91.7%)patients. Percutaneous abscess drainage failed in 5 (8.3%) patients. There were no major complications. The drainage catheter was removed on average 14 days after insertion. We believe that percutaneous drainage of hepatic abscesses guided by computer tomography is an effective alternative to operative drainage, espacially in severely ill patients.

Key words: liver abscess; drainage; tomography, x-ray computed

Introduction

The incidence of hepatic abscesses has not changed significantly in the past 50–60 years, but with respect to age, incidence has shifted to older population.[1]

At the turn of this century, the majority of hepatic abscesses were amoebic in origin.[2] Non-ameobic abscesses, in particular pyogenic abscesses, may spread by direct propagation of contagious disease processes such as cholecystitis or peptic ulcer. However, other modes of transportation of bacteria's virulent strains are drainage via the portal system, such as necrotic inflammed bowel, trauma with penetrating injuries and direct introduction into the liver, and blood-borne infections via hepatic arteries.[2–4]

Traditionally, abscesses have been treated surgically, with wide incision and drainage as the main principles of surgical treatment. The incorporation of computed tomography and ultrasound (US) allows detection and accurate location of fluid collections in hitherto inaccessible sites. This has led to the development of diagnostic aspiration which is now being extended to terapeutic aspiration of the located fluid.[5, 6] In 1978, Gerzof[7] advocated percutaneous catheter as routine treatment for abscesses. In 1983, Walch[8] concluded that percutaneous catheter drainage had then been acknowledged as "one of great advances in abdominal surgery in the past few years". We present our favorable experience.

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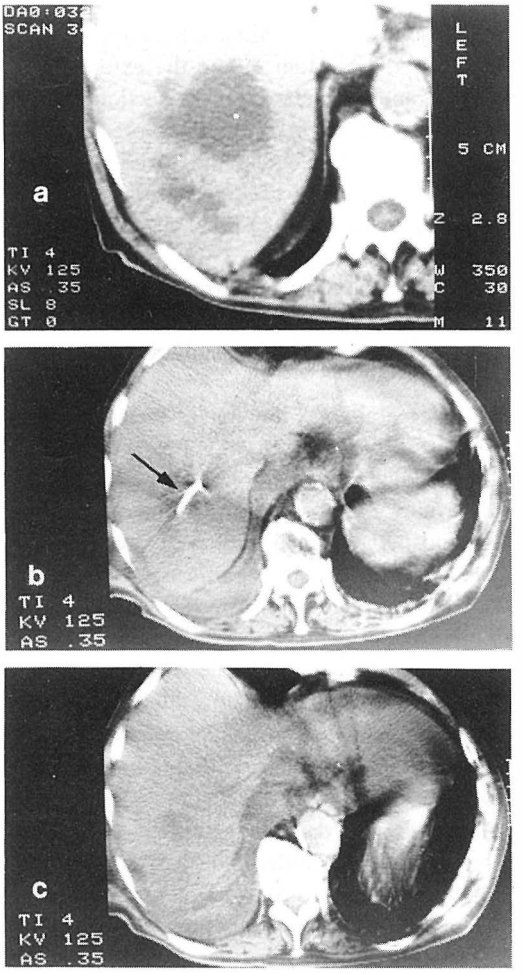
Materials and methods

Percutaneous hepatic abscess drainage was performed on 64 occasions in 60 patients during a five-year period (1988–1992) Amoebic abscess was present only in one patient. Piogenic abscesses were present in 39 (65 %) patients. Four of them had two abscesses in the liver. Hematoma and tissue devitalization after blunt trauma to the liver were the sites of abscesses in 20 patients.



Figures 1a, b, c. Percutaneus drainage of hepatic abscesses: a) Contrast-enhhanced CT scan revealing abscesses in the rigt liver lobe; b) CT scan after percutaneous drainage with an 8F multi-side-hole catheter (arrow) within the abscess cavity; c) CT scan one month after the removal of the drainage catheter.

CT was performed with Somatom DR Siemens scanner. Examinations were performed in the supine position, and prone and lateral decubitus position were added when required. All patients received 60 to 90 ml of ioheksol contrast medium (Omnipaque – Nycomed). When optimal visualization of the lesion was achieved and the puncture site selected, an opaque marker was placed on it and scan repeated to confirm the position. The site adjacent to the lesion was selected and the intended depth and angle of puncture were calculated from measurements made on the console monitor. Rescanning with a needle in site was performed after aspiration to abscess the amount of residual fluid. After localization, the site selected for puncture was sterilized and local anesthetic injected. Initially, an 18 gauge teflon-coated catheter-needle combination was used. When thick pus was encountered, this catheter was exchanged for a larger one by using a guide-wire. As much fluid as possible was withdrawn and bacteriologically and chemically analysed (Figures 1a, b, c). The total volume of the aspirate was measured and compared to that estimated from scan. If a gross discrepancy was found, a repeat scan is indicated to rule out an undrained loculus, since this may require a second drainage catheter. The catheter was left in situ and removed when the temperature and white blood cell count returned to normal and when daily drainage volumes decrease to less then 5–10 ml per day. A final CT scan is generally unnecessary, but may be used to confirm the result.

Results

Percutaneous aspiration was performed in five patients with hepatic abscesses. One of them was a patient with amoebic abscess. A single drainage procedure was sufficient in 51 (92.7 %) out of 55 patients. Multiple punctures were required in the remaining four patients who had a second catheter placed. Drainage of the cavity was accomplished in 59 (92.2 %) out of 64 abscesses.

Percutaneous abscess drainage failed in five cases. In all these patients, drainage of nondis-

crete areas of necrotic material was attempted. In two patients surgical exploration was performed on the fourth day and in three patients six days after the percutaneous drainage.

Three collections recurred. One was an inadequate drainage of infected hematoma after a blunt liver trauma, and two were inadequate drainages of pyogenic abscesses. This recurrent collections were retreated percutaneously.

The smallest fluid collection aspirated was 10 ml in a patient with amoebic abscess, whereas the largest was 500 ml in a patient with infected hematoma. Mean fluid collection by drainage was 124 + 74 cc. Fifty-three (96.4 %) out of 55 patients with sufficient percutaneous abscess drainage became afebrile within 48 hours and leukocytosis returned to normal within 7–10 days. When the temperature and white blood cell count returned to normal, and daily drainage volumes decreased to less than 5–10 ccm, the catheter was removed. The duration of the percutaneous drainage was 6–21 days, mean 14 + 5.

Discussion

The percutaneous drainage of abscesses is becoming an accepted treatment method in many hospitals. The optimal use of this procedure requires close cooperation between a radiologist and the referring physician. The radiologist performing the procedure should decide on the optimal modality to image the abscess and if one method is found to be inadequate, there should be no hesitation trying another one.

The following criteria should be considered in attempting percutaneous abscess drainage: 1) a well-defined abscess cavity, 2) a safe percutaneous access route, 3) concurring surgical opinion and 4) capability for immediate operative intervention in case of failure or complication.[9,10] Contraindications include the absence of any of the above criteria or the presence of a bleeding diathesis.[9] Some authors[11–13] consider multiple and complex abscesses as a contraindication to percutaneous drainage. Dondelinger[14] in his study showed scarcely any difference in the clinical outcome when comparing multiple or complex abscesses with unilocular abscesses. Internal loculation of abscess is not a contra-indication for percutaneous drainage[10] since it occurs rarely and since loculated hepatic abscess may be treated by placement of separate catheter to drain each loculus.

Because the radiologist's role of treating abdominal abscesses and fluid collection has extended beyond the traditional task of detection, to the additional steps of percutaneous needle aspiration and percutaneous drainage, an integrated and complementary use of CT and US is essential. However, even if the fluid collection is delineated by initial US study, CT may be required to further define the extent of the process and to relate the collection to the surrounding structures. Once the presence and location of the fluid collection have been determined, percutaneous needle aspiration and subsequent percutaneous catheter drainage can be performed.

A small abscess may be treated by complete aspiration of pus via a needle without using catheter.[16] We used this technique in five patients.

For percutaneous drainage of hepatic abscess the shortest possible route to abscess cavity that avoids vital structures should be selected. Drainage route must avoid the gallbladder, portal vein and hepatic flexure of the colon.[17]

Many abscesses have significant internal pressure, and rapid free flow of pus is quickly accomplished by aspiration with a large syringe. At the initial procedure, the abscess cavity is completely evacuated. The catheter and the cavity are irrigated with sterile saline. This step prevents early blocking of the catheter by necrotic tissue and debris.

The utility of daily irrigation of catheter is debatable. Some authors do not irrigate the catheter as long as the purulent material is draining.[18] In Gerzof[19] experience, lavage caused rupture of abscesses precipitating emergency surgery treatment and at least one consequent death. Haaga[6] preferes irrigation with a smaller amount of normal saline, 1–25 ml/hr, depending on the size of the cavity, with gradual decrease in the amount of irrigant until it is

injected only once every day. We prefer such irrigation in our patients. Van Weas suggests instillation of a proteolyitic agent (acetylcystein), antibiotics, or both.[20] Miller[21] irrigates the abscess cavity with normal saline immediately after catheter placement and follows this with constant gravity drip of saline at 50–100 ml/hr.

Surgeons have traditionally racommended dependent or gravitational positioning of their drainage catheter. Gerzof[19] finds such positioning to be unnecessary. Most percutaneous catheters are placed anteriorly and experience has shown they drain well against gravity. Because both the abscess wall and the abdominal wall remain intact, they transmit increasing intra-abdominal pressure on any residual abscess fluid, forcing it out of the drainage catheter. Even when the initial pus in very thick, as soon as the pressure in the abscess is relieved the ensuing exudate produced by the abscess wall is very thin and drains easily.

The first 72 hours of drainage are the most important for determining its adequacy. During that time most patients become afebrile. If clinical sings of sepsis persist beyond 24–48 hours, percutaneous drainage may not have been sufficient. A repeated CT is then required to rule out undrained residuum.[19] Success of catheter drainage can be assessed by clinical, catheter, and radiological follow-up. The clinical features of drainage success are decrease in fever, pain, local tenderness, and leukocytosis. Catheter features are decreased drainage, and return of clear irrigated saline. Radiographic feature is the diminishing of the cavity on CT scan, US or contrast abscessogram.

Clinical response of patients with pyogenic hepatic abscess can be dramatic. Prompt defervescence and fall in leukocytosis, along with an improved sense of well-being, are customary. However, one or more temperature pikes may occur in the hours following catheter insertion. Reduction of the local pain and tenderness are additional positive signs.

Gradual decreases in the amount and viscosity of the catheter drainage are characteristic in successful cases. However, a sudden cassation of catheter output may indicate catheter plugging by necrotic debris. This can usually be corrected by performing irrigation on ward.

Follow-up by subsequent US, CT or abscessogram is valuable to assess the cavity size and to disclose walled-off or undrained loculi. A direct contrast abscessography is more powerful than either US or CT.

The average hospitalization time[22,23] is 40 days, compared to 21 days with percutaneous treatment. In our patients mean hospitalization time was 23 days.

Percutaneous treatment of liver abscesses should be considered the treatment of choice when a suspicious image is evidenced on US or CT. Complete cure is achieved in 76 %[24] to 100 %[25,26] of cases. In our research percutaneous treatment of liver abscesses was much more effective than surgical drainage in 55 (91.7 %) patients. When an underlying causal disease persists, this should be treated secondarily in order to prevent abscess recurrence. Septic complications and bleeding at the time of drainage are exceptional. The mortality associated with percutaneous treatment of liver abscess is less than 5 %, which compares very favorably with the surgical literature.[12]

Conclusion

Percutaneous drainage of liver abscesses is a rapid, safe and highly effective method of treatment which, in most cases replaces major surgery. CT should be used in all instances for diagnosis, location of the lesion and for planning optimal approach to drainage, as well as to access the degree of aspiration achieved during and after the procedure. Surgical exposure provides decompression and evacuation, and surgically placed drainage provides continuous drainage. These mechanical processes are performed by percutaneously placed drainage without a damage of surrounding tissues. The most essential advantage of percutaneous drainage over operative drainage is the total avoidance of general anesthesia. Percutaneous drainage in hepatic abscesses, compared with surgical treatment, yields a higher success rate

with a shorter hospitalization and correspondingly lower rates of complications, recurrence and mortality.

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Radionuclide studies of the reproductive system and their significance in clinical practice

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Radionuclide studies of the reproductive system are used to evaluate perfusion and function of this system and are frequently complementary to morphological studies such as ultrasound and X-ray investigations.

Radionuclide scrotal imaging remains the most effective method in the evaluation of acute hemiscrotum to assess testicular perfusion and differentiate between testicular torsion and epididymitis. Labelled red blod cells are used successfully for varicocele detection in infertile men. Only radionuclide techniques (radionuclide hysterosalpingography) allow for noninvasive assessment of functional tubal patency in infertile women. Assessment of penile blood flow, using labelled red blood cells and/or xenox clearance, can play an important and useful role in evaluating men with impotence due to vascular causes.

Key words: urogenital diseases-radionuclide imaging

Introduction

In contrast to morphological investigations, such as ultrasound, MRI and X-ray, radionuclide studies of the reproductive system are used to evaluate its function and perfusion, and can be frequently considered as complementary rather than competitive to studies mentioned above.

Clinical conditions, where radionuclide investigation have proven useful, are acute hemiscrotum, where perfusion and blood pool imaging of the testes with pertechnetate is used to evaluate its perfusion, male and female sterility, i. e. detection of varicocele in males and determination of functional fallopian tube patency in females, and studies of penile blood flow in the assessment of male impotence (Table 1).

Table 1: Radionuclide studies of the reproductive system.

1.	Evaluation of acute hemiscrotum
	Differentiation between torsion and inflammation
2.	Evaluation of sterility
	Male: detection of varicocele
	Female: functional patency of the fallopian tubes
3.	Evaluation of male impotence
	Diagnosis of arterial insuficiency
	Diagnosis of venous leakage

This paper was presented in shortened version as a Keynote address at the IAEA/WHO Seminar on Gastrointestinal and Urogenital Functional Studies with Radionuclides, Vienna, 16–19 August 1993.

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Acute hemiscrotum

The most common and most widely accepted radionuclide technique of investigation of the reproductive system is perfusion and blood pool imaging of the testes with pertechnetate to evaluate testicular perfusion in the evaluation of acute hemiscrotum, to differentiate between torsion of the testes, which is an absolute surgical emergency, from other less urgent conditions, such as epididymitis, which are usually treated conservatively.

Pathophysiology

The testis, tightly attached to the epididymis, is suspended in the scrotal sac by the spermatic cord composed of the entering arteries and draining veins, the spermatic duct, lymphatics and nerves. Normally, the testes is covered partially by tunica vaginalis and firmly fixed posterolaterally to the epididymis and scrotum, what makes torsion of the cord impossible. Two malformations, complete investment of the testes with tunica vaginalis, which precludes tight fixation of the testis and epididymis to scrotal wall, and elongated mesorchium, i. e. attachment of the testis to epididymis, permit spermatic cord to twist.[1, 2]

Complete torsion will result in infarction of the testis due to impaired arterial blood supply. Spermatogenic capability is lost within a few hours. Incomplete torsion, where arterial blood supply is still sufficient, will also cause ischemia and infarct due to venous obstruction, but more slowly.

Three or more complete turns of the spermatic cord are sufficient for irreversible ischemia to occur within a few hours, whereas up to 24 hours are necessary with a single 360 degree twist. Salvage of the testes has been reported after 30 hours with incomplete twist.[1]

Clinical presentation

Most common causes of acute hemiscrotum include inflammation (epididymitis or rarely orchitis), torsion of the testes and trauma, which can also lead to infection, as well as torsion.

Peak incidence of torsion is in adolescents, around puberty. Patient presents with abrupt, excruciating pain. Fever and urinary tract symptoms are absent and urinalysis is normal. Hemiscrotum is swollen and edematous. Elevation of the scrotum will intensify the pain.

Typical patient with epididymitis is young adult, with more gradual onset of pain, which is also less intense than in torsion. Dysuria and burning with urination are common, as well as moderate to high fever. Elavated number of white cells is present in urine. On physical examination, hemiscrotum is swollen and erythematous. Elevation of the scrotum causes relief of pain.[1]

Unfortunately, clinical presentation of these conditions is often, in up to 50 % of the cases, not sufficiently typical for torsion to be confirmed or excluded with confidence. Without a reliable way to exclude the possibility of testicular torsion in a patient with acute hemiscrotum, immediate surgical exploration has been recommended to maximize testicular salvage, but at the cost of many unnecessary operation. Torsion is easily remedied by detorsion and orchiopexy, but surgical exploration in inflammatory conditions carries a small, but real risk of complications.[3]

Therefore, the difficulty lies not in treatment, but in diagnosis.

Diagnostic methods

Scrotal perfusion scintigraphy, grey scale ultrasonography, continuous-wave and conventional duplex Doppler imaging and colour Doppler have been used for this purpose.

1. Scrotal perfusion scintigraphy.

Usually the study is performed with patient positioned supine, with scrotum elevated, as close to the gamma camera as possible. Penis is taped cephalad, and positioning of the scrotum should be such that raphe are in midline, a necessary condition for comparison of perfusion of both testicles.

600–800 MBq (adult dose) of 99 m Tc pertech-

netate are injected as bolus and dynamic study of the first pass is acquired using magnification. Usually two high quality static images, one with and one without markers, using magnification or pinhole collimator, are acquired immediately after the dynamic phase. In some laboratories a lead shielding interposed between the thighs and scrotum is used for static images.[2]

Additional processing of the data, such as time activity curves over the testicles does not seem to provide any essential additional information.[4]

In cases of normal perfusion of the testes dynamic images show only the iliac and femoral vessels with a low grade blush visible over the scrotum.

Scintigraphic findings in torsion corespond to viability of testes because the extent of ischemia will vary depending on the duration and degree of twist of the spermatic cord. In the early phase increased activity in the testicular artery up to the site of twist ("nubbin sing")[5] is occasionally seen. In the late dynamic and static images there is absent activity in the region of affected testis. Such images are very specific for acute torsion. This phase is seen up to 4--6 hours following complete twist, and can be seen after a longer interval if the twist is incomplete. In this phase surgical salvage is virtually 100 %. Later the testis progresses to infarction and scrotal wall becomes hyperemic, appearing with time as increasingly hot rim around the photon deficient testis. Likelihood of testicular salvage approached zero in one study[5] when scrotal activity exceeded that of the femoral arteries. Images of so called "missed torsion" are not specific, and have been observed also in a number of other conditions.[6, 7, 8]

If spontaneous detorsion occurs the study may be normal or show only reactive hyperemia.[9] In such case immediate emergency surgery is not necessary but there is still deffinite indication for elective operation (orhiopexy) as soon as feasible.

In epididymitis epididymal perfusion is increased, while in epididymo-orchitis both epididymis and testis show an increased tissue phase activity.

Findings in torsion of a testicular appendage are usually normal, or show slight hyperemia as is seen also in mild inflammation or spontaneous detorsion.

In testicular trauma diffuse hyperemia may be seen. In postraumatic torsion photodefficient area of the size of the tesis is seen, and is usually larger than photodeficiency due to testicular hematoma or contusion, if present.[1]

2. Conventional grey scale ultrasonography.

Grey scale sonography provides high resolution images of the testis and epididymis. However, morphological abnormalities on torsion and epididymo-orchitis are identical, and ultrasonography provides no information about blood flow.[10, 11] Therefore it is not adequate for the evaluation of acute scrotal disorder, but is frequently useful in further diagnostic work-up, after normal blood flow to the testes has been documented.

3. Doppler ultrasonography.

Doppler sonography allows also for evaluation of blood flow.

Continuous wave Doppler was found to produce false negative results in up to two thirds of cases, because it is difficult to distinguish arterial flow in peritesticular vessels from intratesticular blood flow with nonimaging equipment.[12]

Duplex Doppler instruments combine pulsed Doppler and gray scale ultrasonography. It was found that this procedure is time consuming, operator dependant and not very reliable in acute hemiscrotum, since testicular arteries are difficult to evaluate because of their small size and low flow even in normal testes.[9, 12]

Colour Doppler ultasound allows simultaneous real-time display of tissue morphology in gray scale and blood flow in colour. Some recent reports have shown the sensitivity in diagnosing testicular torsion to be between 86 and 100 %, and specificity 100 % in small series of patients.[9, 12] It is important, that for the assessment of acute hemiscrotum a high frequency transducer, 7.5 MHz or more is used for high quality results.[13]

Diagnostic value

To be useful, a diagnostic test for acute hemiscrotum must be immediately available, quick to perform and very sensitive. It should be also noninvasive and simple to perform.

The study should be completed as soon as possible after presentation of the patient because viability of the testes can be preserved only if surgery is performed before 4–6 hours after the onset of symptoms. It should not be used in patients with typical symptoms which have to be explored surgically immediately, but to exclude torsion in cases, where conditions other than torsion are suspected.

Scrotal perfusion scintigraphy should be regarded as an evaluation of current testicular perfusion rather than a method to diagnose a specific condition. Properly performed, it has sensitivity and specificity of over 90 % for the presence or absence of intact blood supply to the testes. Normal or moderately increased testicular perfusion does not rule out the possibility if incomplete or spontaneously resolved torsion, in which case surgery is also indicated, but usually not as an imminent emergency. Scintigraphy has no use for the evaluation of neonatal torsion, which is virtually the only condition of scrotal swelling at this age.

Perfusion scintigraphy is more accurate than grey-scale ultrasonography, continuous wave and conventional duplex Doppler imaging, while some reports indicate that colour Doppler might be as accurte as perfusion scintigraphy. Advantages of colour Doppler include its ability to provide also high resolution images of the testis and epididymis, and absence of any radiation to the patient. It is operator dependent and can be difficult to perform properly in a young patient with very painful hemiscrotum. Nevertheless, as with any new technique, a prospective investigation using larger numbers of patients is needed to determine ultimate value and indications for this technique.[12]

At present time, perfusion scintigraphy is still the procedure of choice to evaluate testicular perfusion in acute hemiscrotum, as it has the advantage of many years of clinical validation.[14, 15] It has to be available on an emergency basis.

Male infertility

Varicocele due to varicosities of the pampiniform plexus is an important cause of surgically treatable male infertility.

Left testicular vein is draining into the left renal vein at right angle, with resultant increased pressure, permitting retrograde flow in the left testicular vein. Therefore, varicocele is usually left sided and unilateral. Right sided varicocele may form by extension from the left, further affecting semen quality.[16]

Diagnostic methods

Apart from simple palpation, which may miss small varicoceles, and invasive direct venography, which can be combined with therapeutic occlusion, a number of noninvasive techniques, including contact scrotal thermography, ultrasonography and Doppler imaging, and perfusion and blood pool scintigraphy with labelled red blood cells were developed to detect inpalpable, bilateral, or to confirm clinically suspected varicoceles. Difference more than 0.3 degrees centigrade on contact scrotal thermography, diameter of pampinifirm plexus veins larger than 3 mm on ultrasonography, evidence of retrograde flow on Doppler ultrasonography, and pooling of labelled red blood cells on scintigraphy, is considered as positive for varicocele.[17]

Scrotal perfusion scintigraphy

Red blood cells are labelled in vivo, with patient standing in front of the gamma camera. 99 m Tc pertechnetate is injected as bolus and the first pass is recorded as dynamic study. Static blood pool images are acquired usually with and without Valsalva manouver. Increased radioactivity, due to venous blood pooling is seen in the case of varicocele.

Diagnostic value

Sensitivity of radionuclide investigation has been reported to be 92 %.[18] Similar results are

available also for grey scale and Doppler ultrasonography.[17] Scintigraphy using both dynamic first pass and static blood pool images provides useful data on local hemodynamic in the scrotum. According to some investigators no improvement in the semen quality was seen after surgery in patients who showed no scrotal accumulation of radioactivity in the dynamic images, while semen quality did improve after surgery in those with patchy tracer uptake allready in the dynamic phase of the study,[19] so scintigraphy could have also prognostic importance.

Female infertility

Functional or organic obstruction of fallopian tubes is one of the causes of female infertility, especially in regions where tuberculosis of the adnexes is not uncommon.

Diagnostic methods

To assess fallopian tube patency usually contrast histerosalpingography is performed, where contrast medium is introduced under positive pressure intracervically.

Alternatively, observation of spilling of methylene blue dye from the fimbirated ends of the fallopian tubes into the peritoneum at laparoscopy or surgery, after the dye had been introduced into the cervix under low pressure, can be used.

Also, a radionuclide method to assess fallopian tube patency has been developed.[20]

Radionuclide hysterosalpingography

99 m Tc labelled human serum albumin microspheres (37 Mbq suspended in 1 ml of saline) are applied intravaginally directly onto the cervical mucosa. A nonabsorbable tampon is inserted into the vagina after speculum is removed and the patient is imaged 30 min, 1 hour and, if necessary, delayed images up to 4 hours later can be obtained, using a pinhole collimator with approximately 30 degrees caudal angulation to visualise the region posterior to the uterus, which helps to separate ovaries from the uterus.[21] Labelled microspheres normally migrate spontaneously from the vagina to the ovaries, while in the presence of fallopian tube obstruction, fibrosis or lack of motility, migration does not take place. A fallopian tube is considered patent, if a focus of activity is seen in the area of the adjacent adnex, including outlining of the ovary.

Technical and radiopharmacological improvements of the method described are possible. Using SPECT technique spatial resolution of the investigation can be improved, and the dose of the radiation to the ovaries decreased. Recently a technique of labelling the sperm cells using 99m Tc HMPAO for radionuclide hysterosalpingography has been described in animals.[22]

The radionuclide technique is less invasive than contrast hysterosalpingography or laparoscopy with methylene blue applied intracervically under pressure.

Radiation burden to the ovaries during radionuclide hysterosalpingography is lover than in contrast hysterosalpingography.[21]

Diagnostic value

Both the sensitivity and specificity of radionuclide test for the detection of tubal patency and tubal obstruction was reported to be over 90 % when correlated with anatomic criteria.[23, 24] Due to its high sensitivity and specificity the test is useful not only for the evaluation of female infertility, but also in assessment of surgical reanastomosis or tuboplasty for previously ligated or fibrosed tubes, and, alternatively, to confirm the success of tubal ligation.

It seems that radionuclide histerosalpingography has an important advantage over morphological techniques, because it can detect not only organical, but also functional tubal obstruction, what can be otherwise achieved only by direct observation of tubal motility at surgery. The radionuclide study may facilitate detection of diseased but patent tubes and provide useful information about tubal function.[23, 24] Because of this, it has been even proposed that failure of migration of the tracer to the ovaries may render patients with anatomically patent tubes eligible for in vitro fertilisation.[25]

Male impotence

Normal penile erection requires the co-ordinated function of neurological, arterial and venous systems and, even if these systems are intact the process may be inhibited by psychological factors.

Patophysiology

Erection results following penile smooth muscle relaxation. Dilatation of the cavernosal and helicine arteries increases blood flow into lacunar spaces within lacunar bodies. Relaxation of the trabecular smooth muscle enables dilatation of lacunar spaces. The systemic arterial blood pressure transmitted through dilated arteries expands the relaxed trabecular walls against the nonyielding, rigid tunica albuginea and compresses the subtunical venules causing reduction of venous outflow by so called corporeal veno-occlusive mechanism. This reduces venous outflow and elevates intracavernosal pressure causing erection. The intracavernosal pressure during erection is a result of equilibrium between the perfusion pressure in the cavernosal artery and the resistance to blood outflow through the compressed subtunical venules. In normal erection it approximates systemic arterial blood pressure.[26]

The intracavernous injection of potent smooth muscle vasodilators such as papaverine or phentolamine results in erection in normal subjects, as well as those suffering from neurological and psychological causes.[27]

Causes of male impotence are psychological, neurological or organic. It is estimated, that approximately 50 % of men with impotence have an organic etiology and presumably the majority are vascular in origin.

Normal rigid erection following intracorporeal injection of papaverine can rule out vasculogenic impotence.

Vascular causes of impotence can be either due to reduced arterial supply (arterial insufficiency) of excessive venous outflow (venous leak). Arterial insufficiency is consequent to atherosclerotic occlusive disease of the hypogastric-cavernous arterial bed, while venous leak is due to smooth muscle myopathy or poor compliance of the erectile tissue caused by structural alterations in the fibroelastic components secondary to vascular risk factors such as hypercholesterolemia, diabetes mellitus, ageing, previous priapism, surgery or trauma of the penis.

The differentation bettween the two is important for patient management, eg. restorative surgery or implants for arterial insufficiency and ligation of penile vein for venous leaking.[28]

Diagnostic methods

At this time there is as yet no universally agreed upon diagnostic algorithm for vascular evaluation of impotent patients. Vascular impotence has been evaluated by different radionuclide and nonradionuclide techniques, both usually in association with vasodilatation.

For the evaluation of arterial insufficiency:

1. Selective angiography, which is an invasive technique. Significance of arterial lesions are difficult to assess because no functional information is provided.[29, 30]

2. Penile/brachial systolic pressure index, which is not always accurate, since Doppler signal is often obtained from dorsal penile artery and therefore does not correlate with erectile function.[31, 32]

3. Duplex scanning, which can measure changes in individual arterial diameters and peak flow velocities. This method is still under evaluation and is operator dependent.[31]

4. Radionuclide penile pletismography and radionuclide penile blood flow study using 99m Tc labelled red blood cells in combination with papaverine test were used to determine peak corporeal flow and volume changes. Peak corporeal flow correlates well with arterial disease, but does not correlate with venous leaking.[33]

For evaluation of venous leakage:

1. Dynamic infusion cavernosometry[34] and cavernosography[35] during vasodilataion, which are invasive techniques with infusion of large amounts of saline and contrast media intracorporeally, to determine the flow rate required to mantain erection and to demonstrate opacification of pelvic veins.[32]

2. Several 133-Xe clearance studies have proposed to measure penile blood flow. Subcutaneous injection was not appropriate since circulation of the erectile tissues is largely independent of penile skin circulation.

Cavernosal injection in flaccid penile state was not able to differentiate between normal and impotent men.

Also with cavernosal injection and vasodilatation it was reported that xenon outflow alone could not be used to predict competence of veno-occlusive mechanism.[29, 36-38]

3. Injection of 99mTc labelled red blood cells intracavernosally, instead of xenon, has been proposed to evaluate venous leakage. In this case 18.5 MBq of in vitro labelled red blood cells are injected intracorporeally twice, in flaccid state and after vasodilator injection. Data are acquired for 20 min for each study at the rate of 1 frame/15 seconds. Time activity curves are generated and time to half outflow (T50 %) is calculated.

It is significantly shortened in case of venous leakage as compared with normal venous outflow if the study is performed after appropriate papaverine vasodilatation. High sensitivity (100 %) and specificity (92 %) for differentiating venous leak from normal venous outflow were reported for study after vasodilation in a small group of patients.[39]

To determine, if arterial insufficiency is also present, this technique has to be combined with another radionuclide or duplex sonography study.

3. To assess both arterial and venous problems during the same pharmacological intervention, penile pletismography and xenon washout have been successfully used simultaneously by several groups.[40, 41]

Among several similar protocols the technique used by the Cleveland group is decribed, as an example.[41] Red blood cells are labelled in vivo with 200Mbq of 99mTc. The lower abdomen is covered with lead shields leaving only genitalia exposed. A venous blood sample is obtained to convert count rate into mililiters. A butterfly needle is inserted into cavernosal body at the base of the penis. A gamma camera with an all-purpose collimator, set for dual isotope acquisition, is centered over the penis.

200-400 MBq of 133 Xe in 1 ml saline are injected through the butterfly needle and flushed with 5 ml of saline. Data acquisition is started after 2–3 min, at the rate of 1 frame/ 10 seconds for 15 minutes. Vasodilators (papaverine 45 mg and phentolamine 1 mg) are injected slowly and flushed with 1 ml saline through the indweling butterfly needle. Data acquisition is continued at the same rate for 20 min.

Results are presented as time activity curves after correction for technetium downscatter into xenon window. Arterial and venous flows are calculated according to one compartment model from the flaccid through the tumenescent and erect states. (Erection is reduced prior to discharge of the patient).

Combining the results of arterial and venous blood flow during pharmacologic intervention, this technique was able to differentiate between normals, having normal both peak arterial and peak venous blood flow, arterial insufficiency patients, having decreased peak arterial flow and normal peak venous flow, and patents with venous leak, having essentially normal peak arterial flow and markedly increased peak venous flow in a small group of selected patients.[42]

Diagnostic value

Although not yet properly evaluated, these methods may be useful as a screening test in patients with erectile dysfunction to differentiate patients with arterial insufficiency from those with venous leak. The disadvantage of radionuclide methods is their inability to provide anatomic information in comparison with angiographic and duplex sonography, their advantage however is that they are simple to perform, are operator independent, and should be well reproducible, what is useful, especially to follow up the success of surgical treatment of such patients.

Conclusion

Despite the emergence of new, especially cross sectional imaging approaches, radionuclide

techniques maintain a significant role in genital imaging, since they can demonstrate the physiologic status of organs.

Radionuclide scrotal imaging remains the most effective method for differentiating between testicular torsion and epididymitis.[9] Labelled red blood cells are used successfully for varicocele detection in infertile men. Only radionuclide techniques allow for noninvasive assessment of functional tubal patency in infertile women. They can play an important and useful role in evaluating men with impotence.[15]

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New prototype ^{99m}Tc extraction system

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A new semi-automatic extraction system for production of ^{99m}Tc from low specific activity ^{99}Mo, developed in the Department of Nuclear Chemistry of the "J. Stefan" Institute in Ljubljana is described. ^{99m}Tc is separated from reactor irradiated natural molybdenum(VI) oxide by continuous solvent extraction with methyl-ethyl ketone (MEK). The important characteristics and problems related to this new extraction system are discussed.

Key words: technetium-99m, technetium-isolation and purification, isotope production, solvent extraction; molybdenum, molybdenum oxide; nuclear reactors

Introduction

Three decades after the introduction of ^{99m}Tc as an "ideal" radiotracer, it still remains the most widely used isotope for nuclear medicine studies. The pre-eminence of ^{99m}Tc as a medically useful radionuclide is directly attributable to its excellent physical and chemical properties.[1, 2] Technetium, in the from of ^{99m}Tc, is obtained from ^{99}Mo, which is produced by neutron irradiation of molybdenum (of natural isotopic composition or enriched in ^{98}Mo); alternatively, ^{99}Mo may be obtained as a fission product of uranium. Chromatography, sublimation and solvent extraction are three commonest methods used to separate ^{99m}Tc from ^{99}Mo.[3,4,5]

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UDC: 546.718;539.17;546.77

In a nuclear reactor with a relatively low neutron flux (below say 5×10^{13} n.cm^{-2}s^{-1}) the specific activity of ^{99}Mo is such that only the solvent extraction and sublimation methods can be used, as the mass of molybdenum required to be loaded on to a generator column would be too great.

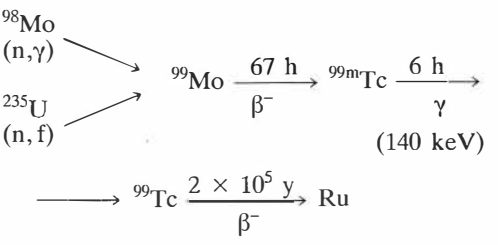


Figure 1. Production of ^{99m}Tc by nuclear reactions.

^{99m}Tc has been successfully produced at the TRIGA Mark low power research reactor (250 kW) of the "J. Stefan" Institute in Ljubljana for almost ten years. By the use of manually

operated solvent extraction system where separation of ^{99m}Tc from ^{99}Mo was based on bubbler extraction, the needs of the two Slovenian largest nuclear medicine institutions, the University Clinic for Nuclear Medicine and the Institute of Oncology has been covered.[6] For the same purposes a new semi-automatic, centralized, computer controlled continuous extraction system has been developed and is described in the present work.

Materials and methods

Apparatus

The purpose of the apparatus is to separate ^{99m}Tc from low specific activity ^{99}Mo by solvent extraction, where some steps of the procedure are automated, and finally to obtain a sterile, chemically pure product in a small volume (cca. 10 ml) of physiological solution for direct medical use.[7] Block and schematic diagrams are shown in Figures 2 and 3. The main parts of the prototype apparatus are as follows:

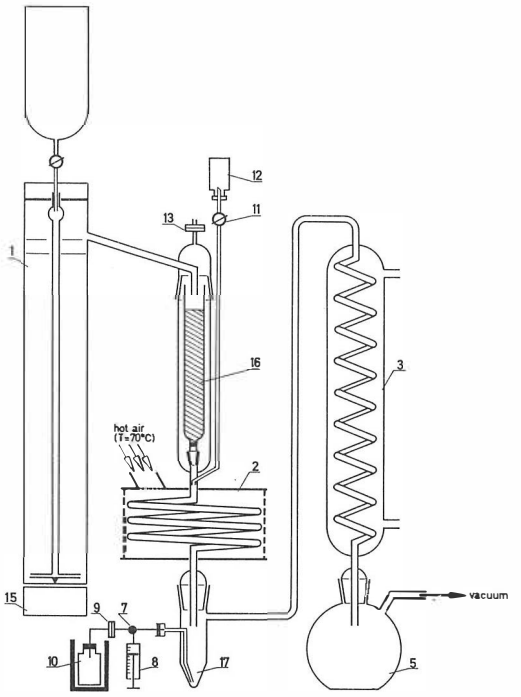
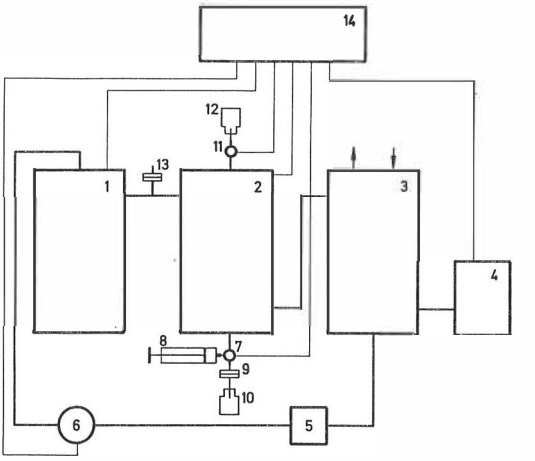


Figure 2. Schematic presentation of the newly developed extraction system.



1. Extraction vessel (V = 200 ml)
2. Evaporator
3. Condenser
4. Diaphragm pump
5. Reservoir for MEK
6. Peristaltic pump
7. Three-way tap
8. Self-filling syringe
9. Membrane filter (0.22 μm)
10. Sterile vial
11. Valve for 0.9 % NaCl
12. 0.9 % NaCl solution
13. Membrane filter (0.45 μm)
14. Control unit
15. Motor
16. Silica-Gel column
17. Reservoir for TcO_4^-

Figure 3. Block scheme of the extraction system.

– extraction vessel (see also Figure 4);

– funnel for methyl-ethyl ketone (MEK); the volume of the glass vessel is 50 ml;

– reservoir for NaCl (0.9 % NaCl); physiological solution is kept in commercial sterile flasks;

– evaporator;

– condenser for MEK: a glass apparatus of 400 ml capacity, connected to the reservoir for MEK;

– silica-gel column, maintained in position inside a glass holder;

– automatic self-filling and dispersing syringe;

– 0.22 μm membrane filters (Millipore or Sartorius);

– sterile vials (commercial);

– Masterflex peristaltic pump with flow rates of 1 – 20 ml per minute;

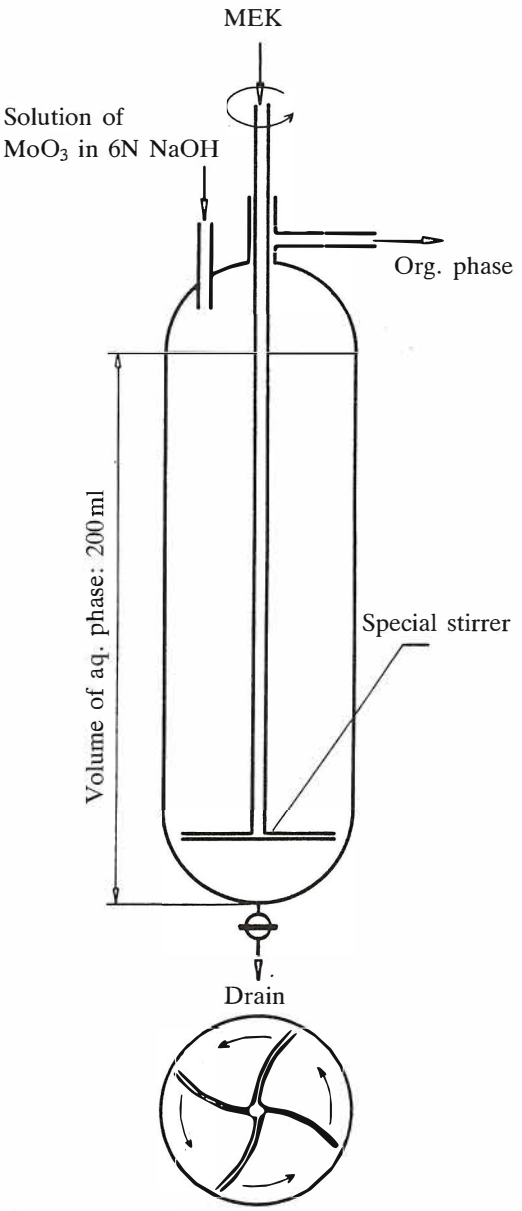


Figure 4. Schematic drawing of new prototype extraction vessel.

– vacuum line maintained by KOMVAK 1 diaphragm pump;

– control unit: this mainatains control over the peristaltic and diaphragm pumps, the mixing of MEK in the generator vessel, the temperature in the evaporator, the dispensing of NaCl (0.9 %), and determines the sequence and timing of the operations.

The time sequence of operations is shown in Figure 5. The whole procedure lasts 45 minutes. At the start the mixer and heater of the evaporator spiral are switched on. After 5 minutes the peristaltic pump for MEK and the membrane pump, which carries over the MEK vapour into the condenser, are switched on. After 35 minutes the extraction is complete and the control unit switches off the heater of the evaporator spiral, the mixer for dispersion of MEK in the extraction vessel and the peristaltic pump. The membrane pump continues to operate another 3 minutes in order to remove all the remaining MEK vapour from the system. In the 38th minue the valve opens to allow 6 ml 0.9 % NaCl to enter the system, thus washing down sodium pertechnetate from the evaporator spiral to the reservoir. In the 39th minute the membrane pump is switched on for one minute to suck all remaining NaCl solution into the reservoir. In the 40th minute the dispenser is switched on to transfer the sodium pertechnetate solution in physiological saline into a sterile syringe. In the 41st minute the dispenser forces the solution from the syringe via a three-way tap and 0.22 μm membrane filter into a sterile penicilin bottle.

All parts of the generator system are directly connected via glass, teflon or PE tubes. The characteristic of the apparatus developed are as follows:

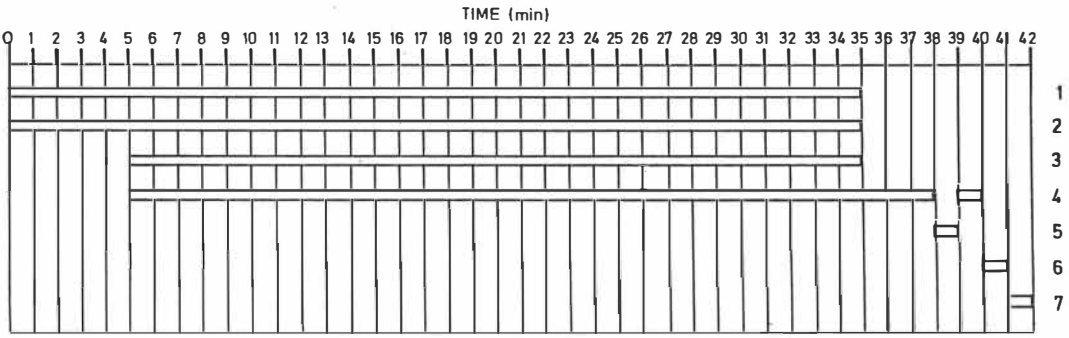
– dimension of the apparatus: 80 × 80 × 80 cm;
– weight: 35 kg;
– voltage: 220 V;
– cooling system: water cooled;
– preparation time: 45 minutes.

Materials

– MoO_3, p.a., Merck, is used for irradiation;

– NaOH, p.a., Kemika, Zagreb, 6 M solution;

– MEK (methyl-ethy ketone), p.a., Merck or Kemika, Zagreb, is used for solvent extraction separation of ^{99m}Tc from ^{99}Mo in an alkaline solution of Mo(VI) and Tc(VII), distillation before use is required;



1) Evaporator heater
2) Mixer
3) Peristaltic pump
4) Membrane pump
5) 0.9 % NaCl
6) Filling of dispenser from reservoir
7) Dispensing into penicillin vial

Figure 5. Time sequence of computer controlled operations.

– H_2O_2, p.a., Belinka, Ljubljana, 3 % solution;

– silica-gel, Kemika, Zagreb, for chromatography, particle size 0.2 – 0.5 mm, washed three times with MEK and then ten times with redestilled water to remove fines, and dried at 105 °C, is used for removal of small amounts of water phase which contains dissolved ^{99}Mo;

– physiological solution (0.9 % NaCl) – sterile.

Irradiation

120 g of MoO_3 are irradiated in an aluminium container in our TRIGA Mark II research reactor. The optimal irradiation time of MoO_3 for continuous production on a three day cycle with our previous generator system,[6] determined by experiment, is three weeks in the F-ring, at a neutron flux of 4×10^{12} n.cm^{-2}s^{-1}, and finally 48 hours in the central channel at a neutron flux of 1.1×10^{13} n.cm^{-2}s^{-1}. This activity is equivalent to the activity of five 800mCi commercial generators. By (n, γ) reactions, ^{99}Mo ($t_{1/2}$ = 66 h) and ^{101}Mo ($t_{1/2}$ = 14.6 min) are formed. Beta decay of these two isotopes gives ^{99m}Tc ($t_{1/2}$ = 6.02 h) and ^{101}Tc ($t_{1/2}$ = 14.2 min). ^{101}Tc in the final product could interfere with radiological investigations, so the irradiated MoO_3 is cooled for some hours to allow it to decay away.

Extraction

In the hot cell, 25 g of irradiated MoO_3 are dissolved in 200 ml of 6 M NaOH, and 1 ml of 3 % H_2O_2 is added to oxidize Mo reduced during irradiation. The solution is transfered to the extraction vessel after 10 min vigorous stiring. The new smaller scale prototype extraction vessel allows 200 ml of MEK as organic phase to disperse through the alkaline solution in a single continuous pass. The MEK is dispersed by means of a special stirrer and is siphoned off above the level of the aqueous phase. For the experiments an extraction vessel made of pyrex glass was used.

With this new system the yield of the extraction is around 85 % (see Table 1), which is very close to the yield of the previous, twice repeated bubbler extraction. Extraction without dispersal, or by bubling as in the previous system did not give good results.

Table 1. Yield of extraction.

Extraction with dispersal, single pass	Without dispersal	Twice repeated bubbler extraction, previous system[6]
86.2 %	5.4 %	87.1 %
85.1 %	7.1 %	82.8 %
83.7 %	8.3 %	86.3 %

The extraction yield is very dependent on the chemical form of technetium, which has to be

in the pertechnetate form. We compared two methods of oxidation, the first being addition of 3 % H_2O_2, and the second addition of a small amount of $K_2Cr_2O_7$. The oxidation efficiency was the same in both cases. For our new generator system oxidation with 3 % H_2O_2 was chosen, as the possibility of contamination of the final product with chromium was eliminated.

Since in the new extraction system continuous extraction is used, we constructed a new continuous evaporator, which is made from a pyrex glass spiral and heated with an electrical heating tape or hot air to 80 °C. The bottom part of this evaporator is directly connected with the reservoir for TcO_4^- and the condenser for MEK, where the vacuum is maintained by a KOMVAK 1 diaphragm pump.

Results and discussion

The final product, solvent extraction produced $^{99m}TcO_4^-$ has the following chemical characteristics:

- pH = 6 – 7;
- ^{99m}Tc: 99 % as pertechnetate;
- ^{99}Mo content: $< 1 \times 10^{-5}$ %;
- specific activity: 4810 MBq.ml^{-1} (130 mCi.ml^{-1});
- volume: 5 – 10 ml;
- trace impurities: ^{95}Nb, ^{188}Re, ^{198}Au.

In quality tests of the final technetium solution we found a measurable activity of ^{186}Re when MoO_3 from Kemika Zagreb was used for preparation of technetium. At the same time, we also found that the chemical purity of MoO_3 produced by Merck is much better, and normally this oxide is used for irradiation. However, if for technical reasons we are obliged to use MoO_3 from Kemika Zagreb, there is possibility to avoid ^{186}Re and ^{188}Re activities by precrystalization of MoO_3.

Tests carried out at the Microbiological Institute of the Medical Faculty in Ljubljana and LEK – Ljubljana showed the product to be sterile and apyrogenic, and non-toxic, respectively.

The apparatus described is for objective reasons not yet used for daily routine production of technetium, but all the tests performed showed that the final product has the same characteristics as TcO_4^- produced by our previously developed system.[8] The main part of the new semi-automatic extraction system – the extraction vessel – will in future be changed from glass to a stainless steel extractor to avoid the problems which can arise from leaching of silica from the walls under the combined influence of intense gamma radiation and strong alkali, leading blockage of the membrane filters. The incorporation of additional electronic controls and connection to the micro-computer should make this system more suitable for simple daily routine work.

Acknowledgement

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Glomerulonephritis and cancer

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Glomerular disease occurring in association with cancer is a rare phenomenon, but it is important because it may precede the appearance, or recurrence, of cancer. The true significance, and further management of a patient, depend on just how rare the association is, and what can be done to treat the tumour. In the earliest report of the association, the incidence of cancer occurring in patients with glomerulonephritis was 11%. This strikingly high figure had a great influence on clinical thinking, but subsequent papers have suggested that the incidence is much lower, perhaps less than 1%.

Three clinical cases are presented which demonstrate the practical management problem of oncology patients who develop glomerulonephritis. Together with a review of the literature, these cases illustrate the relative lack of value of extensive re-investigation of oncology patients who develop glomerulonephritis.

Key words: glomerulonephritis; neoplasms, cancer

Introduction

Glomerular disease occurring in association with cancer is a rare phenomenon in oncology practice, though is more common, and better described, in nephrology patients. However, its importance lies in the fact that nephrotic syndrome may precede or presage the presentation of a new cancer, or relapse of a previous malignancy. In addition, nephrotic syndrome may be significantly morbid because of the substantial loss of protein which can occur. Just how important the development of nephrotic syndrome is, and the further management which is required, depend on the true incidence of the association between glomerular disease and cancer, and on what can be done to treat both the renal and tumour pathology. The commonest clinical presentation of tumour-associated glomerular disease is nephrotic syndrome. This can be regarded as severe proteinuria, and is defined specifically as severe proteinuria (>5 g/24 hrs), with hypoalbuminaemia (<20 g/l) and peripheral oedema.

The first report of malignancy and glomerular disease dates to 1922 when Galloway described a patient with Hodgkin's Disease who develop-

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ed nephrotic syndrome.[1] However, the association was probably unrecognised until the seminal paper by Lee et al. in 1966.[2] These authors reported 11 cases of cancer in 101 patients with nephrotic syndrome. This series of patients very reasonably had a great influence on clinical thinking, chiefly because of the very high incidence – 11 % – of cancer occuring in patients with glomerulonephritis (GN). Subsequent papers however, have suggested that the relationship is less strong, cancer occurring in a smaller proportion of nephrotic syndrome patients (see below). Glomerular disease is known to occur in both lymphomas and solid tumours (Table 1). It has been described occurring as a prodromal illness preceding the appearance of tumour; it may occur in patients with established tumours, though usually early on; and it may presage recurrence. Glomerulonephritis occurring in patients known to have tumours can therefore present an anxious and difficult management problem for the oncologist.

Table 1. Tumours most commonly associated with paraneoplastic glomerulonephritis.

Carcinoma of the bronchus	– notable
Carcinoma of the colon	
Carcinoma of the stomach	
Renal cell carcinoma	
Hodgkin's Disease	– uncommon
Non-Hodgkin's Lymphoma	– very rare

Patients with nephrotic syndrome and no previous history of malignancy normally present to renal physicians, and this scenario is therefore less relevant in oncology. What, then, should the oncologist do when faced with a patient with nephrotic syndrome? Three clinical cases are presented to illustrate the association between GN and cancer and to demonstrate some of the clinical problems which arise from it. With reference to the literature, we hope to provide some guide to the management of these patients.

Case reports

Case 1

A 44 year old painter and decorator, a life-long smoker, presented in 1983 with asthma. At that time he was found to be hypertensive and had significant proteinuria, with a concentration in the urine of 4,3 grams/litre. His plasma albumin was 32 g/l and creatinine clearance 125 ml/min. He was treated for hypertension with nifedipine and diuretics, but was a rather erratic hospital attender. In 1990, his blood pressure was found to be 200/140, his albumin had fallen to 30 g/l, creatinine clearance had worsened to 94 ml/min, and his proteinuria was 6,3 g/24 hours. His ECG showed changes consistent with hyperten-

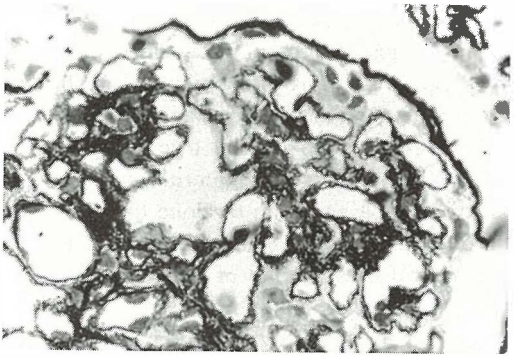

Figure 1a. Renal biopsy from Case 1 showing membranous glomerulonephritis. The glomerular basement membrane appears as a chain-like structure, the silver-positive (black) membrane enclosing the lucent complexes shown in b) (silver methenamine stain × 400 original magnification).

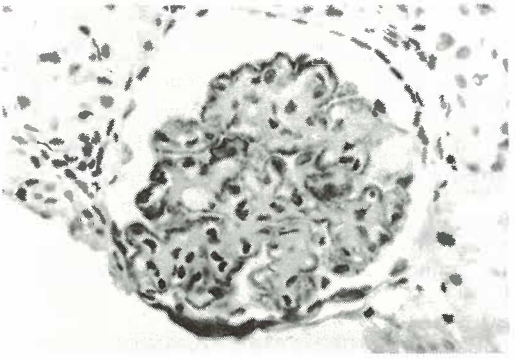

Figure 1b. Renal biopsy form Case 1 showing membranous GN. An immunoperoxidase preparation for IgM, demonstrating granular deposits (black) outlining the capillary loops (immunoperoxidase IgM × 250 original magnification).

sion. The following year he agreed to renal biopsy and was found to have membranous GN (Figure 1). Treatment for his hypertension was continued.

In September 1992, he presented with a 2 week history of shortness of breath and haemoptysis and was found on chest X-ray to have right upper lobe collapse. Bronchoscopy showed a tumour occluding the orifice of the right upper lobe and extending into the right main bronchus. Biopsy revealed poorly differentiated, nonsmall cell carcinoma of the bronchus which was inoperable due to its proximity to the carina. A course of palliative radiotherapy was carried out, giving 30 Gy in 10 fractions over 2 weeks to the right upper lobe mass and mediastinum. This was tolerated well, with resolution of the haemoptysis and shortness of breath. One month after the radiotherapy, chest X-ray demonstrated that the right upper lobe had re-expanded, he remained mildly hypertensive on treatment, and his renal function was unchanged. Seven months later he remained clinically well, with the same degree of renal impairment, and continuing proteinuria of 6 g/24 hours.

Case 2

A 50 year old nursing sister presented with a lump in the left breast in 1989. At that time, she was pre-menopausal. Wide local excision was carried out and histology revealed a pathological T2 grade 2 invasive ductal carcinoma of the breast though some tumour remained at one excision margin. She was clinically node negative. Routine staging was otherwise normal and she was started on Tamoxifen. Radical radiotherapy was given to the whole breast using 50 Gy in 25 fractions in 5 weeks with tangential opposed fields, followed by a boost to the tumour bed of 16 Gy in 8 fractions over 10 days.

Three years later she was found by chance to have a plasma albumin of 27 g/l, but was not investigated further, until a few months later when she complained of tiredness and malaise and had pitting oedema to the mid thigh level and over the sacrum. There was, however, no clinical evidence of recurrent carcinoma of the breast. At the time her albumin was 24 g/l and urinary protein 1.26 grams per litre. The serum cholesterol was slightly elevated at 10.7 mmol/l (normal range 2.3 – 6.9). Renal biopsy demonstrated membranous GN. Shortly after, she became mildly hypertensive and was started on enalapril and frusemide. This treatment improved her blood pressure and her oedema resolved. Though her plasma albumin remained low, the protein loss from the kidneys was reduced to below half of its former level. She currently remains free of clinical evidence of carcinoma of the breast. She has not been formally re-staged.

Case 3

In 1983, a 50 year old university lecturer presented with night sweats, weight loss of 3 kg and lymphadenopathy in the neck and axillae. Biopsy demonstrated high grade non-Hodgkin's lymphoma (NHL) and further investigations revealed Stage 2B disease. He was treated with 6 cycles of chemotherapy, using cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). After 2 cycles he was found to be in complete remission clinically.

For the ensuing 10 years he remained well but in February 1993 he presented with a 10 day history of feeling unwell, and a 24 hour history of periorbital oedema, and swelling of the legs up to the level of the knees. There was no clinical evidence of recurrence of the lymphoma. He had normal renal function but his plasma albumin was slightly low, at 33 g/l. Over the next few days his albumin fell to 22 g/l, and urine collection demonstrated proteinuria of 10.4 g/24 hours. Serum cholesterol was elevated at 13.4 mmol/l, in physiological response to the low albumin. Other investigations including chest X-ray and ultrasound of the abdomen, pelvis and renal tract were normal. A clinical diagnosis of glomerulonephritis was made and renal biopsy showed the glomerular tip lesion, a variant of focal segmental glomerulosclerosis (FSGS) (See Figure 2). This variant of FSGS

described by Beaman et al. in 1987 may be steroid responsive,[3] although 2 patients in this series who did not respond to steroids had malignant disease, renal cell carcinoma and Hodgkin's disease respectively. Our patient was treated initially with frusemide, and following the histology result cyclophosphamide (150 mg = 2.5 mg/kg) and prednisolone (60 mg/day) were added. He developed occasional fevers and night sweats, though no clinical evidence of recurrence. Re-staging was carried out with CT of thorax, abdomen and pelvis, plus bone marrow trephine and aspirate, all of which were normal.

Over the next 3 months his general condition improved and the peripheral oedema was confined to the ankles. The glomerulonephritis also improved, so that by June 1993 urinary protein loss had fallen to 3 g/24 hours. Plasma albumin, thought not to normal, had risen to 29 g/l. Serum cholesterol had dropped somewhat, to 9.7 mmol/l. During this time the steroid dose had been reduced to 20 mg/day, though he remained on cyclophosphamide.

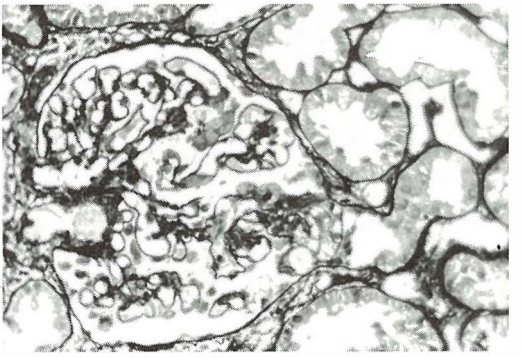

Figure 2. Renal biopsy from Case 3 showing the glomerular tip lesion. There is a segmental adhesion to the origin of the proximal convoluted tubule associated with a collection of foam cells in the affected segment (silver methenamine stain × 250 original magnification).

Discussion

Incidence of cancer in patients with glomerulonephritis

The classic paper by Lee et al. in 1966 reported a relatively high incidence of 11% (11 of 101) of patients with nephrotic syndrome who developed carcinomas.[2] In 7 of these 11 patients the glomerulonephritis preceded discovery of cancer, and all were over 40. Other series have reported rates between 6% and 11%.[4, 5] The two series with these high rates of associated malignancy, in particular, have been invoked to justify the search for malignancy in patients with nephrotic syndrome, particularly with membranous GN histology (see below).[6] However, Kaplan et al.[7] reviewed 14 published series including 1643 patients with nephrotic syndrome, though not those of Lee et al.[2] and found that only 6 had co-existing tumours, an incidence of only 0.37%. In another individual series, Heneghan et al. reported a 1.1% incidence of cancer with GN.[8] Carcinomas are the tumours most commonly associated with GN (Table 1). Hodgkin's Disease is uncommon, and non-Hodgkin's lymphoma extremely rare.[6, 9–11] Benign tumours have occasionally been reported in association with GN, but so rarely that this is probably due to chance alone.[7, 11]

The incidence of the association is also dependent on age. Cancer associated with glomerulonephritis is very rare in children. There were no cases in one series of 121 children with membranous GN, although there have been occasional patients reported in other series.[11] The incidence appears to rise in adulthood, and most of the reported cases have been over 40–50 years of age.[11]

Thus, it would appear, especially from more recent series, that the true incidence of cancer occuring in patients with nephrotic syndrome is much lower than initial reports suggested. This changes the significance of nephrotic syndrome, both in a patient who is otherwise well, and in one who has a past history of malignancy. While a true incidence of cancer developing in patients with nephrotic syndrome of around 10% might well encourage a relatively strenuous diagnostic activity, if the true incidence is as low as $\leq$1%, this may not be warranted, both in terms of psychological cost to the pa-

tient and financial cost to the hospital. Nevertheless, since the appearance of nephrotic syndrome may be the harbinger of new or recurrent cancer, some index of suspicion is appropriate.

Incidence of glomerulonephritis in patients with cancer

Considering all the patients seen by oncologists, it is clear that the occurrence of nephrotic syndrome in patients with cancer is strikingly low, although the exact prevalence is unknown. The incidence of sub-clinical renal abnormalities in patients with cancer is, however, quite considerable. Surveys of cancer patients have shown proteinuria or haematuria in between 15% and 58% of patients.[11, 12] This seems a very high proportion, but is entirely possible that in many of these patients this is not associated with glomerural pathology. Such abnormalities may be discovered simply because these patients tend to be supervised quite intensively. However, patients with active malignant disease who have sub-clinical proteinuria are unlikely to be subjected to intensive renal investigation including biopsy. The relationship of proteinuria to malignancy is probably less strong than these figures suggest. For example, in one survey some degree of proteinuria was found in 22% of hospital patients who were not suffering from malignancy.[12] The incidence of GN in patients with lymphomas, as opposed to carcinomas, has been addressed in 2 large studies, together including a total of 1700 patients with Hodgkin's Disease. Only 7 patients had evidence of GN, an incidence of 0.4%.[8, 10]

Autopsy studies have demonstrated an incidence of immune deposits in the kidney of 11 to 40%, but actual glomerular changes are rare, only 1.5% in one autopsy study.[6, 11] This latter figure is compatible with figures from the larger series of clinical GN. The pathological finding of mesangial and subendothelial deposits may represent non-specific trapping of immune complexes, or more likely tumour antigens, rather than indicating, or indeed causing, glomerular damage.[6]

Evidence of a causal relationship between cancer and glomerulonephritis

Although the association is rare, there is reasonable evidence of a causal relationship. The main evidence falls into 3 main categories. Firstly, a close temporal relationship frequently exists between cancer and the GN.[13] Typically, both conditions occur close together in time. Certainly in the majority of patients GN is apparent within 6 months either side of the appearance of the tumour, although in one series 8–16% of patients had greater than 1 year between the appearance of the 2 conditions.[13] Secondly, remission of the GN is frequently associated with treatment of the tumour, and recurrence of tumour has been described associated with GN.[2, 9, 14, 5] Finally, antigen-antibody complexes have been found in the glomeruli, which in a minority of cases have been demonstrated to be tumour-associated antigen and specific antibody.[6, 11] Non-Hodgkin's lymphoma is rarely associated with GN, which has been invoked as evidence against a causal relationship with this malignancy.[6]

Renal abnormalities in patients with malignancy

Malignant disease may affect the kidney in a variety of ways, directly and indirectly, at both the macroscopic and microscopic level. These

Table 2. Causes of renal abnormalities in patients with malignancy.

Direct infiltration of kidney by tumour
Obstruction of urinary tract by tumour
Renal vein thrombosis due to tumour
Metastases
Fluid imbalance (i.e. pre-renal failure)
Infection
Electrolyte disturbance caused by tumour or treatment (e.g. hypercalcaemia, raised uric acid, tumour lysis syndrome)
Direct toxicity of therapy (chemotherapy, radiotherapy, antibiotics, etc.)
Obstruction by tumour products (e.g. light chain casts in myeloma, mucoprotein from carcinoma of pancreas)
Glomerulopathy

are laid out in Table 2. The only types of abnormality which can be considered paraneoplastic are obstruction by tumour products and glomerulopathy, and it is clear from the table that these causes are uncommon. To some extent, in the context of glomerulonephritis causing nephrotic syndrome, the term paraneoplastic implies uncertainty about the exact aetiology of the condition. Of the direct effects, by far the most common is obstruction of the urinary tract, typically by pelvic and retroperitoneal tumours. Metastatic spread to the kidney is curiously rare, considering the very large renal blood flow.

Types of glomerular disease: The main types of glomerular disease associated with malignancy are shown in Table 3. By far the most common variety is membranous GN. There are differences in the types of GN found in association with carcinomas as opposed to lymphomas. Of all carcinoma patients who develop nephrotic syndrome, 80–90 % will have membranous GN on biopsy.[16, 17] The histological appearances in these patients are identical to those of membranous GN of idiopathic type, with sub-epithelial electron dense deposits which usually prove to be deposits of IgG with or without complement component C3.[11]

Of the remaining cases, minimal change GN is the next most common type of glomerular pathology. This type is classically associated with lymphomas, particularly Hodgkin's Disease, and is uncommon in patients with solid tumours.[11] It appears very rare for renal disease to be associated with non-Hodgkin's lymphoma (NHL). Alpers and Contran[6] reviewed the literature and found only 20 cases associating NHL with any clinically significant glomerular disease, and only 2 of these actually had minimal change GN. They suggest that this casts doubt on the existence of a clear-cut association between NHL and GN.

Occasional cases of lymphoma have been shown to exhibit focal segfmental glomerulosclerosis (FS GS).[6, 18] A few cases of proliferative GN are also seen, generally also associated with Hodgkin's Disease,[19] and crescentic GN has also been associated with tumours.[6]

Pathogenesis: Tumour-associated glomerulonephritis is regarded as a paraneoplastic syndrome, which implies that the pathogenesis is not understood. It seems most likely that glomerular damage is immunologically mediated, although disseminated intravascular coagulation may also be responsible (see Table 4). The condition is probably due to immune complexes which may include tumour-associated antigens in some cases, but in very few patients is the actual antigen identified. The prevailing view now is that immune complexes are most likely to be formed *in situ* by antibody and antigen deposited *separately* within the glomerular apparatus.[6, 11] It is also true that immune complexes may be demonstrated in the kidney which retains normal function and normal histology (see above).

In Hodgkin's Disease it has been postulated that the development of GN may be related to deficient T-cell function. Long-lasting abnormalities of cell-mediated immunity occur in many patients with this condition, with reduction of the ratio of T4 (helper) to T8 (suppressor)

Table 3. Glomerular changes most commonly associated with malignancy.

Membranous GN	– commonest type of GN associated with cancer – typically occurs with carcinoma
Minimal change GN	– usually associated with Hodgkin's Disease
Proliferative GN	
Mesangiocapillary GN	
Crescentic nephritis	
Focal segmental glomerulosclerosis (FSGS)	
IgA nephropathy	
Amyloidisis	

Table 4. Pathogenesis of glomerulonephritis associated with malignancy.

Tumour-associated antigen
Re-expressed foetal antigen
Viral antigen
Autologous non-tumour antigen
Disseminated intravascular coagulation
Amyloid
(Defective T-cell function)

cells.[11, 20] This change has been reported in patients with cured Hodgkin's Disease who subsequently developed GN.[21] Whether this T-cell abnormality is the cause of GN in Hodgkin's Disease is unknown, but it remains a possiblity, since an immunological contribution to the pathogenesis of GN is likely.

Prognosis

In general, the outcome of patients with cancer-associated GN is dominated by the prognosis of the malignancy, rather than the renal disease. There are rather few reported cases of clinical outcome and no clear picture emerges. There is, however, an appreciable number of cases of improvement in GN associated with response to anti-cancer treatments. This applies particularly to Hodgkin's Disease, where treatment of the malignancy is normally accompanied by improvement in the GN.[7, 11] For example, a 13 year old boy with Hodgkin's disease who was found to have nephrotic syndrome at diagnosis was treated with mustine. The tumour responded and the nephrotic syndrome resolved within 2–3 weeks. The Hodgkin's Disease relapsed after 3 years but there was no return of the nephrotic syndrome.[15] Glomerulonephritis associated with solid tumours may also remit with treatment of the cancer. Cantrell[14] reported a patient with carcinoma of the stomach who had GN at the time of diagnosis. Complete surgical resection was carried out with resolution of the GN. Lee et al.[2] also described a patient whose GN "led to the discovery of carcinoma of the colon", and in whom the GN improved after resection of the primary tumour. Where GN has improved with treatment of the tumour, recurrence of the malignancy has often, though not invariably, been associated with recrudescence of the GN.[11]

The level of proteinuria may be a prognostic factor. In cancer patients with GN, Row et al.[5] found a worse prognosis in patients with greater proteinuria. Sawyer et al.[12] extended this, comparing prognosis with the level of proteinuria in 504 patients, regardless of whether they had GN or not. The median survival of patients with proteinuria was only 4.5 months, compared to 10 months for patients without. In addition, the higher the level of proteinuria, the worse the prognosis. The oncology details were not presented and the low median survival implies that the patients in this study had advanced disease. It is quite possible that patients with aggressive disease were more likely to sustain renal complications causing proteinuria, both from GN and other causes such as infection, so that the proteinuria may be purely a marker, and not a cause, of poorer prognosis.

Case discussion

Patient 1 developed nephrotic syndrome several years before presenting with carcinoma of the bronchus. Although nephrotic syndrome may precede the appearance of cancer by a surprisingly long time, the interval in this case exceeds what can be regarded as likely for a causal association. Whilst he had the commonest variety of tumour-associated GN, the majority of patients presenting to renal physicians with membranous GN never develop cancer. No change was observed in the patient's renal status with the development or treatment of the cancer.

Case 2 illustrates the classical dilemma, which leads to a difficult mamagement problem. Although the patient had early carcinoma of the breast, she still has a significant risk of relapse. The development of nephrotic syndrome, due to membranous GN, might presage recurrent disease. Is re-staging or further investigation warranted or necessary in this situation?

The cost of re-staging this patient is shown in Table 5. The financial cost is relatively low, a total of £184 at our hospital, but the psycho-

Table 5. Cost of re-staging Patient 2.

Investigation	Cost in pounds sterling
FBC	5
Biochemistry	13
CXR	8
Mammogram	19
Ultrasound Scan Abdomen	19
Bone Scan	120
TOTAL	£184
Psychological cost	Not assessable!

logical cost is impossible to assess. Since it may take in excess of 1 year after the appearance of nephrotic syndrome for tumour to present, this patient could be faced with a long period of uncertainty about her carcinoma if re-staged. Note that for this patient the more expensive radiological investigations (CT of 1 region, without contrast £90; and MRI of 1 region £300) are not required. The cost of re-staging patient 3, including CT and bone marrow investigations, would have been approximately three times as expensive.

Part of the answer to the question of whether to re-stage depends on whether a tumour recurrence detected earlier yields a higher chance of cure or long-term remission. At present, recurrent carcinoma of the breast is incurable, and nothing is gained by earlier detection. Regrettably, this is true for most solid tumours at the present time. This fact considerably weakens the argument for extensive reinvestigation of patients developing nephrotic syndrome, as opposed to simple, non-invasive routine tests, such as haematology, biochemistry and CXR. One factor which militates in favour of re-staging is the severity of th nephrotic syndrome. Since this may respond to treatment of the malignancy, in some cases of association, investigation in the hope of this may be appropritate if the severity of the nephrotic syndrome is extreme.

In case 3, the duration of follow up exceeds 9 years from the completion of treatment. In the case of high grade non-Hodgkin's lymphoma, this should render the risk of recurrence extremely low. Literature review also suggests that a causal association between nephrotic syndrome and NHL is unlikely. On two counts, therefore, recurrence of disease can be clinically excluded in this patient.

Conclusions

An association between nephropathy and malignancy is well established. However, the true incidence is probably much lower than was once believed, perhaps 1% or less. In addition, there are circumstances in which a causal relationship is unlikely. For example, GN is very rare in association with NHL, suggesting a lack of causality. The clinical behaviour of a particular tumour type may also make the appearance of GN unlikely to be due to relapse.

In spite of the clear association between glomerulonephritis and cancer, the vast majority of patients with nephrotic syndrome never develop a malignancy. In patients with malignant disease, the incidence of glomerulonephritis is extremely low. The glomerulonephritis may act as a marker of disease activity, but in the majority probably does not alter the prognosis, provided that the renal condition is correctly treated. Nevertheless, it seems prudent to carry out simple screening investigations in patients who develop nephrotic syndrome de novo, especially in patients over 50 years of age. For patients with a past history of malignancy, the need or desirability of investigation should probably be assessed on an individual basis, rather than managed with a standard policy. Regrettably, in most tumours, recurrence is usually not curable even if discovered early, and there may be little to gain, and much to lose from over-zealous re-investigation.

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Neoadjuvant intraarterial chemotherapy of malignant soft tissue tumors. A new treatment protocol

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A group of 58 consecutive patients with extremity sarcomas of soft tissue origin (23 primaries, 35 recurrences) received preoperative intraarterial chemotherapy so that the prerequisities for limb salvage surgery were created. The average size of the tumors was 140 cm^2 (25–520 cm^2), thus the only criteria for patients to get into this study was the absence of any sign of distant spread or such local invasion of the tumor that would have rendered any efforts for limb sparing surgery aimless. To achieve the best possible local control, the intraarterial cytostatic infusions were complemented by different interventional radiological procedures including superselective catheterization, chemoembolization, temporary balloon blockage together with applying distal tourniquet in combination with one another establishing a new treatment protocol based on the characteristics of the tumor's vascular supply. The overwhelming majority of 49 patients who received multiple (2–5) treatment cycles showed favourite response rate (4 complete remissions, 16 partial remissions, 14 minimal response, while only one tumor progressed. In 51/58 patients successful limb salvage surgery was performed. The follow up time was 8–79 months (average 26.2 months) for 57 patients (one was lost to follow up due to early postoperative death); 34 of them developed local recurrences after a period of 7–28 (average 12.3) months. Thirty-five patients died of diseminated disease, their survival was 8–42 (average 18.9) months. At present, 22 patients are still alive. Ten underwent another one or two surgeries (follow up 18–48, average 31, months), while 12 patients are alive with no evidence of disease (their survival is 17–79, average 33.2, months)

Key words: soft tissue sarcomas, soft tissue neoplasms – drug therapy, neoadjuvant treatment; infusions, intra-arterial, intraarterial chemotherapy; radiology, interventional; limb salvage surgery

Introduction

With intraarterial (i.a.) chemotherapy the cytostatics are delivered in a greater concentration to the tumor bearing region to reduce the size of the tumor for limb salvage surgery. The benefits of exposing tumor tissue directly to a higher concentration of drug have been confirmed by experimental studies showing a concentration gradient of 3.5–9 between the tumor tissue and the venous blood,[1,2] whereas this factor was 40–50 between the general venous route and the level of subterminal arteries.[1] The gradient is further increased by supplemen-

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tary methods such as superselective catheterization, temporary balloon blockage using an occluding balloon catheter, chemoembolization and applying tourniquet.[2–6]

This study is aimed to summarize our preliminary results obtained by interventional radiology procedures to improve local tumor control and thus promote limb salvage. It is now apparent that nonamputative surgery with neoadjuvant treatment is possible in many patients with malignant soft tissue tumors, with a local control rate that approaches, and in many instances exceeds, that achieved by amputation.[7,8,9]

We have also tried to establish a new neoadjuvant treatment protocol including a multicycle, combined i.a. chemotherapy complemented by interventional radiology procedures which is based upon the consideration of the characteristics of the tumor's vascular supply.

Material and methods

A group of 58 consecutive patients with extremity soft tissue sarcomas of differing histology received preoperative i.a. chemotherapy via a catheter placed percutaneously under fluoroscopy.

The localization of tumors is shown in Table 1. Two thirds of the lesions developed in the thigh and leg (25 and 11, respectively) while true extracompartmental location was encountered only in 10 patients (axillary, inguinal and popliteal regions). The tumor size was established by arteriography. In all tumors, the greatest diameter exceeded 5 cm. According to WHO criteria the correct tumor size was determined as the product of two greatest diameters perpendicular to one another. On the basis of this calculation the size of the tumors varied between 25–520 cm^2 (average 140 cm^2).

Table 1. Localisation of the tumours (n = 58)

Axillary region	3
Upper arm	6
Forearm	3
Hand	2
Subinguinal/Inguinal region	4
Thigh	25
Popliteal region	3
Leg	11
Foot	1
Total	58

Table 2. Distribution of treatment modalities.

Group 1 (n = 19)	Superselective catheterization + Embolization/chemoembolization ± Temporary balloon blockage
Group 2 (n = 19)	Selective catheterization of the main artery of the tumour-bearing region with distal tourniquet + superselective approach of feeder(s) ± Embolization/chemoembolization ± Temporary balloon blockage
Group 3 (n = 20)	Selective catheterization of the main artery of the tumour-bearing region with distal tourniquet

As to the treatment modality three groups were formed according to the characteristics of tumor's vascular supply (Table 2).

Group 1 (n = 19)
All the supplying arteries could be approached superselectively. Superselective catheterization was preferred if it was feasible and in the majority of cases this was supplemented by embolization/chemoembolization and/or intermittent balloon blockage using an occluding balloon catheter (e.g. in deep femoral artery, anterior tibial artery).

Group 2 (n = 19)
If the tumor had multiple vascular supplies which could be catheterized only in part, after treating the neoplasm through the approachable branches by means of i.a. infusions completed by chemoembolization and/or balloon blockage, the main artery of the tumor-bearing region was catheterized. To protect the healthy tissues from toxic-irritative effect of the drugs a pneumatic tourniquet was placed around the affected limb distally to the tumor and was inflated intermittently above the systolic pressure (200–250 Hgmm) during i.a. infusions (e.g. most often in the cases where the tumor of the thigh had supplying branches from deep femoral as well as superficial femoral arteries).

Group 3 (n = 20)
Tumors without selectively approachable arteries were treated by placing the catheter into

the main supplying artery of the affected region as close to the feeders as possible and so called "distal tourniquet" was also applied (e.g. mainly in the supplying area of the axillary artery, superficial femoral and popliteal arteries).

Treatments were performed as a series of chemotherapy cycles with an interval of 3 weeks in between. The number of courses ranged from one (n = 9) to five (average 3), giving a total of 154 cycles. These cycles were carried out in the form of short-term i.a. infusions which usually lasted for 20–40 min.

The basic drug used was doxorubicin (ADM) which was administered as monotherapy in 11 patients. ADM was applied in combination with cisplatin (CDDP) in 34 patients, while a combination of ADM, CDDP and dacarbazine (DTIC) was used in 13 cases. Both ADM and CDDP were applied in concentrated solution (20–25 mg/10 ml). DTIC was solved in its solvent and 1 % lidocaine in a ratio of 1 : 1. The total amount of drug was 50–450 mg (average 220 mg) for doxorubicin, 50–220 mg (average 150 mg) for cisplatin and 400–1200 mg (average 800 mg) for dacarbazine depending mainly on the number of cycles per patient.

In several cycles of 16 patients embolization and mainly chemoembolization was carried out using application of Gelfoam or a mixture of Gelfoam and 10–20 mg doxorubicin and/or cisplatin.

In 5 patients (13 cycles) balloon blockage (so called occlusion-infusion) was performed after inserting a balloon catheter into the given supplying artery. It was carried out in 10 cycles in a branch of deep femoral artery while in 3 in the anterior tibial artery.

Tumor response was established by computerized tomography (CT), arteriography and pathological evaluation and was classified as follows: complete tumor response (CR), partial tumor response (PR) where there was 50 % or more regression in size. The group of minimal response (MR) was further divided into 2 subgroups: $MR_{50\text{-}25}$ where tumor regression was between 50 % and 25 %, and $MR_{<25}$ where tumor response was less than 25 %.

Besides the generally used category of overall response rate (CR + PR) we recommend the use of the notion of favourable response rate which included overall response rate with $MR_{50\text{-}25}$.

Results

For different reasons 9 out of 58 patients received only one chemotherapy cycle so the evaluation of treatment in these cased had to be based exclusively on pathological examination of the surgical specimen (6 patients refused additional cycles whereas 3 patients appeared again far beyond the optimal time for the repetition of cycle). That is the reason why only the data on other 49 patients, who received 2–5 chemotherapy courses and were followed up also by imaging modalities (CT, arteriography), are discussed here.

Table 3. Relationship between the tumour size and the efficacy of treatment consisting of multiple (2–5) cycles (n = 49).

Size before treatment (cm^2)	CR	PR	$MR_{50\text{-}25}$	$MR_{<25}$	P
25– 50	2	7	3	3	0
51–100	0	7	5	0	0
101–200	2	5	4	1	0
201–300	0	2	0	1	0
301–400	0	0	0	1	1
401–500	0	1	2	1	0
501–	0	0	1	0	0
Total	4	22	15	7	1

Table 3 shows the relationship between the tumor size and the effectiveness of treatment. In the group of tumors of small and medium size (25–200 cm^2) the majority of lesions (23/39, 65 %) showed CR and PR, while in 12 the degree of response was $MR_{50\text{-}25}$. So the favourable response rate was 35/39 (89 %). Although there were four tumors (among them 3 were the smallest) which responded poorly ($MR_{<25}$) despite their small size. In the group of big tumors (greater than 200 cm^2) 6/10 lesions showed PR and $MR_{50\text{-}25}$, respectively, while 3 $MR_{<25}$ were encountered and there was only one tumor showing progression.

Table 4. Relationship between the number of cycles and the effectiveness of treatment.

Number of cycles	CR	PR	MR_{50-25}	$MR_{<25}$	P
a. Combination of doxorubicin and cisplatin (n = 28)					
2	0	1	2	1	0
3	1	7	6	2	1
4	2	3	3	0	0
	3	11	11	3	1
b. Triple combination of doxorubicin, cisplatin, DTIC (n = 11)					
2	0	2	0	2	0
3	1	3	3	0	0
	1	5	3	2	0

The relationship between the number of cycles and the effectiveness of treatment is seen in Table 4. By increasing the number of cycles, better responses can be obtained in both subgroups (using double and triple combination of drugs). Although a trend can be calculated from these data, the diference is not significant because of the small number of cases.

Table 5 shows the distribution of responses of sarcomas to multiple (2–5) chemotherapy cycles (n = 49). The table contains also data related to previous chemo- and/or radiotherapy in recurrent lesions. Recurrent tumors are divided according to histological grading, while all the primaries belonged to the group of high grade sarcomas.

All the primary lesions except one showed favourable responses including CR, PR and MR_{50-25}. In this group there was only one tumor where the treatment resulted in $MR_{<25}$ only.

All low grade sarcomas (n = 5; 4 myxoid liposarcomas, 1 myxosarcoma) responded well and PR occured, although these tumors have been generally considered to be chemotherapy resistant.

In the group of high grade recurrent sarcomas two subgroups were formed depending on whether the tumors had been treated by surgery alone or by surgery and chemotherapy and/or radiotherapy. We did not find any significant difference between the two subgroups which might indicate a possible chemotherapy resistance. The favourable response rate (CR, PR, MR_{50-25}) in the patients who had undergone surgery alone was only slightly better (12/15 = 80 %) than that of those receiving also chemo- and/or radiotherapy (6/9 = 66 %).

We tried to find any relationship between the response rate of the primary and the high grade reccurrent sarcomas. The overall response rate (CR and PR) was 11/20 (55 %) for the primary and 10/24 (41 %) for the recurrent lesions. The number of favourable responses (CR, PR, MR_{50-25}) was 19/20 (95 %!) and 18/24 (75 %), respectively.

Recurrence-free state and survival was calculated from the beginning of neoadjuvant i.a. chemotherapy. One patient, who died of pulmonary embolism 3 days after surgery, was excluded from evaluation.

The follow-up time was 8–79 months (average 26.2 months) for the remaining 57 patients, 34 of them developed local recurrence after a period of 7–28 (average 12.3) months.

Table 5. Response of sarcomas to multiple (2–5) chemotherapy cycles (n = 49)

Response	Primary tumours	Recurrences HG	HG	LG	Total
		Surgery alone*	Surgery + chemo- and/or radiotherapy*		
CR	2	1	1	0	4
PR	9	4	4	5	22
MR_{50-25}	8	7	1	0	16
$MR_{<25}$	1	2	3	0	6
P	0	1	0	0	1
Total	20	15	9	5	49

HG = high grade
LG = low grade
* = previous treatment

Table 6. Survival (n = 57).

Dead (n = 35)	Alive (n = 22)
8–42 (Average 18.9 months)	10 With recurrent tumours (1–2 surgeries, 4 amputations) 18–48 (Average 31 months) – 12 With no evidence of disease 17–79 (Average 33.2 months)

From the evaluation of recurrence-free state additional 3 patients were excluded in whom amputative surgery had been carried out shortly after the attempt for limb sparing surgery (due to insufficient venous drainage of the affected limbs). Thus the local recurrence-free state lasted for an average of 19.8 months in the evaluated 54 patients.

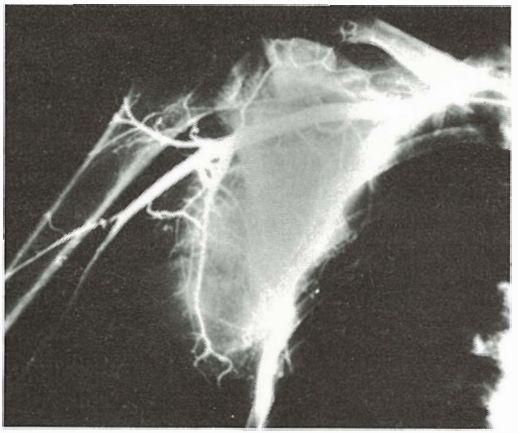

Figure 1a. Primary fibrosarcoma of the axillary region, mid-arterial phase.

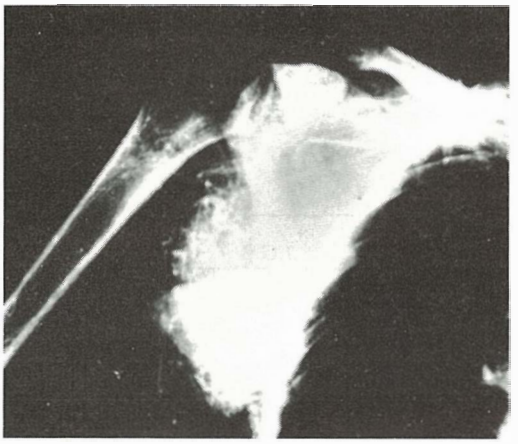

Figure 1b. Primary fibrosarcoma of the axillary region, parenchymal phase. Both phases (1a, 1b) show a considerably hypervascular tumor having multiple vascular supplies from the axillary artery and extension onto the chestwall.

The survival was 8-42 months (average 18.9 months) for patients who died of the dissemination of their disease (n = 35) (Table 6).

At present, 22 patients are still alive, of them 10 underwent another one or two surgeries (during which the affected limbs could not be spared in 4). Their follow-up was 18–48 (average 31) months. Twelve patients are alive with no evidence of the disease and the survival of 17–79 (average 33.2) months.

Complications

Apart from frequent and mild side effects such as temporary erythema with a few blisters appearing on the skin, attributable to the local irritative effect of drugs (mainly of doxorubicin), 16 severe complications including vessel occlusion, extensive desquamation and necrosis of the skin were encountered in the course of 154 cycles.

Arterial occlusion was seen in five patients and four remained symptom-free while in one patient successful fibrinolysis was carried out.

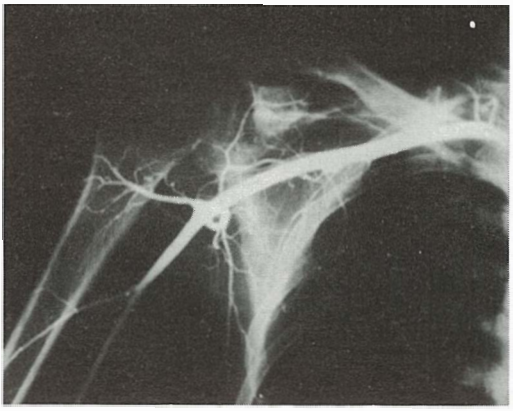

Figure 1c. Primary fibrosarcoma of the axillary region. After 2 cycles of distal tourniquet infusion containing triple drug combination the tumor has completely disappeared and there is no sign of any pathological vessels.

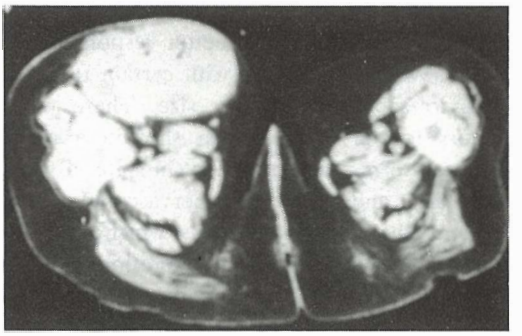

Figure 2a. Primary mesenchymal tumor of the right thigh. CT scan obtained before treatment shows a huge solid tumor originating from the anterior part of the thigh.

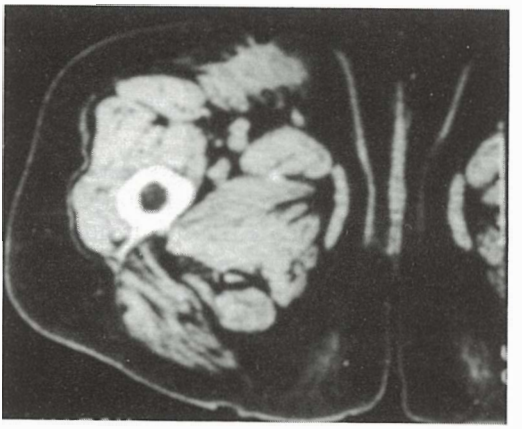

Figure 2b. Primary mesenchymal tumor of the right thigh. After two cycles of ADM, CDDP and DTIC administered by superselective i.a. infusion (in deep femoral artery) and by i.a. infusion of the superficial femoral artery together with distal tourniquet partial remission occured.

Apart from this latter case where the cause of the occlusion was inadvertent injection of a clot which had formed within the 3-French coaxial catheter, occlusions could be attributed to superselective i.a. infusions and/or embolization. In one patient with a marked stenosis of the arterial tibial artery caused by a plaque of arteriosclerotic origin the stenotic lesion turned into total occlusion after 2 cycles of distal tourniquet infusion.

In our series 11 patients developed superficial skin necrosis with an average size of 40 cm^2 (1–90 cm^2). In all but one cases superselective drug infusions complemented by chemoembolization and/or balloon blockage were carried out with an obviously higher local cytotoxic concentration increased further by ischemia. There was only one patient, treated by catheterization of the main artery of the affected region with distal tourniquet, who developed skin necrosis. It was caused by an accidental "overinfusion" of a small vessel originating at the proximity of the catheter tip into which the tip temporarily wedged.

It has to be stressed that the above mentioned phenomena appearing on the skin did not occur in the distal parts of the limbs when a pneumatic tourniquet, placed distally to the tumor, was applied.

Discussion

Embolization/chemoembolization as well as balloon blockage presume the feasibility of superselective catheterization. Once superselective catheter has been positioned it seems to be useful to increase the local cytotoxic concentration further by producing local ischemia and slowing the speed of circulation of the artery to be treated. Theoretically, all these interventions may considerably increase the local effect of the drug(s) used in the form of i.a. infusion by means of prolonging the contact-time between the tissues and drugs.

Recently, experimental investigations have demonstrated that an increase of 30 times can be achieved in the local concentration if the artery is obstructed proximally by a balloon during the infusion.[10] There are, however, difficulties with balloon occlusion including the possibility of backflow in the tumor through collateral arteries[2,10] annihilating the effect of the occlusion. Another possible danger is intravascular clot-formation with all its sequellae even if systemic heparinization is done. Therefore, we used this method in all but three cycles in the deep femoral artery where an inadvertent vascular occlusion does not threaten with severe sequellae including the loss of the limb. Complications did not occur. Nevertheless, there have been very few observations regarding its applicability in humans so far.

Chemoembolization also aims at increasing the local effect of drugs by maintaining a constantly higher cytotoxic concentration along with ischemia. This method integrating the advantages of arterial infusion and embolization can be accomplished by the use of microencapsulated agents or particulate emboli with drugs.[2,5] In addition to the direct effect of ischemia on the tumor vascular bed and besides increasing tumor-drug contact time as well as local drug concentration, at least in theory, even tissue permeability is increased because of the anoxia.[2] The cytotoxic effect is exerted not only on the neoplasm but on the vessel embolized and infused, producing vasculitis, edema and occlusion,[11] and is directly proportional with the drug concentration. All the local complications including desquamation and necrosis of the skin as well as vessel occlusion can be ascribed to these effects. All these observations seem to be supported by our clinical data presented.

With the use of a distal tourniquet efforts were made to decrease the arterial flow rather than interrupt it, which may lead to a more even distribution of the drug in the extremity.[3] The local cytotoxic concentration can be promptly increased in the tumor region,[4] while the drug concentration and the possible complication rate in the limb distally to the tourniquet can be decreased significantly as we have presented earlier.[12,13]

In order to improve the local tumor control, we have created a new treatment protocol applying some interventional radiology procedures in combination with one another. The basic principle of our study was to exploit as far as possible the nonspecific cytotoxic effect of the drugs complemented by methods producing local ischemia. All of our efforts have been made in the hope of accomplishing maximum cell destruction in the tumor.

The relatively low number of cases and the consequent heterogeneity of our material, however, have not yet made it possible to draw conclusions concerning the real value of our protocol.

In general, it can be stated that with increasing the number of treatment cycles, and the total dose of drugs used, better responses can be achieved. This is true with certain reservations irrespective of tumor size. There were tumors in our series which showed a good response to regional treatment in spite of their huge size and extreme hypervascularization, whereas there were sarcomas which did not show the expected significant alterations neither in size nor in structure although they were small. It is possible that in these cases also the cell resistance to chemotherapy might have played a certain part. This assumption seems to be supported by the fact that the primary tumors showed slightly more favourable responses in comparison with high grade recurrent lesions. The overall response rate, i.e. CR + PR, was 11/20 (55 %) at first treatment and 10/24 (41 %) at treatment high grade recurrencies.

The favourable response rates were better for tumors when treated first 19/20 (95 %) as compared to 18/24 (75 %) for the treatment of recurrences. It should be stressed that from the viewpoint of limb – sparing surgery, a kind of result consistent with $MR_{50\text{-}25}$ may be enough to achieve oncologically adequate margins and to preserve vital structures. On the other hand, this may be true for some cases of $MR_{<25}$, especially if the tumor has not an extreme size originally.

It can be stated that the majority of tumors, irrespective of their size, were demarcated well from their neighbourhood, thus promoting appropriate surgical margins. In 51 out of 58 patients successful limb sparing surgery could be carried out. 3/4 patients with CR did not undergo surgical intervention, (in one no residual tumor could be found at surgery). Severe venous insufficiency developed in 3 patients in the early postoperative stage which was followed by amputation. In one patient, a very rapid systemic progression of the tumor made it aimless to attempt for surgery.

In the past the rate of amputations for soft tissue sarcomas of the extremities was 40-47 %.[14,15] It was well known that conservative local resection was associated with an unac-

ceptably high rate of local recurrences, in the range of 65–90 %.[14]

Recent attempts at limb salvage have used various combinations of surgical resection, radiation and regional intraarterial chemotherapy.[8,9,14,16–20] These include preoperative intraarterial chemotherapy and preoperative radiotherapy[8,9,16,21] or i.a. chemotherapy as well as pre- and postoperative radiotherapy[20] which are followed by surgical resection, or a combination of surgery and postoperative irradiation.[18,19] There have also been attempts to improve local tumor control by hyperthermic perfusion complemented by local excision and postoperative radiation therapy.[17]

With combination of modalities, limb salvage can be practiced currently in the majority of patients with (extremity) soft tissue sarcomas of the extremities. The overall disease-free survival rate at five years was 61–65 %,[8,19] and the local recurrence rate was 8–22 %.[9,17-19] The limb salvage was possible in about 90 % of patients.[8,9,14,16,18,20]

In the light of the data from literature, our results are not comperable in many respects. But in the evaluation of our preliminary results one must take into account that the patients for this study have not been selected. The only criteria for patients to get into this protocol was not to have any sign of distant spread and such local invasion of the tumor that would have rendered any attempts at limb sparing surgery aimless.

Although rare, the soft tissue sarcomas remain among the most difficult to treat, even though over the years there has been significant progress made in the fields of diagnosis and successful local control. In order to achieve the best possible local control we have tried to create a new protocol based on the application of different interventional radiology procedures in combination. Even if from several points of wiew this study is too limited to permit any conclusions as to the long-term results of our treatment protocol, the fact remains that in the majority of cases treated by this kind of therapy, it proved to be fairly effective. The study requires further evaluation of this method. Since it is well known that multimodality treatment can control local disease in most patients with soft tissue sarcomas[7,9] in theory, it can be assumed that a complex treatment modality which attacks in several places at the same time (i.e. by cytotoxic/cytostatic effects together with hypo-/anoxia) can accomplish more extensive and profound effect than that attainable by each method alone. It seems, however, that the confirmation of this hypothesis still requires further investigations.

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Reconstruction of cutaneopharyngeal fistula of the neck

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Seven patients with great cutaneopharyngeal fistulae, occurring several months following the surgery of pharyngeal and laryngeal cancer, are reported. Reconstructions of neck fistulae were performed using a local skin flap three times, latissimus dorsi once, deltopectoral once and microvascular radial free flap three times. One pacient developed relapse of the fistula. Advantages and disadvantages of the methods used for the cutaneopharyngeal fistulae reconstruction have been discussed. Local flaps are considered to be the simplest, but not always applicable. Pedicle flaps have their advantages and disadvantages. Microvascular free flaps, especially the radial one applied by the authors who point out its advantages, will be proved to play an important role in defect reconstructions of the orofacial area and closure of the cutaneopharyngeal fistulae in the future.

Key words: pharyngeal neoplasms-surgery; laryngeal neoplasms-surgery; postoperative complications; fistula-surgery; pharynx

Introduction

Nowadays, defect reconstruction performed immediately after radical resections of oropharyngeal and laryngeal cancer is a commonly used method.

Use of local, distant pedicle flaps and more and more of microvascular free flaps, has essentially reduced morbidity, and accelerated rehabilitation of patients.[1]

Defects of the anterior part of the neck occur most frequently as a consequence of extensive resections due to tumours of following laryngopharyngectomy.[2]

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Cutaneopharyngeal fistulae, as a consequence of ablation of the oropharyngeal area and hypopharyngeal cancer, are most frequently located laterally to the mid-portion of the neck, resulting from the infection and dehiscence of the wound or the flap.

Defects and fistulae, occurring subsequently, are most frequently the result of radiation and represent a special problem.

Cutaneopharyngeal fistulae have been closed in various ways. Zovickian[3] used a shoulder flap, and Bakmjian[4] deltopectoral flap. Ariyan[5] started a new period in defect closure of head and neck area applying pectoralis major myocutaneous flap. Tobin[6, 7] and Morain[8] studied the ramification of blood vessels in pectoralis major muscle, and Tobin divided the muscle into three separate segments. Thus, he successfully

closed cutaneopharyngeal fistula on the neck twice, following cancer resection.

Maisel and Liston[9] used a composite deltopectoral and pectoralis major myocutaneous flap when reconstructing cutaneo-pharyngel fistulae. I. Matulić[2] reported good results and advantages of the cutaneopharyngeal fistula closure with deltopectoral and pectoralis major myocutaneous flap of the same side.

Microvascular free flaps have been little used in fistulae reconstruction of the neck, but in our opinion they seem to have their place and indications in this pathology.

The purpose of this paper is to present our own experience and ways of reconstruction and closure of cutaneopharyngeal fistulae.

Material and methods

Seven patients with cutaneopharyngeal fistulae after the surgical and radiological treatment for oropharyngeal, hypopharyngeal and laryngeal cancer during a two-year course (1990 and 1991) at the Maxillofacial Surgery and Otorhinolaryngological Department of the Clinical Hospital Center in Rijeka, are reported.

All the cutaneopharyngeal fistulae presented, occurred several months to one year following surgery, for the difference from those occurring in the early postoperative period, most frequently because of infection and wound dehiscence, and healing spontaneously or with minor surgical treatments after overcoming the infection.

The most extensive cutaneopharyngeal fistulae resulted from radiation.

Two neck fistulae appeared after oropharyngeal surgery, two of them following surgery of the hypopharynx and three after a laryngeal surgical intervention. Four patients were radiated postoperatively.

We used classical methods in the surgical treatment of cutaneopharyngeal fistulae. Necrotic, fibrous or otherwise changed tissue of the skin, soft parts of the neck and the pharyngeal mucous membrane was completely removed. We managed to close the communication to the pharynx, and to make conditions for placing the flap on the site of the defect of soft tissues and the skin of the neck in all the patients by mobilization of the mucous membrane and interpolated local flaps of the adjacent soft tissue.

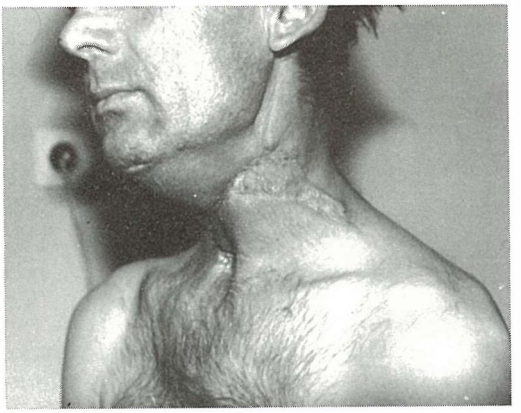

Figure 1. Local skin flap.

For this purpose we used local latissimus dorsi, deltopectoral and microvascular flaps.

Local skin flap was applied in three patients who were not postoperatively radiated (Figure 1).

Local rotational skin flap was used twice and the local sliding flap once.

We used latissimus dorsi flap (Figure 2) as a pedicle flap to cover a great defect on the neck and close the cutaneopharyngeal fistula following the surgery and radiation for hypopharyngeal cancer.

Deltopectoral flap (Figure 3) was used for closure of the cutaneopharyngeal fistulae and

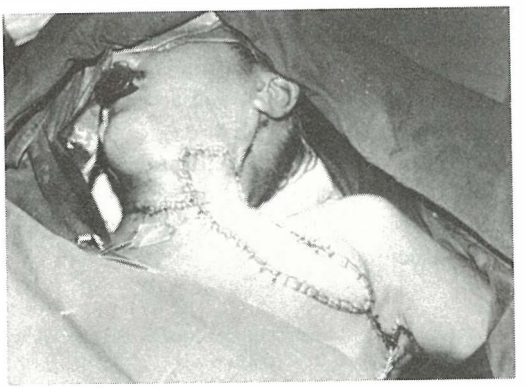

Figure 2. Latissimus dorsi flap.

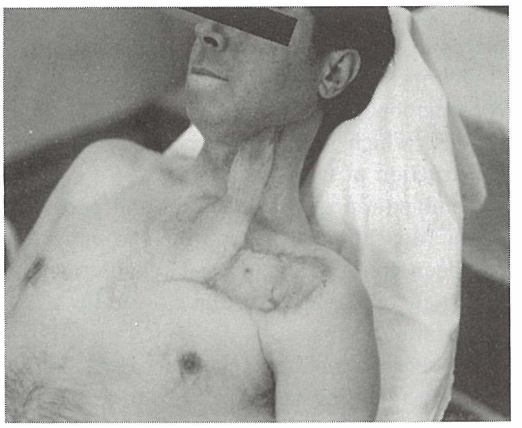

Figure 3. Deltopectoral flap.

compensation for great loss of neck skin following the surgery and radiation for laryngeal cancer.

We used microvascular radial free flap (Figure 4) for the cutaneopharyngeal fistula closure after the surgery and radiation for laryngeal cancer in two patients and once for the closure of relapsing neck fistula in the same patient.

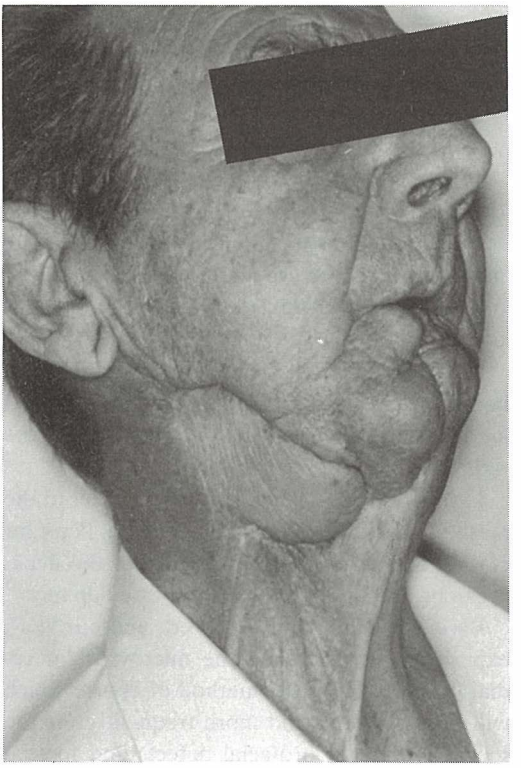

Figure 4. Microvascular radial free flap.

When closing relapsing cutaneopharyngeal fistula we applied microvascular radial free flap, folded it up and closed the neck fistula in two layers.

Microvascular anastomosis was carried out to v. facialis and a. facialis on the opposite side of the neck.

Results

We were successful in six (86 %) patients where cutaneopharyngeal fistulae were definitely solved. One patient (14 %) who had fistula closed with a local skin flap developed relapsing cutaneopharyngeal fistula.

The relapsing neck fistula was closed with a folded up microvascular radial free flap. One of its parts closed fistula to the pharynx, while the other one compensated for the skin defect on the neck.

We had a partial suture dehiscence in four patients, one in the group where cutaneopharyngeal fistula had been closed with a local flap and the same number in each group where the reconstruction of fistula had been performed with deltopectoral, latissimus dorsi and microvascular free flaps.

Dehiscences usually appeared between the fifth and the tenth day following surgery. Wounds spontaneosly closed with usual therapy between the fifteenth and the twentieth day after surgery.

Two patients, who had cutaneopharyngeal fistulae closed with latissimus dorsi and deltopectoral flaps, developed infection after the same time interval following surgery. Following antibiotic treatment (parenteral and local), the infection disappeared without any consequence for the flap.

All the patients were maintained on nasogastric probes at least two weeks following surgery.

The act of swallowing, i.e. normal food intake, was regular in all the operated.

Three patients compained of tightening and light pain in the throat when swallowing. Cuta-

neopharyngeal fistula was closed with deltopectoral flap in one patient, with latissimus dorsi flap in the second one, and with microvascular radial free flap in the third one.

Donor site of the local flaps has been on the neck, being usually covered with a free skin graft after Thiersch, disfiguring the normal appearance of the neck (Figure 1). No functional disturbances were observed.

The donor site of the latissimus dorsi flap was primarily closed without greater functional and aesthetic disturbances (Figure 2).

Chest defect had to be covered with a free skin graft after Thiersch, following the deltopectoral flap elevation, causing aesthetic changes and functional disturbances at the donor site of deltopectoral flap (Figure 3).

After the transfer of microvascular radial free flap the defect was covered with a free skin graft after Thiersch.

After donor site reconstruction on the forearm with an insular flap, the complications of this donor area were minimal, with satisfying appearance and function.

Discussion

Cutaneopharyngeal fistula treatments have been carried out in all seven patients in the same way. Fibrous and changed tissue of the pharyngeal mucosa, the canal of fistula and the neck skin were removed.

We succeeded to close the fistula to the pharynx and to accomplish conditions for placement of the flap to the site of defect of the tissue and the neck skin in all the cases by mobilization of the pharyngeal mucosa and the adjacent soft tissue of the neck.

Local skin flaps of the neck are suitable for closing of such fistulae. They are extremely problematic on a radiated neck, being practically of no use in such cases. Therefore, we used local flaps for closing of cutaneopharyngeal fistula only in cases of noniradiated neck.

Latissimus dorsi was used as a pedicle flap, but it could be applied as a free microvascular flap,[10] usually serving for reconstruction of large defects and the neck skin. Having sufficiently long pedicle, it could reach the most distant places of the orofacial area without tension.

Deltopectoral flap[4] is reliable for neck reconstruction. The advantage of this flap is its expanse which renders it very suitable for reconstruction of large defects.

Combination of deltopectoral and pectoralis major Myocutaneous flaps from the same side has been considered the most reliable method for cutaneopharyngeal fistula closure by Misel[9] and Matulić.[2]

We reconstructed cutaneopgaryngeal fistulae and one relapsing neck fistula with radial free flaps in two patients.

The advantages of this flap are as follows:

– the possibility of flap size selection

– its reasonable thickness and pliancy for possible forming of twofold ("sandwich") flap for closure of fistula from the pharyngeal side and the neck

– a sufficiently long pedicle for microvascular anastomosis to the opposite side of the neck

– the donor site with only slight aesthetis and functional disturbances

– the possibility of two teams working together in order to shorten the duration of surgery.

No adverse effects of greater significance were associated with this type of flap.

Finally, closure of cutaneopharyngeal fistulae of the neck by means of local skin flaps have been considered the simplest, if applicable (for minor fistulae with a moderate size of defect of the soft tissues and neck skin, and nonirradiated neck).

Pedicle and microvascular free flaps should be used for closure of cutaneopharyngeal fistulae with large skin defects and the skin on the radiated neck.

Latissimus dorsi flap has been considered the method of choice among the pedicle flaps for closing cutaneopharyngeal fistulae of the neck. It can be used as a microvascular free flap too.

Based on the results achieved, and our work experience, we consider the microvascular radial free flap to be the method of choice which will be used more and more trequently for the reconstruction of orofacial defects and for the closure of cutaneopharyngeal neck fistulae.

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Leiomyosarcoma of the maxilla: report of a case

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A case of medulary bone origin leiomyosarcoma in the maxilla is presented together with a review of the literature. The main symptom was slowly enlarging, painless mass wich exulcerated later on. Special staining methods and imunohistochemical analysis are necessary for dignosis of this tumor. Radical surgical excision remain the mainstay of treatment.

Key words: maxillary neoplasms; leiomyosarcoma

Introduction

Tumors of the smooth muscle origin may occur anywhere in the human body where smooth muscle is present. They occur with a significant frequency in the alimentary tract but are decidedly unusual in the oral cavity, pharynx and upper respiratory tract.[1] There have been a total of 116 cases of oral leiomyoma described in the literature,[2] and only 25 cases of primary oral leiomyosarcoma were reported,[2-5] those arising centrally within bone are extremely rare.[1, 5] This paper reports an additional case of leiomyosarcoma which originated in the maxilla.

Case report

In our case, a 29-year-old Caucasian male was admitted on 2 October 1991. His chief complaint was a painless swelling on the right side of the palate, first noticed in August 1991, which exulcerated later on. He had also noticed loosening of the teeth in the region.

Clinically, a shallow lesion with diameter of 2 cm and central ulceration was present (Figure 1). Specific ulceration was excluded by dermatovenerologist. Local x-ray picture and panoramic radiograph showed partially well and partially illdefined radiolucency of the alveolar

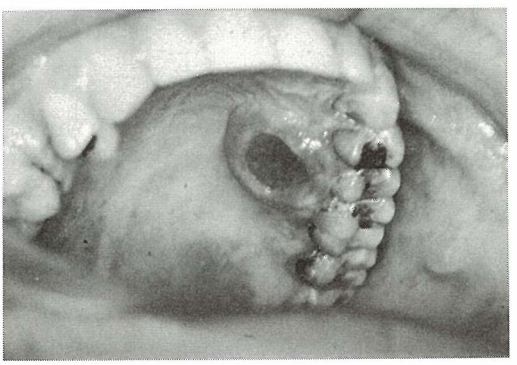

Figure 1. Preoperative intraoral view of the exulcerated tumor arising from hard palate.

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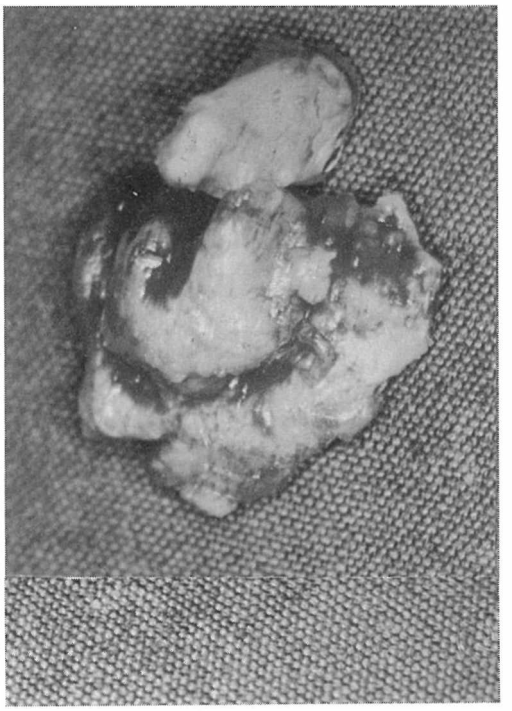

Figure 2. Gross appearance of the tumor after enucleation.

process of maxilla on the right side. A biopsy was performed. The initial histological diagnosis was leiomyoma. The lesion was treated by enucleation and tooth extraction. On surgery, the tumor has been shelled out from the bone (Figure 2). Because of the expansion of the tumour into the bone, a medullary bone origin of it was suggested. Histological examination of the surgical specimen showed that the tumor was leiomyosarcoma, moderately differentiated. Histologicaly, a dense population of neoplastic spindle cells was seen, showing low to moderate mitotic activity (13 mitoses per 50 HPF). Tumor cells showed reactivity to smooth muscle actin. Resected margins were not free of tumor at the base of lesion, so additional surgical management was necessary, without preoperative chemotherapy, which was not indicated because of low mitotic activity of the tumour. Before undertaking further local therapy, the search for a possible primary tumor on other location and/or metastases was performed, with negative results. Therefore, a second surgical procedure, i.e. partial maxillectomy was performed. The resected bones were macroscopically free of tumour, which was confirmed by frozen sections and also by definitive paraffin sections (Figure 3).

Presently, 19 months after surgery, the patient seems to be free of disease (Figure 4). There are no signs of local recurrence, regional and distant metastases and he is prostheticaly successfully rehabilitated (Figures 5, 6).

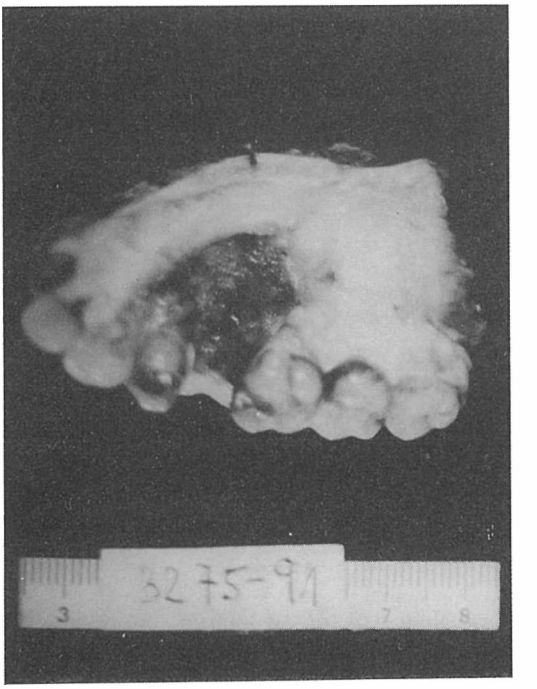

Figure 3. Surgical specimen after partial maxillectomy.

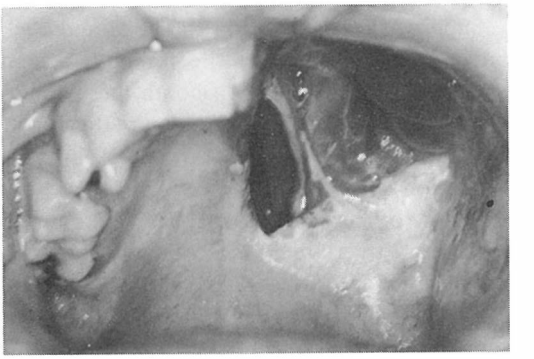

Figure 4. Postoperative intraoral view, two month after partial maxillectomy.

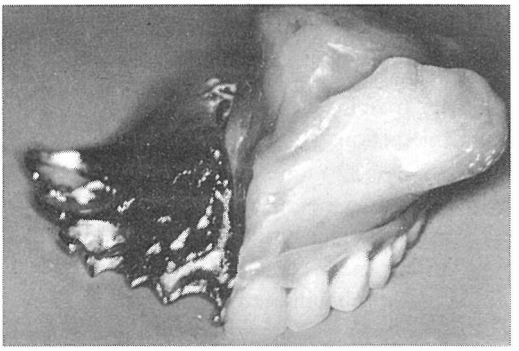

Figure 5. Maxillofacial prosthesis.

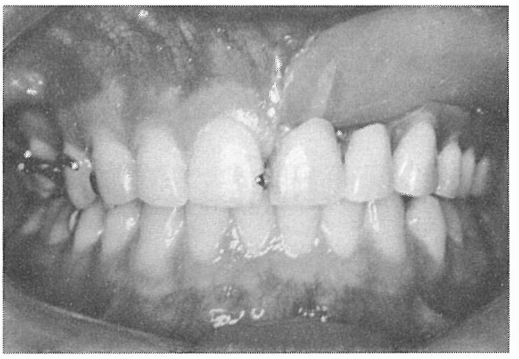

Figure 6. Prosthetically successfully rehabilitated patient.

Discussion

Less than 1% of all cancers are soft-tissue sarcomas and, of these, only 2 to 8% are leiomyosarcomas. Leiomyosarcomas arise most commonly in the gastrointestinal and female genital tract.[6]

Superficial soft tissues in the head and neck area are not uncommon site for both benign and malignant variants of smooth muscle neoplasm. Approximately 25% of superficial soft tissue leiomyosarcomas were from this anatomical region.[7]

On the other hand, the oral cavity and upper respiratory tract are unusual sites of origin for smooth muscle neoplasm.[1, 8]

The leiomyosarcoma is a malignant tumor of smooth muscle origin. It is very rare in the oral cavity and whether it develops through malignant transformation of leiomyoma or *de novo* is not known.[9, 10] To account for the origin of smooth muscle tumors in areas normally deficient in smooth muscle, three explanations have been given: 1. origin from aberrant undifferentiated mesenchyme, 2. origin from smooth muscle elements in the walls of blood vessels, 3. origin from both sources.[1]

The tumour was found in patients of almost all ages ranging from 10 months to 88 years.[1, 9-11]

In oral leiomyosarcomas no sex predilection was apparent,[9] but some another reports suggest a predilection of this tumour for males.[10, 11]

Leiomyosarcomas have been reported in the cheek, tongue, palate, floor of mouth, gingivae and mandible. Where information is available, leiomyosarcomas of this region appear to be lethal lesions in nearly one-half of the patient.

Central (intraosseous) smooth muscle tumors are extremely rare.[1, 5, 10, 12, 13] The maxilla seems to be the favourite site for the occurrence of oral leiomyosarcoma. Of the 21 cases described in the literature, nine were in maxilla, including the palate, as their primary location.[11, 12, 14]

Leiomyosarcomas pose a diagnostic challenge both clinically and microscopically.[3] Clinically, the lesion presents as a painless swelling in some patients while in others a chief complaint is a painful swelling without other clinical characteristics.[9] In one study, an ulceration was seen in only two of 21 cases, one showed a decubital indentation corresponding to the opposing teeth, and other exhibited a true neoplastic ulceration.[11] In the cases in which tumour originated from the jaw bone, the regional teeth became loose at an early stage[9,11] and that could lead to a mistaken diagnosis of advanced periodontitis and subsequent mismanagement of patients.[3] It was suggested that the most common clinical sign was slowly enlarging, nonulcerated, painless mass in the early stage which was hard and well-circumscribed giving an impression of a benign tumour.[11, 12]

At the microscopic level this neoplasm can be confused with other lesions. Special staining methods and immunohistochemical analysis are useful for diagnosis of this tumour. The immunohistochemical reactivity of the tissue to de-

smin has been demonstrated to be highly characteristic for leiomyosarcomas and rhabdomyosarcomas. Two features serve to differentiate between the two: the absence of striated-muscle differentiation in leiomyosarcoma and the reactivity to myoglobin in rhabdomyosarcoma.[3]

Radical and complete surgical excision with wide margins of normal tissue remain the mainstay of the treatment, for both primary and recurrent leiomyosarcoma in the head and neck region, with irradiation and chemotherapy as adjunctive treatments.[3, 10, 11, 15, 16]

Oral leiomyosarcomas may metastasize to the cervical lymph nodes and lungs with equal frequency, whereas tumours in other sites metastasize to the lung and liver.[3]

The prognosis for this neoplasm is guarded. Oral leiomyosarcomas showed a high incidence of local recurrence, metastasis and poor prognosis. A 50 % recurrence and metastatic rate have been reported, with a mortality of 40 %. Reported survival rates were 4 weeks to 5 years for the patients with metastases.[10, 11]

Metastasis of a leiomyosarcoma to the oral cavity is an extremely rare event.[15] In general, the treatment of intraoral metastatic lesion is palliative or is included in the medical treatment of the primary lesion (radiation or chemotherapy). Resection of metastatic tumours is undertaken infrequently.[15]

Because of the relatively high mortality and recurrence rate, a long-term follow-up of the patient is mandatory.

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Breast cancer screening

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The present state of mass-screening for early breast cancer is reviewed. Some early reservations like radiation hazard of mammographies and overreferral to unnecessary breast biopsies are shown as unsubstantiated and a clear benefit of such screening is demonstrated particularly in post-menopausal women. Modern radiological equipment and highly skilled examiners are prerequisites. High costs of this screening and lack of trained professionals remains the main difficulty in many countries including Slovenia.

Key words: screening, mass screening; breast neoplasms, breast cancer; review, update; objections and arguments; in Slovenia

Introduction

In Slovenia, breast cancer is expected to soon afflict about one woman in 20 whereas in some other countries the rate has already doubled and is still rising.[1-3] The etiology of this tumor is unclear and the method of prevention unknown. In spite of many therapeutic improvements its 5-year survival is hardly above 50 %,[1, 4] and has remained so for decades. The individual prognosis depends much on the tumor size at the time of first therapy, and in (UICC) stage I. tumors the 5-year survival is around 90 %.[2, 4, 5] Early detection by mass-screening of apparently healthy women at risk is thus a medical challenge and a matter of great public health interest. Screening and screening procedures, however, have been subjected to criticisms which will be briefly discussed in this article.

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To screen or not to screen?

This basic question seems to have been answered by the single most important screening trial initiated in 1961 by the Health Insurance Plan of Greater New York and commonly known as HIP. By 1971, the follow-up of about 60.000 trial and control women demonstrated that physical examinations (PX) and mammographies (MG) reduced mortality by 30 % in the 50–64 year age group.[6, 7, 8] After 18 years the study showed that also women aged 40-49 benefited a 21 % death reduction.[2, 6] Contrary to that, a similar nation-wide program conducted in Canada 20 years later did not seem to reduce the mortality in either group at its 7-year evaluation.[4] Nevertheless, HIP and many other studies have led to the firm belief that mass-scree-

ning of women at risk is currently the only method capable of reducing breast cancer mortality by 16–25 % and according to some reports even by more.[4, 6, 9] In spite of the generally recognised advantage of mass-screening a number of reservations have been voiced.

An early and then relevant objection was the radiation risk induced by mammography which is best suited for detecting unpalpably small, curable tumors.[10, 11] In the early 60's the dose absorbed in the midbreast during two-view mammography was anywhere between 0.3 and 7 cGy allegedly rendering the radiation hazard comparable to the benefit of repeated examinations.[2, 5, 12] Later technical advances in MG reduced the exposure substantially, down to 0.05 cGy and simultaneously increased its sensitivity by a factor of 2-4.[2, 5] One very conservative risk-to-risk assessment assuming a 0.8 cGy glandular dose and 18 yearly examinations concluded that the risk of radiation-induced cancer-deaths is less than 1/10th of the risk of early death caused by omission of this examination.[13] The radiation hazard involved in MG with a modern equipment is, indeed, much lower and now considered negligible.[2]

Another serious objection was that there would be an increase in unnecessary breast biopsies owing to an overinterpretation of mammograms and resulting in a referral-to-surgery rate as high as 10 % of all screenees.[14, 15]

It was shown, however, that well trained and highly skilled radiologists can cut the rate of negative biopsies down to an acceptable level of 1/4[6] or even 1/7.[16]

An obvious problem of mass-screenenig is the sheer size of the task. It was estimated that in the USA every radiologist would have to interpret 10 MG daily if screening were conducted according to current recommendations.[15]

Nevertheless, a number of developed countries including the United Kingdom, Canada, the Netherlands and the Scandinavian countries embarked on large-scale screening programs, mostly to evaluate their feasibility, benefits and cost.

The last and the most important common objection to mass-screening is that it should not be considered unless it proves to be a valuable health service in terms of the cost-benefit ratio. In a free-market environment the direct cost of a single screening is easy to assess and reportedly amounts to between 25–250 $ per case, with the mean around 100 $.[1-3, 15, 17] It seems that both the costs and benefits increase with the length of the follow-up[4, 19] but according to some estimations the expenses of including women aged under 50 years are not acceptable when compared with the number of tumors detected.[19] Indirect costs including downstream diagnostic procedures, lost working days and other are more difficult to determine.

The benefit of a medical procedure may be measured in a number of ways ranging from life-years saved to social and personal benefits expressed in some arbitrary units. In the Netherlands one such study showed that one year of life saved by mass-screening (5 invitations in 20 years) costs 3800 $ directly plus the same amount of marginal expenses.[4] It is true, of course, that in the long run expenses of health services cannot be expected to drop before the number of advanced cancers decreases. The immediate costs of screening clearly outweigh the savings[6] and, thus, remain prohibitive for most countries.

Who to screen and how often?

Most breast cancers occur after age 35 and their frequency increases steadily thereafter. Two thirds of patients are older than 50 years.[19] Does it make sense, then, to screen indiscriminately all women at risk? Since general screening is an expensive task aimed primarily at saving lives it should embrace only that part of a population in which a sufficient number of early cancers in a curable stage can be expected. Some workers argue that the life of a cancer patient after 75 can be neither saved nor prolonged by screening owing to the natural course of the disease and life expectancy at this age.[20] On the other hand, there are women at high personal and familiar risk which are an obvious target group, though not easy to identify. As to the age of screenees, the first results of the

HIP study already demonstrated its life-saving effect in women over 50 years of age which was amply documented thereafter.[6] Eventually, the HIP and other studies suggested but not unanimously confirmed a similar benefit between age of 40 to 49 years,[6, 21] so that some European researches have remained skeptic particularly if only MG is employed.[8, 22]

About 90 % of breast cancers are self-referred when the tumors reach palpable size.[5] Thanks to the sensitivity of MG, screening programs detect cancer usually at an early, non-palpable and still curable stage. The initial yield of such programs is, therefore, usually larger than expected. At subsequent screenings the detection rate decreases to the prescreening level.[6, 14, 23] This "lead-time" was suggested to be also an optimal interval for examinations because it minimalizes the occurrence of interval tumors and decreases expenses.[6, 9] The proposed intervals range from 1–3 years and tend to be shorter in the USA than in Europe.[8, 19, 22] Most programs have, thus, adopted a 12–18 months interval for women under 50 and 2–3 years for older ones.

How to screen?

HIP and many subsequent studies demonstrated that PX and MG are the cornerstones of early breast cancer detection which can save about 30 % of lives,[2, 5, 7] On the other hand, single oblique view MG used as the sole detection modality in the first ("two-county") Swedish study also decreased mortality in women over 40 years of age by 30 %.[2, 6] The idea to cut down expenses and to limit examinations to MG only, seemed inviting and prompted a number of studies for its evaluation.[2,5,7,14,21,23] It is now recognised that both modalities are needed. The group led by L. Tabar,[6, 21] however, is putting more weight on MG. Nevertheless, up to a quarter of tumors may remain undetected by MG and nearly half of them may escape PX.[5, 7, 14] PX is more likely to miss smaller tumors in women over 50 while false negatives in MG vary between 10–20 % regardless of the tumor size but are more likely to occur in younger populations.[14, 23, 24]

To cut down examination expenses, attempts have been made to recruit specially trained prescreeners, i.e. general practitioners and technologists to interpret MG and nurses to perform PX.[7, 17] It turned out that such personnel may be useful if properly trained but any prescreening, in fact, increases expenses because expert reviews are required.[17] In addition, it was found that non-radiologists are less accurate in interpreting MG than trained radiologists[9] whereas nurses miss slightly more tumors at PX than oncologists.[7] It is now generally accepted that screening programs ought to be performed by highly trained professionals and that quality-assurance, information feed-back, informal team-work and continuous training are essential prerequisites for inexpensive and efficient cancer detection.[3, 6, 17, 20, 21, 25] Comprehensive dedicated communal breast centers were suggested as the proper environment in which to perform this task.[3]

Screening in Slovenia

In Slovenia, there are some 180.000 women aged 50–64 and 120.000 aged 40–49 years. The present equipment consists of 8 modern mammographs but this number is expected soon to increase. There are only about 10 competent radiologists capable of interpreting MG because the professional training curriculum shows little understanding for and grossly neglects this field.[26] Similarly, only a few dozen oncologists, some surgeons and a few gynecologists are familiar with PX of the breast. A hypothetical, full employment of these resources would allow about 75.000 examinations per year, which does not warrant any nation-wide breast screening program.

The available means are, however, sufficient to run about 10 breast-diagnostic centers which take care of referred or self-referred women. In addition, three of these centers (Ljubljana, Maribor and Nova Gorica) initiated a screening feasibility trial which involves 12.400 randomly selected women aged 50–64. The screenees are

offered PX and a single-view MG. The first results are expected by the year 2000.[27]

At present, no nation-wide screening program can be considered. Its cost could not be realistically estimated because of the fluctuating prices of materials and services. It is precluded also by the lack of properly trained personnel. Before starting any comprehensive nation-wide program a radical change in the teaching of oncology should occur and special training of clinicians, radiologists and technologists for breast examinations should be made available and mandatory in order to achieve a workable professional level of such an undertaking.

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Report

Visit to Centre Hospitalier Lyon Sud, France

Visit to Radiotherapy Dept. of the Centre Hospitalier Lyon Sud in Lyon, which was made possible by the help of Tempus – ESTRO fellowship program, commenced on July 1, 1993. This study stay was combined with a brief visit to the Radiotherapy center in Mestre (head Prof. Dr. Pizzi), and on the way back also with visits to the hospitals in Bern and Arrau in order to see their X-ray machine with C arc. Namely, I was particularly interested in the equipment for localization of implants in brachytherapy, since our department of brachytherapy at the Institute of Oncology in Ljubljana needs to be newly equipped because the existing facilities are worn out and insufficient. According to Prof. Pizzi, the basic equipment should comprise two X-ray units, C arc for diascopy and a stronger (high power) X-ray machine for imaging of the pelvis in lateral projection.

After having visited the center in Mestre, I continued by travel to Lyon where I stayed from July 4–17, 1993.

During my study stay there, I attended work at the Department of Radiotherapy (headed by Prof. Dr. Jan Pier Gerard) of the Centre Hospitalier Lyon Sud, Centre for Oncology Leon Berard and at the private clinic for radiotherapy Sant Jean.

At Prof. Gerard's department I had the opportunity to follow the whole working process, though I took particular interest in brachy therapy.

During the two weeks of my visit I attended more than 30 brachyradiotherapeutic procedures, of these 20 at the department of Prof. Gerard, and over 10 at Leon Berard Oncological Center (dept. head Dr. Ardieu). High quality of work in these centres is obviously attributable to their good equipment as well as the experienced staff. Therefore, apart from replacing our inadequate and worn out equipment, at the Institute of Oncology in Ljubljana we should make some other improvements, such as:

1) More accurate and frieldly exchange of information among the staff collaborating in the process of comprehensive oncological patient care. Namely, our physicians are informed through indirect communications, which are often rather incomplete as they sometimes even lack information on the basic diagnosis, but above all, these communications are not nearly as direct and personal as those written by the French colleagues.

2) Their applicators, designed specially for the implantations of anorectal and ureteral cancers, are more suitable than ours which are not specifically adjusted to the appointed localizations. It is worth mentioning that our colleagues in Lyon have gained a remarkable experience in these types of implantations as the patients with anorectal and ureteral cancers are referred to their center not only from all parts of France, but also from Italy and other countries.

3) I was also impressed by the simple technique they use for imaging of the tumor site in correlation with the implant. Our method is considerably more complicated and therefore rarely used. We are going to introduce the simple and effective Lyon method into our clinical practice as soon as possible.

4) Certain importance should be attributed also to a combination of LDR and HDR brachy therapy. According to their reports, the use of HDR in clinical practice significantly increases the scope of indications for brachytherapy. Almost a half of all their procedures are now performed by means of HDR technique.

5) I also had the opportunity to observe intraoperative irradiation, and a very interesting technique of pelvioscopy performed by Prof. Dr. Daniel Dargent. The latter method provides such a relevant information that its introduction into our practice at the Institute of Oncology in Ljubljana would be more than justified.

Concluding this report, I should point out

again that the differences in the methods of work between the center in Lyon and our Institute are primarily attributable to the great differences in the facilities available. Working hours from 8 a.m. to 6 p.m. with a lunch break contribute to significantly more rational use of staff potential. Though all the activities are performed unhurriedly, in a way which is more friendly taboth the patient and the staff, I have got the impression that the center, and particularly the team of Prof. Gerard with some of the most exposed radiotherapists, are all the time using their maximum potentials.

I was somewhat surprised at their attitude to occupational radiation exposure. In our case, we try to avoid unnecessary exposure whenever possible, though our workers, unlike their French colleagues, are also entitled to some benefits on account of their occupational exposure. While the main consideration in Lyon center is the legally determined dose limit, one at times gets the feeling that the dose could nevertheless be decreased, should the involved staff really care to do so.

Also their use of available equipment was not always fully rational. Thus, diascopy is not always employed though it helps to avoid later active implant corrections. For the same purpose, ultrasound is used much more frequently in our Institute, partly also because we do not have diascopy facilities.

On my return to Slovenia I visited the centers in Bern and Arrau. There I saw C-arc which, apart from diascopy, enables also imaging of the pelvis in lateral plane, which is essential with implantations of this site. Should we manage to obtain such a device in our Institute, we might spare ourselves the costs of an additional X-ray unit.

Hopefully, my recent visit in Mestre, Lyon, Bern and Arrau will promote further development of brachytherapy in Ljubljana, and help to establish closer collaboration with radiotherapists in the visited centers.

Prof. dr. Janez Kuhelj
Institute of Oncology, Ljubljana

Notices

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

Endocurietherapy

The "16th Annual Mid-Winter Meeting of the American Endocurietherapy Society" wild be held in Phoenix, Arizona, USA, *December, 8–11, 1993.*

Contact American Endocurietherapy Society, 101 Market Street, Philadelphia, A 19107, USA; or call + 1 215 57 43 158.

Thoracic surgery

The course "Specially Review in Thoracic Surgery" will be offered in Chicago, Illinois, USA, *January, 10–15, 1994.*

Contact National Center for Advanced Medical Education, 707 S. Wood St., Chicago, IL 60612, USA; or call + 1 312 633 2600.

Molecular biology

The meetings "Molecular Biology of Human Genetic Disease" and "Gene Therapy" will be held in Copper Mountain, Colorado, USA, *January, 15–22, 1994.*

Contact Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA; or call + 1 303 262 1230.

Radiology

The "18th International Congress of radiology" will take place in Singapore, *January, 23–28, 1994.*

Contact 18th ICR '94, Kent Ridge, P.O. Box 1052, Singapore 9111, Rep. of Singapore; or call + 65 77 61 981; Fax: + 65 77 62 081.

Radiation Oncology

The "24th Annual University of Florida Radiation Oncology Clinical Research Seminar" will be offered in Gainesville, Florida, USA, *February, 3–5, 1994.*

Contact Robert B. Marcus, 1994 Seminar Coordinator, Dept. of Radiation Oncology, Univ. of Florida Health Science Centre, P.O. Box 100385, Gainesville, FL 32610-0385 USA; or call + 1 904 39 50 546; Fax: + 1 904 39 50 546.

Laryngeal Cancer

The "2nd World Congress on Laryngeal Cancer" will be held in Sydney, Australia, *February, 21–24, 1994.*

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The "International Congress on Advanced Diagnostic Modalities and New Irradiating Techniques in Radiotherapy" will be held in Perugia, Italy, *March 9–11, 1994.*

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The "4th European Conference on Clinical Aspects and Treatment of HIV Infection" will be offered in Milan, Italy, *March, 16–18, 1994.*

Contact Organizing Secretariat, Franco Rosso Health Congress, Corso Vittorio Emanuele, 26 20122 Milan, Italy; or call + 39 2 7600 8561.

Computers in radiotherapy

The "11th International Conference of the Use of Computers in Radiotherapy" will take place in Manchester, U.K., *March, 20–24, 1994.*

Contact J.M. Wilkinson, Secretary to Local Organizing Committee, North Western Medical Physics Dept., Christie Hospital and Holt Radium Institute, Withington, Manchester M20 linical, U.K.

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Dear Colleagues,

Summer in Ljubljana is slowly turning to fall and the mornings are becoming cold and foggy. The temperature in the Secretariat however, is rising and efforts for the preparation of a successful event are intensifying. Two hundred and fifty-four abstracts, mainly from Europe, but also from Canada, China, India and USA, were submitted in reply to the Call for Papers. They were reviewed by members of the Scientific Committee and, finally, 196 were accepted for presentation at the Congress and publication in the Transactions. The preliminary Congress programme is now ready and authors have been notified of acceptance of their contributions.

The scientific importance of the Congress will be augmented by two invited lecturers: Dr. Niels Kuster will report on Progress in High Frequency Dosimetry, and Dr. Clay E. Easterly will present an Assessment of the Literature regarding Health Risk Effects from Exposure to Power Frequency Electromagnetic Fields. Our invitations have also been kindly accepted by Dr. Jocelyne Leal, who will tell us about the development of the European Centre for Bioelectromagnetics, and Dr. Zlatko Koren, who will give an Annual Project Status Report for 1993 on COST 244: Biomedical Effects of Electromagnetic Fields. The Role of Electromagnetic Fields in Biomedicine - Panacea, Placebo or Poison, will be addressed in the Congress opening lecture by Dr. Lojze Vodovnik. The work of the Congress will run in plenary sessions of which the probably the most interesting to the readers of this journal would be Experimental Oncology, Immunology, Clinical Applications and Health Risk Effects, all of them related to electromagnetics.

Following the EBEA Congress (December 10-12, 1993), Bled will also host the COST 244 Workshop and the Managing Committee meeting. In the frame of the Workshop, three working groups will focus on i.) Epidemiology and human health effects, ii.) Basic research, and iii.) System application engineering; in the extremely low frequencies domain and in the mobile communication frequency range.

The Preliminary Programme is available upon request from the Congress Secretariat (address bellow).

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WELCOME MESSAGE

Dear Colleagues,

Slovenia has the honour to host and organize the 2nd Central European Conference on Lung Cancer under the auspices of the International Organization for the Study of Lung Cancer. The Conference will take place in Ljubljana on April 13 to 16, 1994.

The aim of the meeting is to bring together in a stimulating and agreeable environment researches and clinicians from Europe concerned with various problems of lung cancer. Plenary lectures given by invited speakers from distinguished medical schools will throw light on the state of the art in all aspects of lung cancer. Specialists in different disciplines will report their experience and results. Colleagues involved in the diagnosis, therapy and epidemiology of the disease, as well as those working in biology, pathology and other related fields are invited to participate.

The Conference will be held in a modern Congress centre in Ljubljana, the capital of our young independent Republic of Slovenia. The Organizing committee will spare no effort to make your attendance professionally and socially rewarding. Our objectives are to provide you with an opportunity to update your knowledge, present the results of your research and clinical work, and meet colleagues in a pleasant, relaxed atmosphere.

We hope to welcome you to our Conference in Ljubljana and look forward to showing you our lovely country, situated in the south of Central Europe, on the sunny side of the Alps, touching the Mediterranean.

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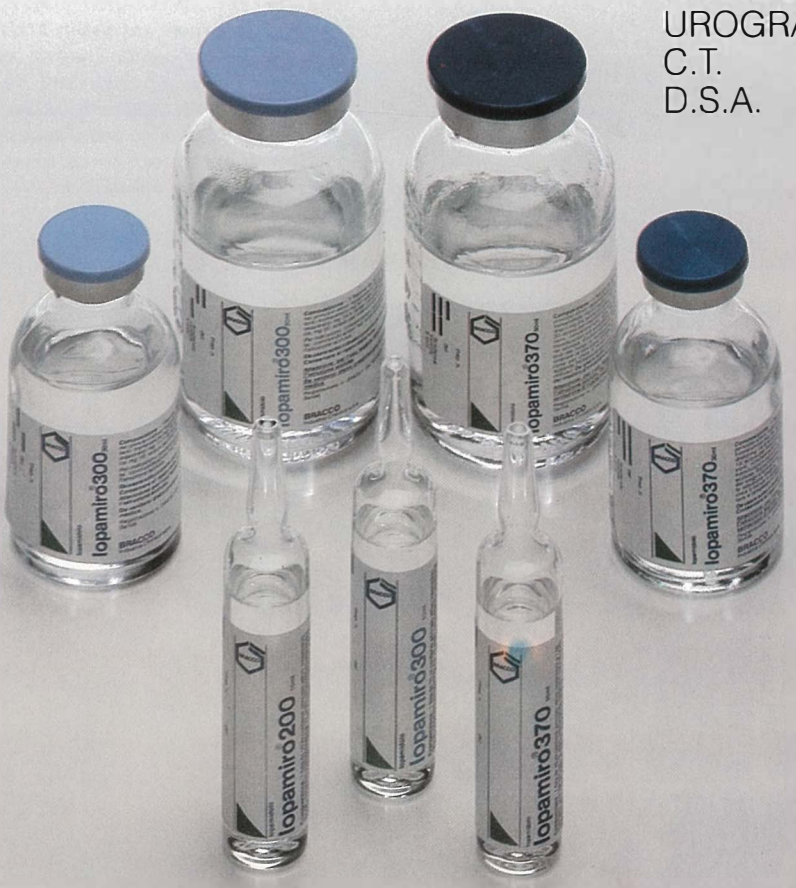

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Contraindications

Pefloxacin is contraindicated in patients with known hypersensitivity to quinolones, in pregnant women, nursing mothers, children under 15 years of age, and patients with inborn glucose-6-phosphate dehydrogenase deficiency.

Precautions

During pefloxacin therapy exposure to strong sunlight should be avoided because of the risk of photosensitivity reactions. In patients with a severe liver disorder dosage of pefloxacin should be adjusted.

Side effects

Gastro-intestinal disturbances, muscle and/or connective tissue pains, photosensitivity reactions, neurologic disturbances (headache, insomnia), and thrombocytopenia (at doses of 1600 mg daily) may occur.

Dosage and administration

The average daily dosage for adults and children over 15 years of age is 800 mg.
Oral: 1 tablet twice daily after meals.
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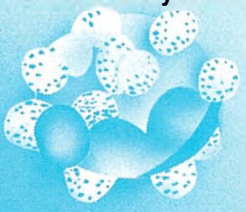

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Precautions: Klimicin should be prescribed with caution to elderly patients and to individuals with a history of gastrointestinal disease, particularly colitis.

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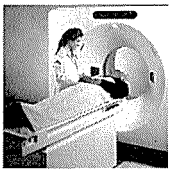

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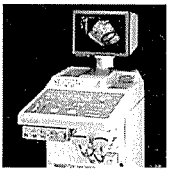

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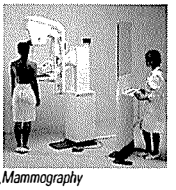

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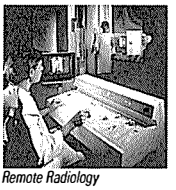

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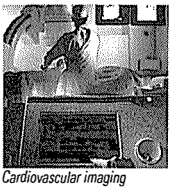

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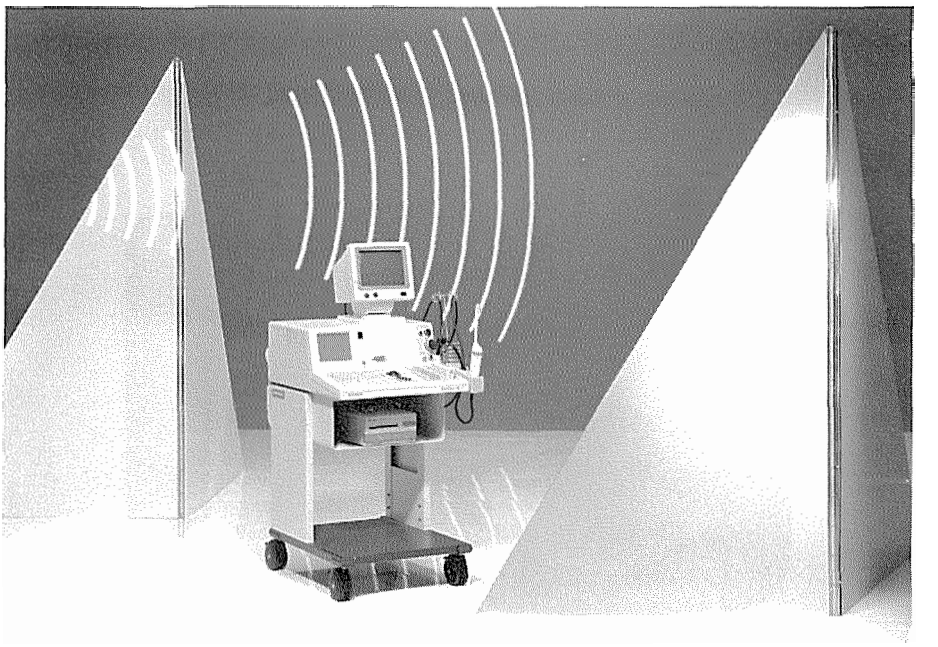

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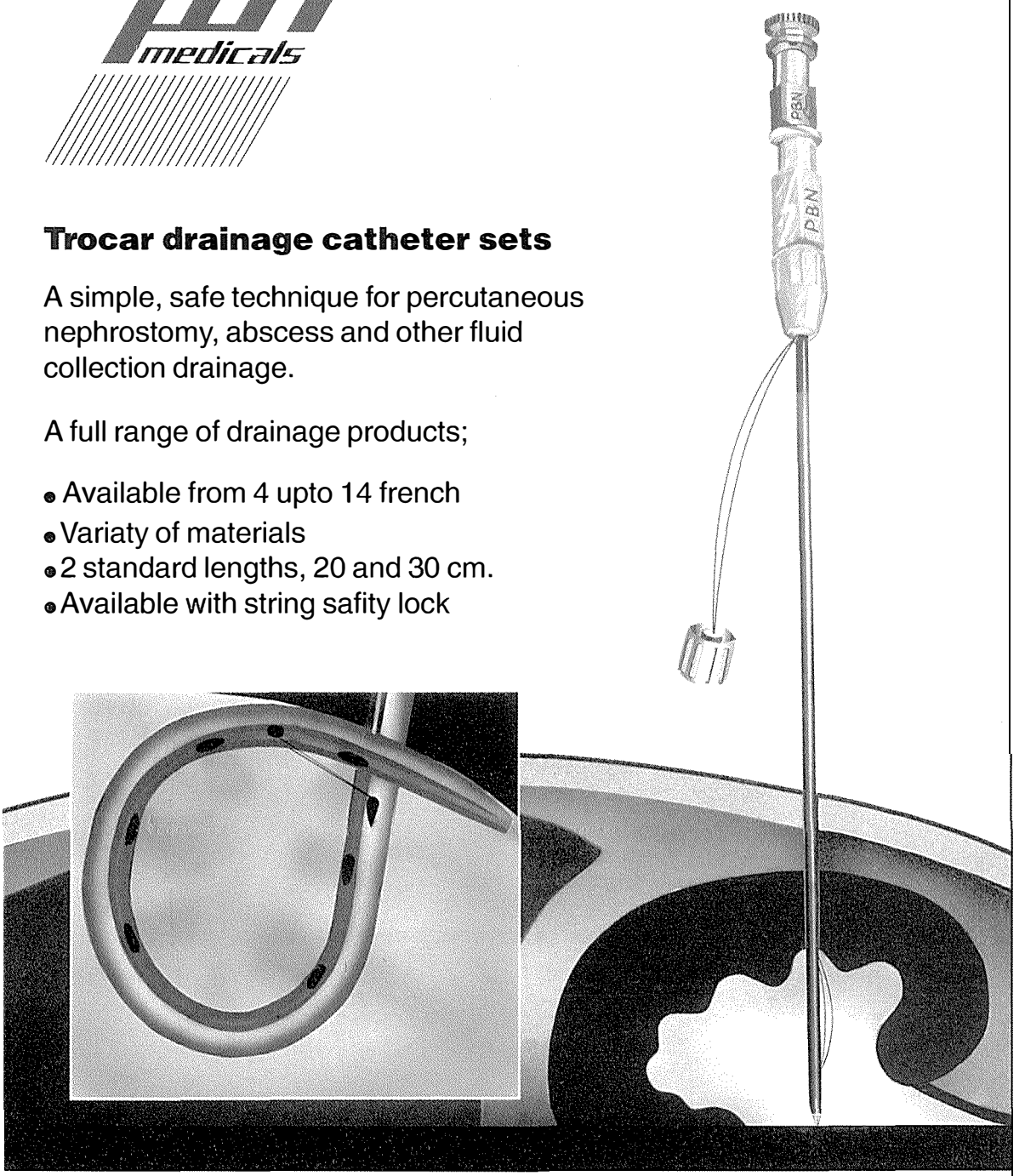

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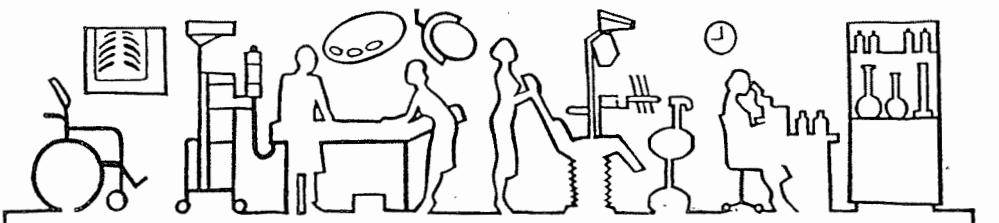

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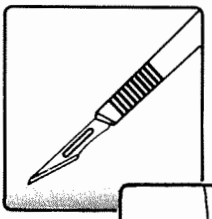

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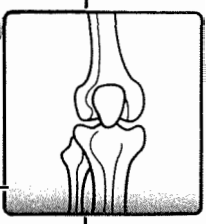

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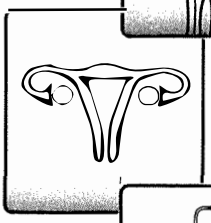

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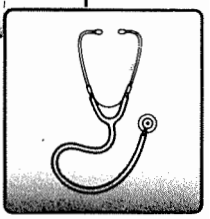

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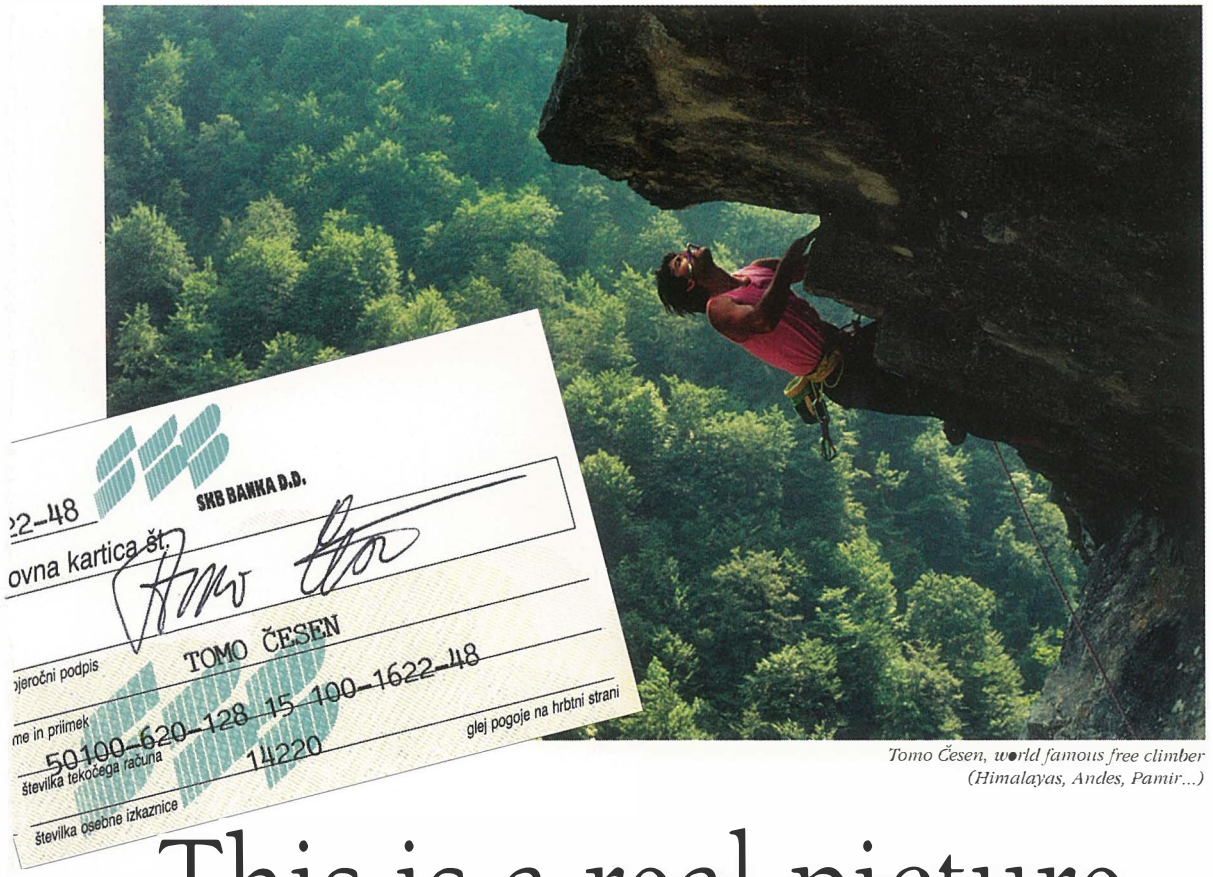

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