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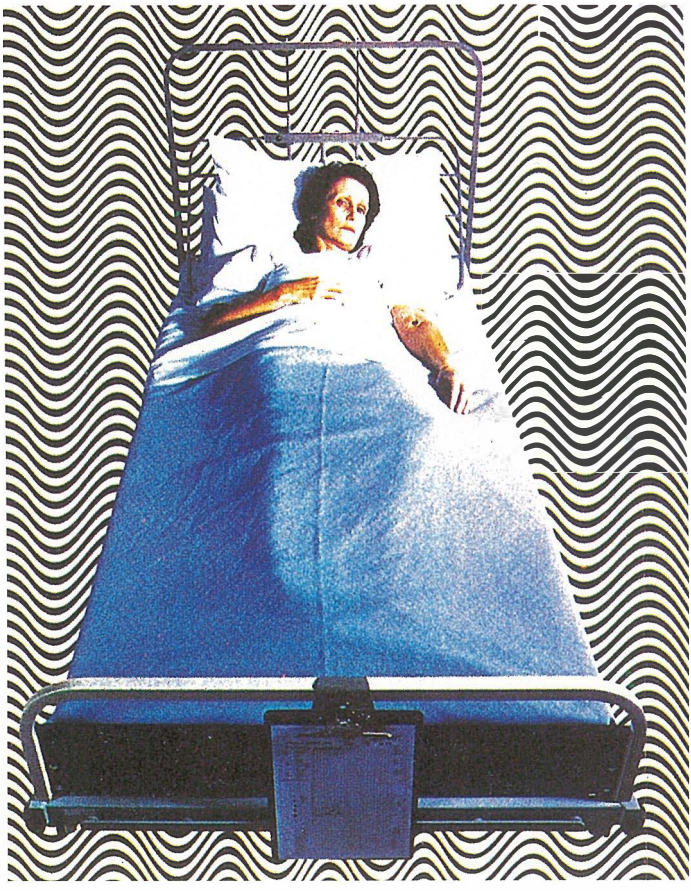

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Albuminuria after selective renal angiography: influence of contrast media

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The purpose of the study was to evaluate the influence of various urotropic contrast media on albuminuria after selective renal angiography. We tested ionic and non-ionic contrast media of low and high osmolarity. Influence of different contrast media on albuminuria frequency, after selective renal angiography proceedure, with various physical and chemical properties was evaluated. The contrast media were also tested in vitro with 20% sulphosalicilyc acid to exclude positive reaction on contrast media alone. The contrast media we tested were: a.) ioxithalamat meglumin, b.) diatrizoat meglumin, c.) iohexol and d.) meglumin ioxaglate.

Presence of albuminuria was determined by precipitation method with 20% sulphosalicyl acyd in urine samples after 6, 12, 24 and 48 hours. Results were statisticaly evaluated by Fisher-Exact test. Albuminuria was often present after use of ionic contrast media with high osmolarity.

Results of the in vitro study demonstrated that early positive urin reaction (6 and 12 hours) with sulphosalicil acyd is unspecific.

Comparison of albuminuria frequency for two high-osmolal ionic contrast media (ioxithalamat meglumin, diatrizoat meglumin) demonstrated statisticaly significant difference ($P>0.05$) 48 hours after procedure.

Comparison of albuminuria frequency between two low-osmolal contrast media (iohexol, meglumin ioxaglat) did not demonstrate statistical difference. Comparison of albuminuria frequency between high-osmolal and low-osmolal contrast media demonstrated statisticaly significant difference in all time sequences studied.

Key words: renal artery – radiography; albuminuria

Introduction

Urotropic intravenous contrast media are water-soluble iodin preparations bound with benzen ring, and have renal excretion.[1] The pharmacology and chemistry of the water-soluble contrast agents have been widely reviewed.[2, 3] Previous contrast media have high osmolality and cause adverse reactions,[4] while the recent ones demonstrate lower toxicity in animal experiment,[5] as well as better tolerance in everyday use.[6] The study published by Committee for contrast media at International Society of Radiology found that there were 4,73% adverse

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reactions after use of intravenous contrast media in 302.083 patients.[7] Intravenous contrast agents possess toxicity because of hyperosmolarity,[8] chemotoxicity[3] and additives.[9, 10] Nephrotoxicity is a well known fact, while intravenous urotropic contrast media are excreted by kidney. As 90% of applicated dose is excreted by kidney it can result in various degree of kidney damage.[11–14] The patients with diabetes, multiple myeloma, oliguria and advance stage of arteriosclerosis are in high risk group of developing damage to renal function.

Patients and methods

We tested urine with 20% sulphosalicilyc acid from forty patients (19 female and 21 male) with normal renal function who underwent selective renal angiography with Seldinger technique. The contrast media we tested were: a.) ioxithalamat meglumin, b.) diatrizoat meglumin, c.) iohexol and d.) meglumin ioxalat.

The contrast media were also tested in vitro with 20% sulphosalicilyc acid to exclude positive reaction on contrast media alone.

The patients were divided in to four groups, according to contrast media used. Every group had ten patients. In each group we administrated different intravenous contrast media. The patients with albuminuria, diabetic patients, patients with history of previous adverse reactions, patients with paraproteinemia, as well patients under eighteen years were exluded from the study.

The tip of the chateter was placed in to the renal artery. The choice of contrast media which were included in the study was done by random scheme. Automatic injector with flow of 5 mll/sec. and total dose of 10 mll. was used. Qualitative evidence of albumen in the urine was demonstrated by precipitation method with 20% sulphosalicyl acid. The samples were taken at 6, 12, 24 and 48 hours after selective renal angiography. The results were statistically evaluated with Fisher-Exact test.

Results

In vitro results demonstrated precipitation with 20% sulphosalicilyc acid in ioxaglat meglumin and diatrizoat meglumin while ioxehol and ioxitalhamat meglumin did not show any precipitation.

In ten patients who received ioxithalamat, Group A., albuminuria was demonstrated in six patients after 6, 12 and 24 hours. After 48 hours there were no signs of albuminuria in the group.

Group B. with diatrizoat meglumin demonstrated albuminuria in seven patients after 6 hours and six patients after 12 hours. After 24 and 48 hours albuminuria was found in four patients.

The patients (Group C.) who received iohexol did not demonstrate albuminuria 6, 12, 24 and 48 hours after proceedure.

In the Group D. where selective renal angiography was performed with meglumin joxalat, albuminuria was registered in three patients after 6 and 12 hours while after 24 and 48 hours there were no signs of it. Distribution of patients with albuminuria caused by various contrast media is demonstrated in Figure 1. Time dependance for albuminuria of four analyzed contrast media is demonstrated in Figure 2.

Comparison of albuminuria frequency for two high-osmolal ionic contrast media (ioxithalamat meglumin, diatrizoat meglumin) demonstrated statisticaly significant difference ($P>0.05$) 48 hours after proccedure.

Comparison of albuminuria frequency between two low-osmolal contrast media (iohexol, meglumin ioxalat) did not demonstrate statistical difference. Comparison of albuminuria frequency between high-osmolal and low-osmolal contrast media demonstrated statisticaly significant difference in all time sequences studied in Figure 3.

Discussion

Difference of albuminuria frequency between high and low-osmolal contrast media in our results demonstrated statistic significance at 24

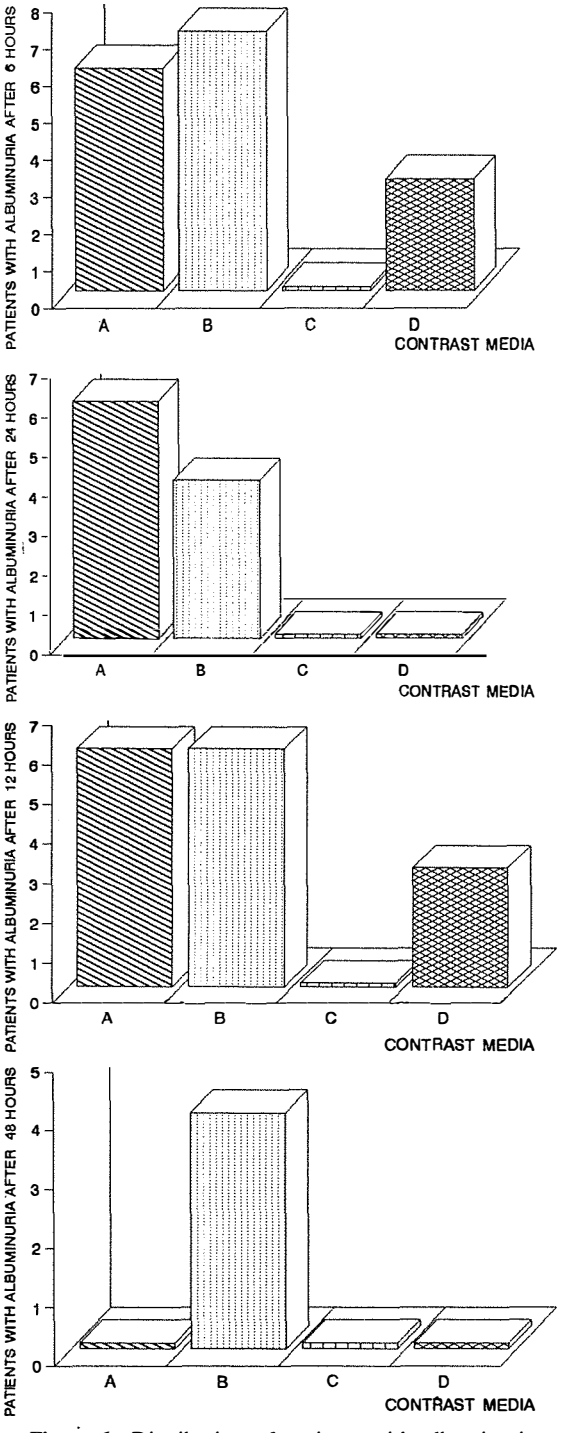

Figure 1. Distribution of patients with albuminuria after 6, 12, 24 and 48 hours caused by various contrast media. A = ioxithalamat meglumin, B = diatrizoat meglumin, C = ioheksol, D = meglumin ioxaglat

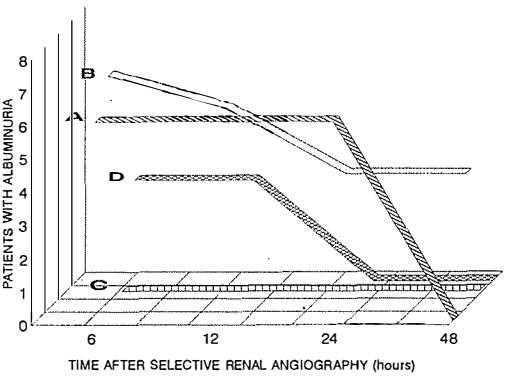

Figure 2. Time dependance for albuminuria of four analyzed contrast media. A = ioxithalamat meglumin, B = diatrizoat meglumin, C = ioheksol, D = meglumin ioxaglat

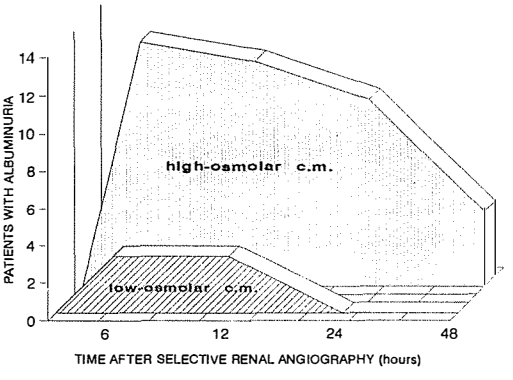

Figure 3. Comparative analysis of patients distribution with albuminuria after 6, 12, 24 and 48 for high-osmolar and low-osmolar contrast media

and 48 hours. These results confirm that osmolality is one of numerous factors which have effect on albuminuria.[15] Other factors, like nobium and chemichal structure of contrast media according to Holmes[16] and Golman[17] are also present. Positive reaction in vitro after 6 and 12 hours with 20% sulphosalicilyc acid with ioxaglat meglumin and diatrizoat meglumin is due to contrast media alone and that is why early reaction at 6 and 12 hours is unspecific.[18]

Nephrotoxicity after renal angiography probablly has different mechanism of origin than tissue toxicity according to work of Port et all.[14] They found vacuolization of proximal tubular cells in 20% of patients who underwent angiography.[14] Animal studies demonstrated that

proteinuria is often found after renal angiography and is dependent on quantity of contrast media used.[16] Mechanism of developing albuminuria after selective renal angiography is not completely known. Factors are complex and numerous, osmolality,[15] structure,[19] charge[20] and quantity of contrast media.[21] Although well known, order of importance of all these factors in post-angiography albuminuria is not clear. Various factors of nephrotoxicuty can cause renal failure after contrast media use such as: glomerular, vascular and tubular damage.

Contrast media flow initialy diminishes periphery resistance in renal vessels with short increase of flow, after which rising of periphery resistance with diminishing of renal blood flow follows.[22] These changes are due to activity of vasoactive substances such as renin, prostanglandin and kalikrein, and also to influence on eritrocytes and damage to vessels endothel.[23] Chemotoxicity and osmolality of contrast medica are possible factors because osmolal solution of NaCl or glucose can also induce similar chemodynamic changes.[24]

Glomerular damage was observed after intravenous urography and angiongraphy, induced by increase permeability with albuminuria.[25] After angiography, high concentration of albumen was observed in urine of canines and humans.[15] Since albuminuria is found in low and high-osmolality contrast media, hiperosmolality is exluded as the only factor in glomerular membrane damage.[16, 20]

Tubular obstruction is also possible as the consequence of tubular cell damage caused by contrast media.[26] Renal angiography increases excretion of tubular cell enzyms such as: lactasis, catalasis, dehydrogenasis, and creatinphosphokinasis a few minutes after injection of contrast media.[23] Tubular cell damage, caused by contrast medica of high-osmolality, according to work of Moreau.[27] is the consequence of chemotoxicity, rather than high osmolality alone.

Positive enzime findings in urine indicate tubular cell damage.[28] Since tubular enzyms are found in low and high-osmolal contrast media chemotoxicity seems to be more important than osmolarity.[29]

Our results which demonstrated the lack of albuminuria with low-osmolality contrast media compared to high osmolality contrast media, differ from some other literature data.[16, 19, 20] The reasons is probably in different proteinuria tests used, and a relatively small number of cases in our series. Contrast media concentration should not be the reason for albuminuria after selective renal angiography, while renal failure can be found even after i. v. urography where concentration of contrast media in kidney is much smaller.[21] Although the kidney is the target organ for toxic response, nephrotoxicity is relatively low after urographic contrast media. We conclude that low-toxicity and lack of albuminuria after selective renal angiography in our patients, examined with ioxehol in all time sequences, is due to combination of low osmolality, low chemotoxicity and absence of sodium ions.

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Radiol Oncol 1995; 29: 272–8.

Imaging modalities in diagnosis of cystic neoplasms of pancreas: review of the literature and a case report of pancreatic cystadenoma

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The review of the literature about the different imaging modalities in the diagnosis of cystic neoplasms of pancreas is presented together with recent considerations of the subject. A case of a 18 years old female patient with fairly uncommon solid-cystic pancreatic cystadenoma is reported with the findings of ultrasound (US), computerised tomography (CT), digital substractional DSA and US guided fine needle aspiration biopsy (FNAB).

US should be used as the primary imaging method in diagnosis of neoplasms of pancreas, followed by CT which has proven to be the most accurate imaging modality. Other studies have a secondary role. Presumptive diagnosis should be always confirmed by the fine-needle biopsy.

Key words: pancreatic neoplasms diagnosis; cystadenoma; diagnostic imaging

Introduction

Cystic pancreatic neoplasms, also called proliferative pancreatic cysts, are rare lesions; however they are nowadays more frequently detected, due to the continual advances in imaging technology. We report a case of a fairly uncommon papillary-cystic (solid-cystic) type of a serous cystadenoma of pancreas. The literature is reviewed and some recent considerations of the subject are presented. The described case confirms the peculiar features of the tumour, reported in the literature: no specific symptoms or signs, low rate of metastasising, difficult preoperative diagnosis and possibility of complete resection.

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Case report

An 18-year old female with a rapidly increasing palpable mass in the upper abdomen, slightly right from the midline, and a history of vague abdominal pain in the last 2 months is presented. Initial laboratory tests demonstrated mild elevation of alkaline phosphatase, serum amylase and AST, and fairly elevated ALT and GGT. Other laboratory test were normal. Previous patient history and family history were

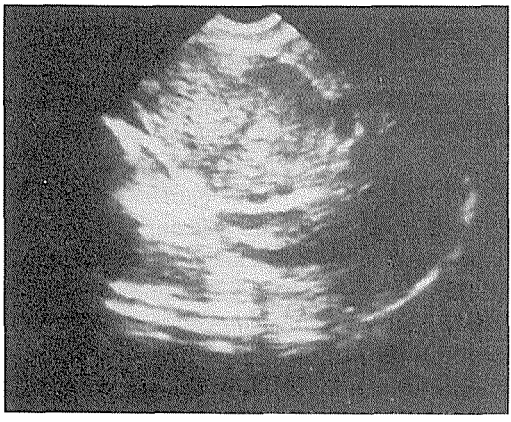

Figure 1. US image of rounded expansive process of heterogeneous echogenicity, measuring 8.5 × 8.0 cm in the pancreatic head, with sharp margins and clear delineation from the surrounding organs.

unremarkable. Physical examination revealed only the well-defined epigastric mass palpable below the liver margin, as well as a palpatory painful lymph node on the right side of the neck, approximately 1 centimetre in diameter.

Sonographically, a round expansive lesion of heterogeneous echogenicity, measuring 8.5 × 8,0 cm was noted in the head of pancreas, with sharp margins and clear delineation from the liver and the right kidney (Figure 1).

On CT examination of the upper abdomen a well-defined neoplastic mass was noted, located retroperitoneally in the pancreatic head, measuring 7.2 × 8.1 cm, with attenuation coefficients in the range from 25 to 49 HU, corresponding to the gelatinous-necrotic to soft tissue density. The right hepatic lobe was slightly compressed and dislocated anterosuperiorly. The right kidney was dislocated inferoposteriorly (Figure 2).

Contrast enhanced scans revealed inhomogeneous opacification with increased density peripherally, in the capsule of the tumour. Neither signs of adjacent structures infiltration, nor the abdominal lymphadenopathy could be noted (Figure 3).

These CT features pointed cystadenoma to be the most likely diagnosis. Another entities that could not be excluded were haemorrhagic pseudocyst and, less likely a cystadenocarcinoma.

Ultrasound guided fine-needle biopsy was performed to verify the diagnosis. The cytological analysis showed a high cellularity, with numerous papillary fronds, composed of fibrovascular stalks with narrow capillaries, surrounded by acellular and hyalinized rims, and lined by one or more layers of cuboidal cells with variably abundant eosinophilic cytoplasm. The cells had round or oval, euchromatic nuclei, with monotonous appearance and smooth contours. Foamy cells were also seen.

The selective DSA of celiac trunk revealed splaying of common hepatic artery and its bran-

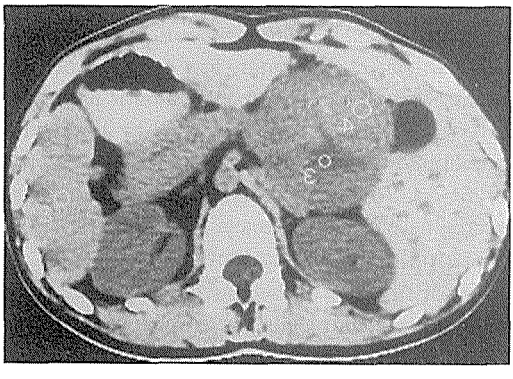

Figure 2. CT image of a well-defined neoplastic mass in the pancreatic head, measuring 7.2 × 8.1 cm, with attenuation coefficients from 25 to 49 HU. The right hepatic lobe was slightly compressed and dislocated anterosuperiorly and the right kidney was dislocated inferoposteriorly.

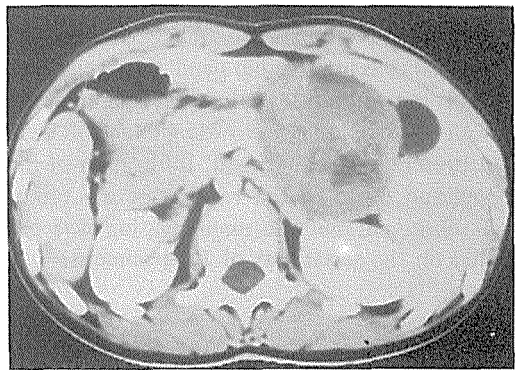

Figure 3. Contrast-enhanced CT scan with inhomogeneous opacification of tumor with enhanced capsule of the tumor.

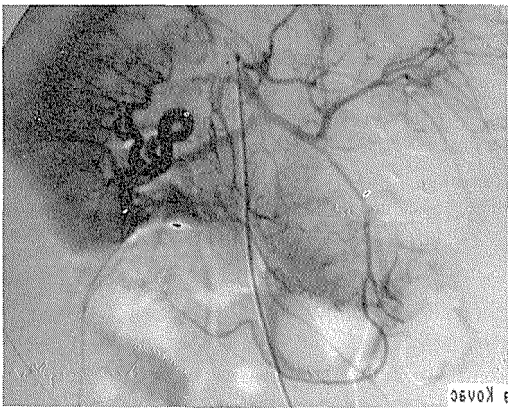

Figure 4. The selective DSA of celiac trunk with visible splaying of common hepatic artery and its branches in the inferior part of right hepatic lobe, and inferior dislocation of the gastroduodenal artery. Lack of signs of infiltration of stenosis of the vessels.

ches in the inferior part of right hepatic lobe, while the gastroduodenal artery was dislocated inferiorly. There was no evidence of infiltration or stenosis of the vessels. Branches originating from the celiac trunk and splenic artery were arcuary bent, coursing within the capsule of an avascular tumorous lesion of the pancreatic head. (Figure 4).

On surgery the cephalic duodenopancreatectomy and cholecystectomy were performed. The resected tumour measured $13 \times 8 \times 7$ centimetres. It had a smooth surface, and was clearly delineated from the rest of the pancreas. When the tumor was cut, the cystic macrostructure with considerable amount of solid tissue among the cysts was noted. Histologically the tumor was predominantly made of cuboidal epithelial cells arranged in papillary formations, as well as solid masses. There was no evidence of cellular anaplasia or crowding. Nucleoli were not present in the specimen. Infiltration of the neoplastic tissue in the capsule of the tumor was observed, but the angioinvasion was not noted on the serial cuts of 10 specimens.

Discussion

Most cystic lesions of the pancreas are pseudocysts or retention cysts. However 10–15 % cystic lesions are neoplasms, and cystic tumors represent 1 % of all pancreatic neoplasms. Although cystic pancreatic neoplasms occur most commonly in middle-aged and older patients,[1] there are cases reported in pediatric population – even in newborns,[2] and during gestational period.[3] More than 70 % of patients with cystic pancreatic neoplasms are women. Serous cystadenoma may be associated with von Hippel-Lindau disease.[4] There are reported cases of their association with giant-cell tumour,[2] malignant fibrous hystiocytomas,[5] and von Recklinghausen's disease.[6]

The pathological and clinical classification, as well as the prognosis of cystic pancreatic tumors, are quite controversial. There are two major types of cystic pancreatic neoplasms: (1) benign serous cystadenoma (SCA) which can be (a) microcystic, (b) papillary-cystic (solid-cystic) and (c) macrocystic,[7] and (2) mucinous cystic neoplasms comprising (a) potentially malignant macrocystic (mucinous) cystadenoma (MCA) and (b) apparently malignant cystadenocarcinoma. Cellular proliferative activity in SCA is as low as in normal pancreatic ducts, which reflects biological behaviour of these lesions that have a very low risk of malignant transformation.[8] Cellular proliferative activity in MCA is only slightly higher than in SCA but significantly lower than in adenocarcinomas.[9] Nevertheless, malignant tranformation may occur in MCA.[10] Histopathologic findings consist of cystic cavities with single lining epithelial cells which are columnar, low cuboidal or flattened, and contain intracytoplasmatic abundant glycogen.[11] The cavities can also be lined with papillomatous vegetations (papillary-cystic type of SCA). Mitose and hystologic solid growth correlate with malignancy as well as signs of anaplasia, crowding and infiltration.[1]

Cystic tumours of the pancreas originate from pancreatic acinar cells or from ductal epithelium. However, the case of SCA with endocrine component have been reported.[11] In our case such elements were also noted. Mucin-producing pancreatic tumour (MPPT) represents a recently recognized new human neoplastic entity. Although MPPT is not a real cystic tumour,

there are opinions that MCA and MPPT can be classified into the same conceptual category. MPPT is, in fact, a papillary adenoma with excessive mucin secretion situated inside the pancreatic duct. It may be well visualized on pancreaticograms.[12] The possibility of malignant transformation in suggested. This kind of (cyst)adenoma can cause acute pancreatitis due to the ductal obstruction.[13]

Macroscopically, cystadenomas appear as well defined, usually spherical or ovoid, often lobulated masses, containing many cysts. The SCA comprises often innumerable tiny cysts, less than 2 cm in diameter, giving it a honeycomb appearance. The cysts usually contain proteinaceous, amorphous and stringy fluid. The MCA contains fewer (less than 6) cysts of greater diameter. The SCA may at times appear as a small mass, without macroscopically visible cysts.[14] Eccentric solid component may be seen within the cysts, as well. Mean tumor size is about 6 cm, with range from 2 to 20 cm.[14] Cystadenomas are commonly hypervascular,[15] but may also may be hypovascular, as in our case. SCA is usually located in the head of the pancreas while MCA predominantly involves body or tail, which are the commonest sites of cystadenomas (77 %), as well. Occasionally SCA may be multifocal. Pathoanatomically pancreatic cystadenomas may closely resemble ovarian cystadenomas.

As a slow growing tumour, cystadenoma usually becomes rather large before becoming symptomatic, remaining localized for a long period of time. Even one third of patients does not have any symptoms, so the disease is diagnosed incidentally. More common symptoms are upper abdominal pain (95 % of patients), palpable mass (52 %), weight loss (38 %), jaundice (14 %), maldigestion, diarrhoea, nausea and vomiting. Jaundice is observed in cases of tumors located in the head of the organ, but the patients with cystadenomas are less likely to have jaundice, in comparison with those with cystadenocarcinoma, although other symptoms may be similar in both groups. Portal hypertension due to the portal vein compression is not a rare complication. Exceptionally, the patient manifests suppuration, spontaneous cyst rupture of fistula formation. Unresected cystadenoma may undergo malignant transformation or cause significant morbidity as a result of local complication.[16] Exocrine and endocrine pancreatic functions are frequently weakened in the presence of cystic pancreatic neoplasms, which may lead to false presumptive diagnosis of chronic pancreatitis. Laboratory studies are not specific. Elevation of CEA and CA 19-9 are characteristic for malignancy.

The imaging methods are crucial in diagnosing cystic pancreatic neoplasms. CT and US undoubtedly play the most important role. Moreover, sonographic or CT features may be typical and may allow accurate preoperative differentiation of these tumours. In the last decade US has become the effective screening method in cases of suspected pancreatic tumor.

US appearances of the cystic neoplasms depend upon the morphologic differences in these tumours, primarily upon the size of the cystic components. When the cysts are relatively large, cystic tumors have the appearence of a fluid collection – anechoic mass with enhanced through transmision – and may be easily confused with the pseudocyst. Their appearance is more specific if there are internal septations or polypoid solid components, when the diagnosis of MCA should be suspected. Large cysts are consistent with their malignant counterpart – mucinous cystadenocarcinoma. Small, often peripheral areas of calcification are more likely to be visualized by CT than by US.[14] US appearance is quite different when the cysts are very small as it is the case with SCA. In this situation US will reveal a well-marginated cyst with predominantly echogenic or mixed hypoechogenic/hyperechogenic pattern. Namely, in mycrocystic adenomas multiple acoustic interfaces result in multiple hyperechoic foci that give the tumour a solid appearance.[13] Only the high-gain scans will reveal the characteristic fine mycrocystic echo pattern. A central stellate scar with »radiating« bands of connective tissue may occasionally calcify, therefore becoming easily recognisable sonographically. Endoscopic US could visualize DEMCA and its details such

as papillae, better than conventional US (sensitivity 68% and 93%, respectively).

The reliable visualization with accurate morphologic characterisation and preoperative staging of sonographically suspected cystic pancreatic tumour is best achieved by means of CT, particularly by utilizing sequential bolus dynamic CT-technique.[17] CT shows a low density mass, with attenuation coefficients close to that of water on native scans. Good postcontrast enhancement indicates good vascularization. As well as US, CT cannot identify individual microcyst. Calcified central starlike scar in SCA may be detected with either US and CT and is considered to be a very specific sign.[18] Dystrophic calcification is present in 10–20% of cases of MCA and is often peripherally located. The presence of marginal calcification on CT is therefore considered to represent a sign of (pre)malignancy.[1] Internal septations are occasionally only faintly noted on CT scans (but intra – or pericystic solid components are often well visualized.[13] Although US is more sensitive than CT for diagnosing most small tumours, CT may better detect small tumors in the pancreatic tail than US.[13]

When a large retroperitoneal mass is present, the differentiation between pancreatic and nonpancreatic origin of the mass may be uncertain with US. CT is essential in the evaluation of the local extension of cystadenocarcinomas; it allows better delineation of the status of the vessels around the pancreas. CT is also useful in the evaluation of the extension into the peripancreatic fat, although such extension may be evaluated with intraoperative US. Generally speaking, CT is best for the analysis of contours, whereas US is most useful in the analysis of the tissue structure. The two methods are thus complementary.[13]

Although CT and US allow excellent preoperative assessment and some degree of differentiation, the attempt to distinguish histological variants, especially when the features are not typical (e.g. sunburst calcification) may be hazardous. In a great retrospective study of Mayo Clinic the authors report that an unequivocal preoperative CT diagnosis was not reached even in a single patient.[4] So, the preoperative diagnosis should always be reached by fine-needle biopsy specimen analysis.[16] The combined use of imaging modalities and fine-needle biopsy specimens allows correct characterization of the cystic pancreatic tumours in 90% of the cases.

The additional use of cyst fluid analysis for CEA and viscosity measurement enhance the sensitivity of the cytologic diagnosis of mucinous cystic neoplasms. Since cystadenomas (and even cystadenocarcinomas) are often misdiagnosed as pseudocysts with internal septations, amylase level measuring in the content obtained by fine-needle aspiration may help to avoid the confusion.[19]

The other imaging methods nowadays play a secondary role and are used mainly when CT is equivocal or nondiagnostic. Angiographic findings are nonspecific with the masses being either hyper- or hypovascular.[20] Hypervascularity is present in one third of the cases.[21] Arteriovenous shunts and neovascularization may be seen.[15] On MRI SCA have lobulated margin containing multiple cysts and septae. The cysts have a reduced signal on T1- and increased signal on T2-weighted images. MCA demonstrate larger cysts, thicker septae and a more variable signals on T1- and T2-weighted images. MRI is equally worthy like CT in demonstrating septae, but superior in delineating the cystic components. Calcification is more readily apparent on CT. ERCP findings are rather nonspecific. This method has only a few indications: it is very sensitive for the detection of small tumours within or adjacent to the main pancreatic duct,[13] showing a narrowing or a filling defect of contrast medium. The sign may however indicate either benign or malignant tumour.[1] ERCP does not show communications between pancreatic ductal system and cystic cavity in the cases of cystic neoplasms, but shows opacification of ectatic ducts in mucinous ductal ectasia,[1] occasionally with amorphous filling defect of mucin.

The problem of an emergent histological diagnosis can occur in the case of spontaneous rupture and the suppuration of the cystadeno-

ma. Although the data provided by US and CT are crucial, the misdiagnosis of "pseudocyst" may occur, which can result in an inappropriate treatment.[15] Intraoperative examination of the frozen sections is of the paramount importance for the choice of the surgical procedure and, consequently, for the patient prognosis. Every MCA should be completely examined in carefully prepared specimens in order to identify the signs of malignancy.

All the cystic lesions of pancreas without the history of acute pancreatitis or trauma should be completely surgically removed, even if the Whipple procedure has to be performed. This is particularly important for MCA because of its potential malignant alteration. However, there are opinions that SCA in high-operative-risk patients might be treated conservatively if it is asymptomatic and the diagnosis is confirmed histopathologically.[1] Some authors feel that the slow growth rate and low risk of malignancy permit surgery after a previous drainage or by-pass procedure. The other recommend that internal drainage or marsupialization procedures should not be performed.[22] Anyway, the current role of conservative treatment remains questionable, particularly according to recent reports about the potentially malignant macrocystic variant of SCA.[7, 23]

The patients with cystic pancreatic neoplasms have a significantly better prognosis as compared to other pancreatic cancers and can be cured if diagnosed early and if complete resection is performed. The resectability rate of cystadenoma and cystadenocarcinoma is 91% and 67%, respectively.[16] The 5-year-survival rates are 90% and 72%, respectively. [16] SCA has substantially lower rate of the long-term mortality than mucinous cystic lesions (MCA and cystadenocarcinoma).

In conclusion, cystic neoplasms must always be considered when dealing with cystic lesions of the pancreas. US should be used as the primary screening method, followed by CT which has proven to be the most accurate imaging modality for the diagnosis and characterization of pancreatic masses. Other studies have a secondary role. Presumptive diagnosis should be always confirmed by the fine-needle biopsy and histological analysis of the specimen. Surgery is the treatment of choice.

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Interventional, diagnostic and therapeutic use of chest ultrasonography

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On the basis of the well-known practice of using ultrasonography for resolving pathological changes in the thoracic region, we concentrated in our study on peripheral lesions affecting the pleura, parenchyma or mediastinum.

In our Institute during a one year period we carried out diagnostic and therapeutic interventional procedures, ultrasonically guided in 85 patients (69 men and 16 women). In all our patients an adequate aspiration sample was obtained (100 %), with 80 %, sensitivity.

The pleural effusions were mainly of an inflammatory etiology (73 %) – nonspecific (38 %) and specific (35 %) – malignant (11 %), and the cytological finding was nonspecific in 16 %.

Percutaneous needle aspiration biopsies of peripheral solid lesions which were accessible to US detection were performed in 14 patients. The aspirated sample was adequate and positive; of malignant etiology in 86.5 % patients, and inflammatory in 13.5 %.

As a complication in one of our patients pneumothorax occurred.

Key words: thoracic interventional radiology; thoracic sonography; peripheral thoracic lesions

Introduction

The use of ultrasonography is well known in the diagnostics of pleural, peripheral parenchymic and mediastinal lesions in chest diseases.[1] Lesions in the peripheral zone of the thoracic region frequently pose diagnostic problems.[2] They are usually inaccessible for endoscopy or do not provide adequate exfoliative samples of sputum for cytological analysis. There are numerous techniques of percutaneous needle aspiration biopsy with diascopic control or CT, the first of which was that of Chandasekar et al, 1976, who performed percutaneous puncture of peripheral masses in the lung parenchyma with ultrasonographic guidance.[3, 4] However, the use of ultrasonography in the diagnostics of chest disease is hindered by technical difficulties, i.e. only when the peripheral lesion is in contact with the chest wall, providing an acoustic window and permitting penetration of ultrasound, can it be detected.[5] In our hospital we paid special attention to peripheral lesions affecting the pleura, parenchyma or mediastinum.

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Patients and examination methods

In our Institute during a one year period diagnostic and therapeutic interventions were carried out, using ultrasonography in 85 patients (69 men and 16 women). In the majority of cases (71) puncture of the pleural effusion was performed, and in 14 patients percutaneous needle aspiration biopsy of peripheral solid tumours, which were accessible ultrasonographically was carried out.

All procedures were carried out after conventional radiological examination with a Thosiba Capasse ultrasonic unit and a convex transducer of 3.5 MHz. After application of a local anaesthetic an Xilocainon biopsy needle (Chiba-11 cm long with mandrain) for aspiration of the sample was inserted freely without a fixed guide channel in the sonde, which proved to be better because of anatomic relations in the chest. The material obtained was sent for microscopic analysis – both cytological and microbiological. In the case of parenchymic masses contraindications for needle biopsy were respected, i. e. aneurysm, A-V fistule, echinococcus, pulmonary hypertension, disordered coagulogram, COPD and contralateral pneumonectomy.[6]

Results

An adequate sample was obtained in all 85 patients with pleural effusion and peripheral masses of the lung parenchyma (100 %). In 71 cases the microscopic findings were positive with sensitivity of 80 %. Negative, i.e. nonpecific, cytological findings were found in 14 patients with pleural effusions, while all findings were positive in patients with peripheral solid masses (Table 1).

Microscopic features of the pleural effusion were mainly of inflammatory etiology – nonspecific in 27 patients (38 %) and specific in 25 (35 %). In the remaining patients malignant etiology was determined in 8 (11 %), while in 11 (16 %) it was impossible to determine the etiological sequence of nonspecific cytological findings. In more than half the patients, i.e. 45 (63 %) the effusions were on the right and in 26 (37 %) on the left (Table 2).

Table 1. Results of percutaneous aspiration needle biopsies guided by ultrasonography in 85 patients.

X-ray and Ultra-sonography diagnoses	Adecquate samples				Positive aspiration		Negative cytology	
	N	%	N	%	N	%	N	%
Pleural effusions	71	83	71	83	57	60	14	20
Peripheral solid masses	14	17	14	17	14	20	–	–
Total	85	100	85	100	71	80	14	20

Table 2. Microscopic characteristics of pleural effusions.

Cytological findings	Right side				Left side	
	N	%	N	%	N	%
Neutrophylic	20	28	12		8	
Empyema	7	10	6		1	
Lymphocytyc	23	32	13		10	
TBC	2	3	1		1	
Malignant	8	11	6		2	
Hemorrhagic	5	7	3		2	
Mesothelial cells	5	7	3		2	
Eosinophilic	1	2	1		–	
Total	71	100	45	63	26	37

Microscopis features of the peripheral solid masses of the lung parenchyma showed peripheral malignant processes in 10 patients (71.5 %), one of which was Pancoast sy. Of the remaining 4 patients, in 2 cases mediastinal malignant processes were found (13.5 %), and in 2 inflammatory abscesses (13.5 %). In 8 patients (58 %) the masses were located in the right lung lobe, in 4 (28.5 %) in the left and in 2 (13.5 %) in the mediastinum (Table 3).

Table 3. Microscopic features of the peripheral solid masses of the lung parenchyma and mediastinum.

Cytological findings	Right side		Left side				Media-stinum	
	N	%	N	%	N	%	N	%
Carcinoma	4	29	4		–		–	
Adeno-carcinoma	3	22	1		2		–	
Lymphatic mediastinum	2	14	–		–		2	
Neuroblastoma	2	14	–		2		–	
Abscessus	2	14	2		–		–	
Ca planocell.	1	7		1		–		–
Total	14	100	8	57	4	28,5	2	13,5

In one of our patients minimal pneumothorax developed as a complication, which was conservatively treated.

Discussion and conclusion

On the basis of the well-known use of ultrasonography in the treatment of pathological changes in the thoracic region, we paid special attention to peripheral lesions affecting the pleura, parenchyma or mediastinum.[1, 3–5, 7–10]

Patients with lesions in the peripheral zone of the thoracic region were treated by conventional radiological technique and ultrasonography. In the majority of cases they were pleural effusions of minimal to hypertensive hydrothorax and peripheral solid masses of the parenchyma which were percutaneously punctured, guided ultrasonically. In the case of small effusions, interventions were usually diagnostic, while in larger effusions both diagnostic and therapeutic, particularly in complete evacuation of loculated pleural effusions. Adequate aspiration samples were obtained in all cases (100 %), indicating that this method has high diagnostic value.[7, 12, 13] In 71 patients microscopic findings were positive with sensitivity of 80 %, which agrees with the results of other authors in which the average value was 85 %.[3, 7, 14, 15] All cytological findings were positive for peripheral solid masses of the lung parenchyma, while in 14 patients with pleural effusion the cytological findings were nonspecific, which is an indication that pleural effusions give insufficient diagnostic information (Table 1).

Microscopic characteristics of the pleural effusions in this study were mainly of inflammatory etiology (73 %) – (38 %) nonspecific and (30 %) specific. Malignant etiology was found in 11 % of the patients with pleural effusions. In more than half the patients (63 %) the effusions were on the right and in the remaining patients (37 %) on the left (Table 2).

Microscopic features of the solid peripheral masses of the lung parenchyma and mediastinum were in most cases of malignant etiology (86.5 %), and inflammatory in (13.5 %). In 8 cases (57 %) the processes were on the right, in 4 on the left (28.5 %) and in two cases (13.5 %) in the mediastinum (Table 3).

Complications connected with solid masses of the lung parenchyma in literature are pneumothorax in approximately 3 % of cases, and hemorrhagia in approximately 4 % of cases.[3] We had one minimal pneumothorax (7%) which was detected during regular radiological control following percutaneous puncture and was conservatively treated.

The advantages of ultrasonographic over conventional radiological treatment in pleural effusions are: (1) detection and precise designation even in 5 ml of loculated content;[10] (2) differentiation of the pleural effusion, according to the thickness of the pleura, which is rather more difficult in a very thin layer of fluid; (3) peripheral solid masses of the lung parenchyma can be detected when in close contact to the chest wall, which is also our experience. Using ultrasonography it is possible to show the erasing of the continuity of the pleura in peripheral masses, indicating proliferation and penetration into the wall itself.[16] It is possible to differentiate pulmonary cysts filled with fluid from solid peripheral masses.[10]

Certain technical difficulties were experienced with our convex sonde because of its size and the appearance of acoustic shadows of the ribs, which can create the illusion of dorsal enhancement, i.e. reverberation during detection of peripheral lesions.

The most important advantage of this method is that the patient and hospital personnel are not exposed to ionizing radiation, which enables repeated essential check-ups. The examination is very simple, the method sensitive, inexpensive and equipment easy to obtain.

It should also be emphasized that in the pathological processes interventional diagnostic and therapeutic ultrasonography is second in the algorhythem for detecting disease in the thoracic region, after which microscopic verification leads to the final diagnosis.

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Percutaneous transhepatic biliary drainage under ultrasonic guidance in the therapy of cholangitis due to biliary malignant obstruction

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In patients with unresectable malignant biliary obstruction, percutaneous biliary drainage (PBD) is one of the available methods of palliation.[1, 2] We performed PBD under ultrasonic guidance in 10 patients with obstructive jaundice due to malignancy (11 intubations). Puncture of the left lobar ducts was the method of choice in all patients. Right sided drainage was, added in 3 patients due to high hilar obstruction with the infiltration of both ductal systems. We emphasize the effectiveness of this method in such patients because of the possibility of quick and easy therapeutic approach, cost benefits and avoidance of the radiation during a classically performed procedure.

Key words: bile duct neoplasms – complications; cholangitis – therapy; drainage

Introduction

The prognosis for patients with malignant biliary obstruction is generally poor.[3] PBD is a well established procedure in selected patients.[4, 5]

We present our experience in 10 patients where we performed palliative PBD.

Patients and methods

This report is based on a retrospective review of PBD in 10 patients. All patients were poor surgical candidates with malignant high biliary obstruction (median age 70,5, range 67 to 74 yr.). PBD was indicated and urged in five patients due to the development of severe cholangitis.

Biliary tract was examined by ultrasound (ALOKA SSD 680, 3.5 MHz). Puncture was done by free hand technique described elsewhere.[6] Catheters used for drainage had a 5 to 12 F calibre (Angiomed).

Table 1. Diagnosis and site of ultrasound-guided PBD.

	No. of patients	No. of intubations	
		left	right
Klatskin tumour	4	4	1
Carcinoma of the gall-bladder	1	1	1
Carcinoma of the pancreas	2	2	0
Metastatic carcinoma	1	1	1

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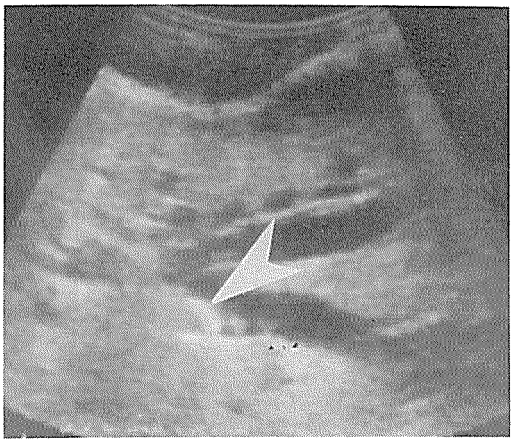

Figure 1. Guide wire in the left hepatic duct.

Results

Drainage failed in 2 patients due to inability to pass the quide wire into the bile duct. Bile cultures obtained at the time of drainage were positive in 40 % patients. Most frequently encountered organisms were Echerichia coli, Pseudomonas aeruginosa, Klebsiela pneumoniae, Citrobacter species, Enterobacter aerogenes. Six out the 8 patients with successful drainage died within the time of this report with a mean survival period of 9 weeks (4–16 weeks).

Discussion

PBD used for the palliation of the malignant obstructive jaundice is a rapidly advancing technique.[7] Following PBD the conditioning dramatically improved within 24–48 hours in five patients with acute cholangitis. Antibiotics were given based on the bile cultures. All of the patients with successful drainage had a significant fall in the serum bilirubin level. Major complications[8, 9] described in the literature (major haemorrhage, bile peritonitis, pleural effusions, severe cholangitis with hypotension) were not observed in our patients. Complications encountered were due to tube dislodgment, tube blockage and leaking bile with resulting cholangitis. In such cases we replaced the catheter with another of a bigger calibre, or continued with more frequent irrigations of the catheter.

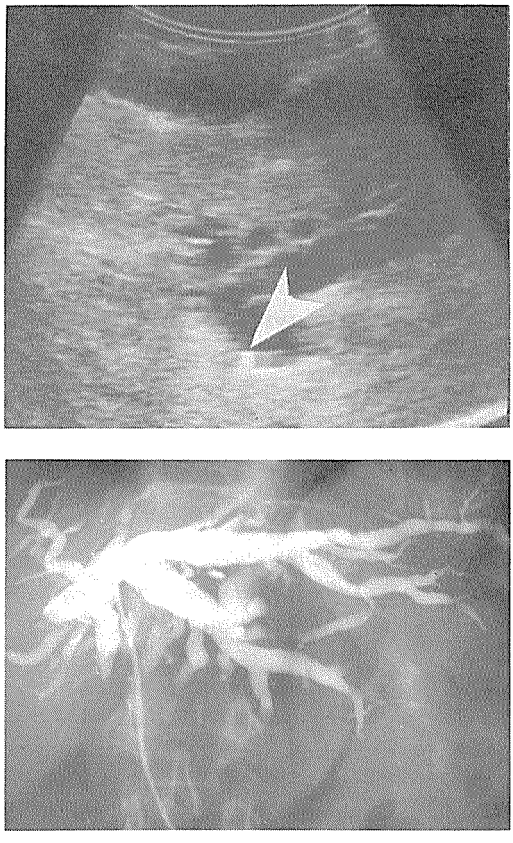

Figure 2. Catheter in the left hepatic duct. a) Ultrasonic feature. b) Radiologic feature.

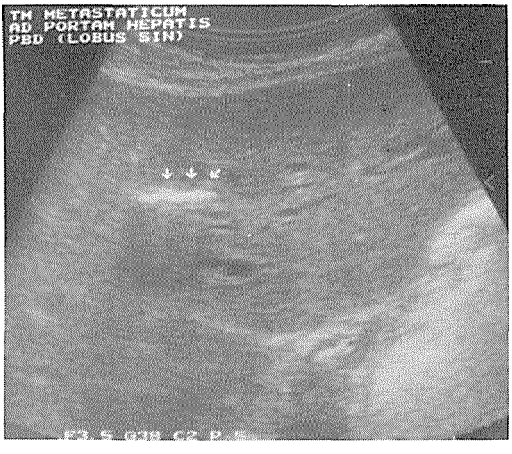

Figure 3. Catheter in the left hepatic duct after drainage.

We think that PBD should be attempted as a routine measure in selected patients with acute suppurative cholangitis caused by malignant biliary obstruction.

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Ultrasonic preoperative staging of rectal cancer

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The possibilities of transrectal sonography of rectal cancer by means of a linear transducer of 7,5 MHz with the purpose of preoperative staging are explored and the results presented.
By this method rectal cancer was classified into three stages: T1, T2 and T3, and the results were compared with the postoperative pathological and histological findings.
On the basis of the presented results the transrectal sonography has been found to be a precise diagnostic method by means of which it is possible to determine with a high degree of reliability the preoperative staging, taking into consideration that the possibilities of linear probe require patient and careful rotating of the whole transrectal probe while analysing the tumor, and the precise estimation of the depth of rectal wall infiltration.

Key words: rectal neoplasms-ultrasonography, rectal wall; neoplasm staging

Introduction

As a cause of death the colon cancer ranks second among the malignant diseases, next to the lungs cancer.[1]

After the establishment of the rectal cancer diagnosis the preoperative staging has to be determined and only after that, the optimum treatment.[1–3]

The pioneer of rectal endosonography is John Wild.[2] In the 1970-ties Lutz and Rosch made a contribution to the further development of endosonography. In the 1980-ties Di Magno and Strohm reported on additional possibilities of endosonography.[4–6] In 1983 Hildebrandt reported on the use of endorectal ultrasound and in 1988 Tio published a review on endosonography in gastroenterology, comparing blind transrectal sonography (BUS) with endoscopic transrectal ultrasonography (EUS).[3, 7]

Today blind rigid probes are used for the rectal endosonography, which can reach 15 cm, possibly also up to 20 cm into the depth of the rectum with linear, sectoral and rotational transducers made by a number of producers (Kretztechnik, Multiplan-Siemens, Hitachi, Aloka . . .).[2]

In this way a clear ultrasonic image of the mucosa, submucosa muscularis propria and the connection of the rectal muscularis with the fat tissue can be obtained (Figure 1).[1, 2]

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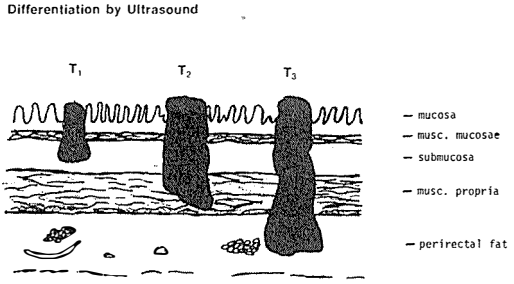


Figure 1. Layers of rectal wall and stages of cancer penetration through the wall. Differentiation by ultrasound, 1.

Materials and methods

For the ultrasonic preoperative staging of rectal cancer the linear Hitachi probe EUP-U 33 (7,5 MHz) is used. It is a rigid non-endoscopic guided ultrasonic probe which enables the displays up to 20 cm deep into rectum. The following is the procedure, we use in preparing the patient for rectal endosonographi of rectal cancer: Coloclens liquid, supositoria for clearning and rectal enema.

Before beginning the examination a rubber baloon is placed over the transducer and then the probe is introduced into the rectum. Before the examination begins the baloon is filled with 40–50 ccm of water through the channel in the probe.

The visualisation of tumour is made by careful movements of the probe in a cranio-caudal direction associated with rotation of probe.

The scanned tumour process is compared with the normal rectal wall ultrasonic image (Figure 2).

By the careful scan of the tumour, which as a rule is hypoechogenic, the depth of the wall infiltration by the cancer is assesed, and by comparing it with the normal rectal wall it is established which of the layers the tumour has penetrated.

On the basis of these findings the tumour is classified as stage T1, T2 or T3.

By this method the rectal tumours in 24 patients were examined and their postoperative staging was determined.

In our patients the rectal cancer was diagnosed by a rectosygmoidoscopy with a patohistologic byopsy.

The study was done durring the period od 1991–1993.

The study is retrospective and only the patients with a diagnosed rectal cancer entered the test group.

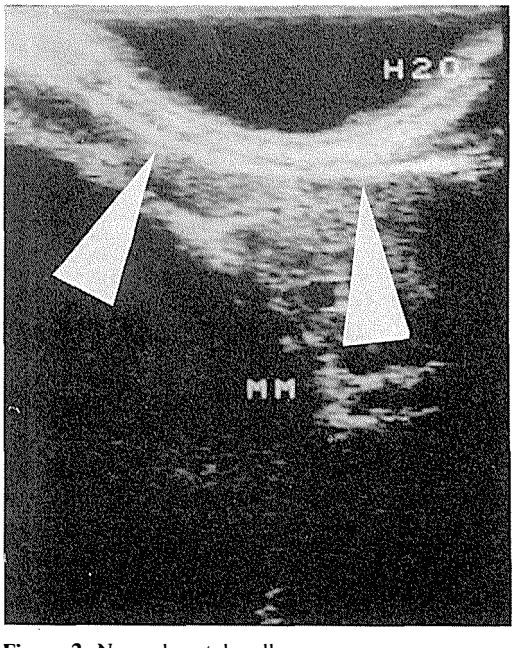


Figure 2. Normal rectal wall.

Results

The results of this study are shown in table 1.

Table 1. Preoperative staging of rectal cancer in 24 patients and pathologic postoperative findings in 21 patients (comparison).

	No	Stage T1	Stage T2	Stage T3
Sonographic preoperative staging	24	7	5	12
Pathologic postoperative findings	21	6	6	9

Wiht 3 patients the resection of the rectum was not performed because it was ascertained by other diagnostic methods that the tumour pro-

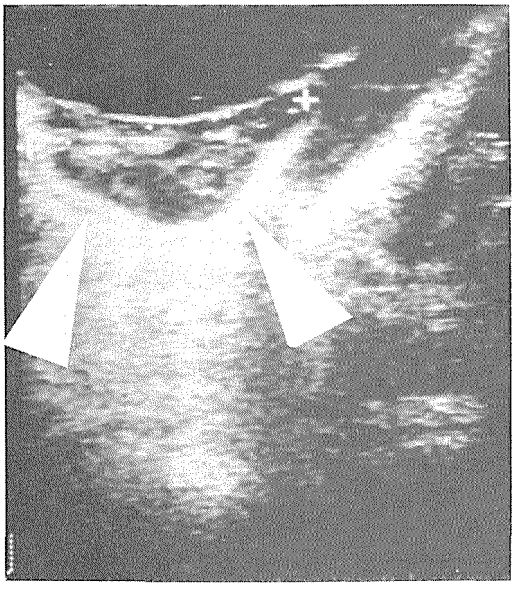


Figure 3. Rectal cancer – T1 stage.

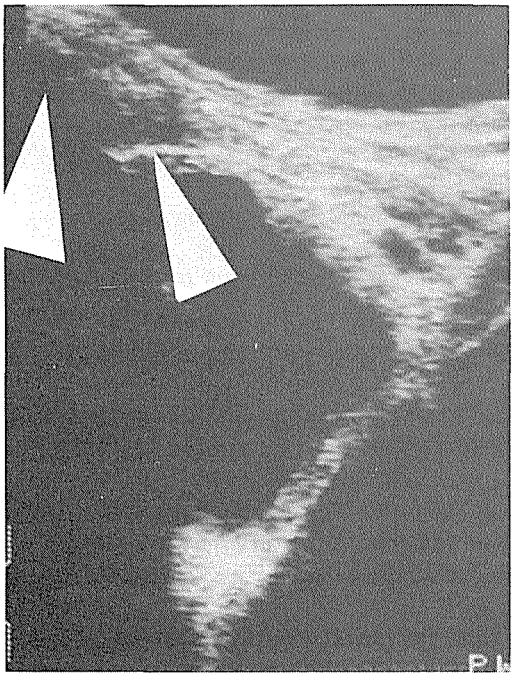
cess had spread to the adjacent organs and that distant metastases exist. The T4 stage was in question. In these patients palliative treatment was applied.

With 6 out of 7 patients with a diagnosed rectal cancer of the T1 stage, the ultrasonic findings were confirmed by postoperative pathologic findings. The T2 stage was confirmed ultrasonically with 6 patients, and by means of a postoperative pathologic findings, with 7 patients.

We had one falsely positive ulrasonic finding, for the T1 stage for the T2 stage one falsely negative finding and for the T3 stage three falsely positive findings (it was a question of T4 stage).

We estimate that the falsely positive findings for the T1 and T2 stage are the consequence of an insufficiently slow and precise rotation of the probe. As a result, during the ultrasonic analysis, the spot where the tumour penetrates the submucosa and infiltrates the muscular layer cannot be seen.

The falsely positive T3 stages appeared with the patients where a large tumour obstructed a part of rectal lumen, so the display with our non-endoscopic guided ultrasonic probe was incomplete.



Fifure 4. Rectal cancer – T2 stage.

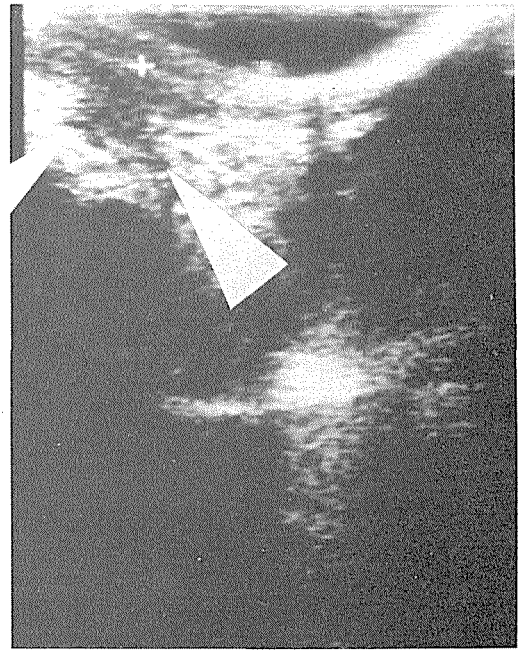


Figure 5. Rectal cancer – T3 stage.

During the examination we had a technical problem. During the entire probe rotation, the water baloon did not follow the probe movements, so the wrinkling of baloon wall obstructed the ultrasonic mucosa display.

Lubricating the baloon with liquid paraffin oil, we solved this problem. After that the baloon glided correctly and followed the probe rotation.

The results show that this method has high degree of reliability with stages T1 and T2, while in T3 stage of rectal cancer it is lower, and amounts 75 %.

Discussion

By transrectal sonography the rectal wall is clearly demonstrated, making it possible to distinguish between the layers. The description of the transrectal ultrasonic picture of the rectal wall layers (3 hyperechogenic and 2 hypoechogenic layers) was given by Boscaini and Montori in 1986.[8]

The inner *hyperechogenic* layer corresponds to the rubber baloon attached to the mucosa. Next to it is the *hypoechogenic* layer representing the mucosa and muscularis mucosa, attached to the *hyperechogenie* layer which represents the submucosa. On the outer side the *hypoechogenic* layer of the muscularis propria follows, and the outer *hyperechogenic* layer which correspond to the connection between the muscularis and the fat tissue.

The description of the wall layers has been evaluated and accepted by other authors (Benyon, Hildebrandt, Feifel, Prevost).[9–12]

The significance of the method is in the fact that by comparing the tumour infiltration of the wall and the intact rectal wall with the preserved layers, it is possible to determine the preoperative staging of rectal cancer according to Hildebrandt 1988.[13]

With ultrasound it is possible to differentiate three levels of invasion (Figure 1):

T1: Tumour confined to the mucosa and submucosa

T2: Tumour confined to the muscle wall up to serosa

T3: Tumour that perforates the rectal wall penetrating into the perirectal fat tissue.

Before making the decision between surgery or paliative treatment and other methods (conventional ultrasound, CT) with patients suffering from rectal cancer, it is necessary to ascertain whether the cancer has penetrated into adjacent organs, whether it has metastatised to the lymph nodes or distant organs (T4 stage). The complete workup of rectal cancer patients makes possible to choose the optimum therapy depending on the stage of the disease according to Hildebrandt 1989:[2]

T1–T2,N0 – local excision
T1–T2,N1 – resection or excision
T3–N0 – radical resection or excision
T3–N1 – radical resection and adjuvant therapy.

This experience, although modest, goes to confirm the well known values of the rectal endosonography mentioned in the literature for the complete and precise workup of rectal cancer patiens. Distinguishing between the T1 and T2 stages is, in our experience, highly dependable. While determining stage T3 is less reliable as 25 % of the patients examined classified as stage T3, had already the adjacent organs affected or had distant metastases, the determining of T4 stage was questionable as welle. The cause of this problem must be partly in the fact that the 7,5 MHz probe yields ultrasonic images to the depth of 5–8 cm, which in some instances will not be sufficient. Another cause is the linear transducer, requiring patient and careful manual rotating of the whole probe, when analysing the tumour.

The results obtained by means of the transrectal sonography with rotational transducer are no doubt even better and more dependable than ours, but on the whole the transrectal sonography with the linear transducer of 7,5 MHz can be considered a good and invaluable examination method.

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Ultrasonography in the staging of urinary bladder tumors

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A total of 67 patients with 86 bladder tumors underwent ultrasonographic examination with transurethral, transabdominal and transrectal probe in an attempt to evaluate its accuracy in the staging of bladder tumors. All tumors diagnosed by ultrasonography were divided into three groups according to the final histopathological diagnosis: (U1) superficial, (U2) muscle invasive tumors and (U3) tumors with perivesical extension. The findings were compared with computed tomography results in the staging of bladder carcinoma. High staging accuracy and low cost confirmed the importance of ultrasonography in staging of bladder carcinoma.

Key words: bladder neoplasms-ultrasonography; computed tomography; neoplasms staging

Introduction

In 80% of bladder carcinoma the lesion is superficial, confined either to the mucosa or lamina propria. Althought two out of three of these patients remain at risk for recurrent disease, their malignancy never becomes invasive and poses a problem only in local management.[1]

Preoperative staging of bladder cancer continues to be important in the management of this urologic tumor. Endoscopy is useful to detect and to assess bladder tumors but problems arise because tumor staging by this technique alone is inaccurate. Computerd tomography is helpful to demonstrate extension of the tumor beyond the bladder but it cannot show the depth of invasion in the bladder wall.[2] Staging is of fundamental importance for choosing a therapeutic program, be it by surgery, chemotherapy or radiotherapy. We herein attempt to evaluate the accuracy of ultrasound in assesing bladder neoplasms.

The purpose of our research is to evaluate the accuracy of UZ by transrectal, intravesical and transabdominal aproach and CT in staging of bladder neoplasms.

All the patients underwent transurethral biopsy as an initial procedure which was followed by more extensive resection for patients with superficial disease or segmental resection or cystectomy for those with more invasive or diffuse tumors.

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Patents and methods

The total number of separate tumors in our 67 patients was 86. Fifty two patients had only one and 15 had multifocal tumors.

We evaluated 49 men between 37 and 85 years, and 18 women between 35 and 86 years in the period of three years.

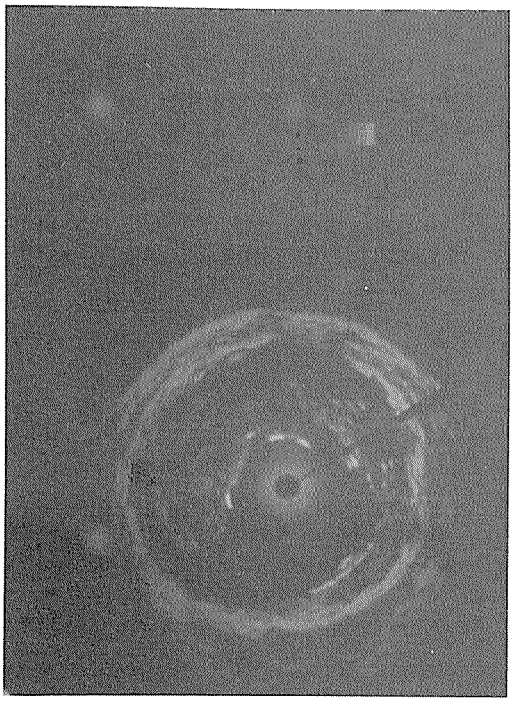

Figure 1a. Transurethral ultrasound scan of urinary bladder demonstrates voluminous vegetative process with complete invasion of bladder wall.

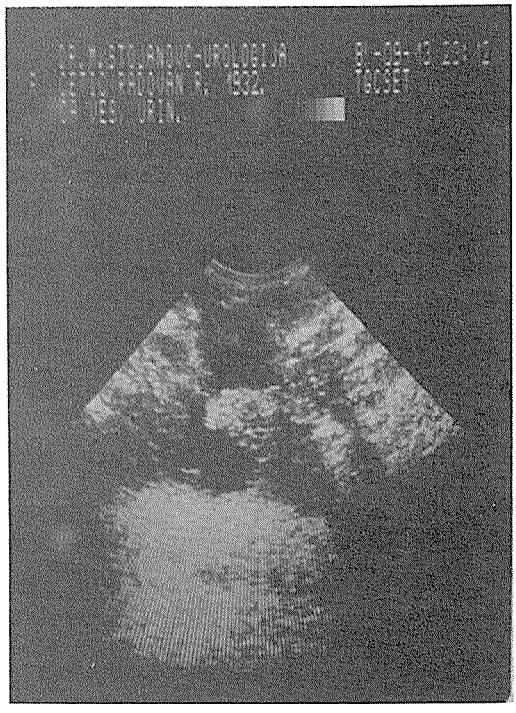

Figure 1b. Transabdominal ultrasound scan of urinary bladder demonstrates voluminous vegetative process with complete invasion of bladder wall.

Tumors varied in size from 0,5 cm to a 10 cm tumor mass. The equipment used was Kretz Combison 111S gray scale scanner and three probes:

Transurethral ultrasound scanning (Figure 1a), is otherwise performed as an integral part of urethrocystoscopy. The optic viewer is removed from the cystoscope and replaced by the scanner. When the scanner is in its place the bladder is distended with fluid, the scanner is started and a dynamic sectional image of the bladder is viewed on the screen. While the scanner is moved back and forth and angulated, different sections of the bladder are visualized in sequence. 6 Mhz probe with focusing depth 45 mm, axial resolution 0,2 mm and lateral resolution 0,5 mm is used. 45 and 90 degree transducer for general use and 135 degree transducer for retrograde imaging of the area around the bladder neck is used.

The transabdominal probe (Figure 1b), in the surveillance of bladder Ca is performed on patients in supine position with a full bladder. 3,5 Mhz probe with focusing depth 80 mm, axial resolution 0,4 mm and lateral resolution 0,9 mm is used in transverse, longitudinal and oblique position.

Transrectal probe (Figure 1c) with high frequency transducer (5 and 6 Mhz) with focusing depth 50 mm, axial resolution 0,2 mm and lateral resolution 0,5 mm is used. Transrectal probe is made of 2 parts; an outer stationary unit provides inflow and outflow parts for the fluid interface and a polyethylene cover to protect the rectal mucosa. The inner assembly is free to move in logitudinal and rotational directions. Prior to rectal insertion the transducer is covered with rubber condom which is filled after insertion with approximately 50 ccm water until it is air tight against the rectal mucosa. The probe is lubricated with a suitable coupling agent, such as Xylocain 2 % jelly and it is inserted with the patient in the lithotomy position. The probe is passed gently 8 to 9 cm above

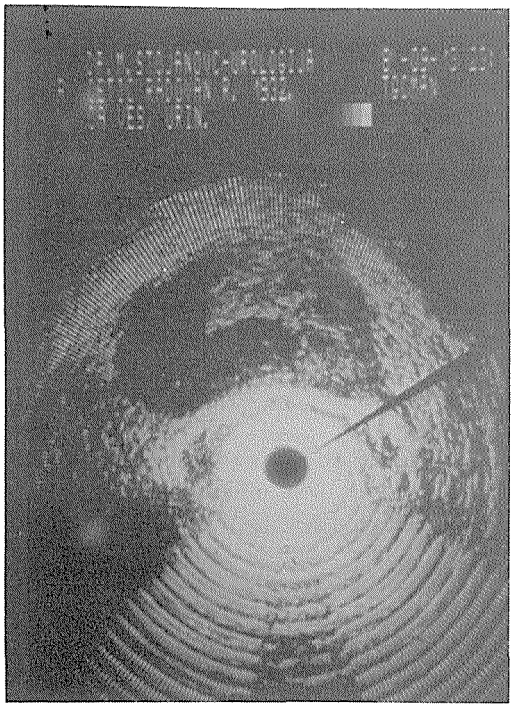

Figure 1c. Transrectal ultrasound scan of urinary bladder demonstrates voluminous vegetative process with complete invasion of bladder wall.

the anal verge.

The ultrasonic examination of bladder tumor displays following factors:

– interruption or irregularity of bladder wall echo with an echogenic mass projecting into the lumen of the echo free urinary bladder;

– diminishing of the echo-intensity of bladder wall due to the hypodense tumor echo;

– thickening of the bladder wall;

– small capacity of the bladder;

– tumors that infiltrate the deeper layers of the bladder may produce a decrease in echo intensity of the muscle and result in the loss of wall mobility, depending on the extent of invasion;

– diminished signal from the perivesical fat-evidence of extension of tumor into the perivesical fat.

CT scans (Figure 2) were performed in 10 mm sections in supine position, using Siemens Somatom SF. Bladder distension was obtained by gas insufflation for a better evaluation of the

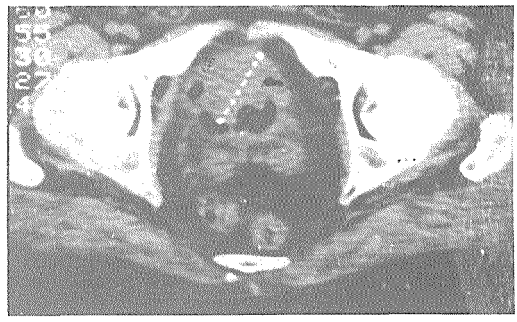

Figure 2. Computed tomography scan of pelvis demonstrating infiltrative bladder tumor.

bladder tumor. Additional CT scans were performed from the iliac crest to the perineal area in order to assess lymphonode involvement of the pelvis and prostate.

Histological sections were stained with hematoksilin and eosin, and examined by light microscopy.

From a total of 86 tumors, 65 superficial or minimally invasive were treated by transurethral resection and 21 infiltrative tumors were treated by radical or partial cystectomy.

All tumors were staged by means of the TNM classification of the UICC, and each staging was compared with its ultrasound appearance in order to establish whether or not there was any reliable correlation between the two.

Because it was not possible by ultrasound to distinguish between T1S, Ta and T1 tumors these categories were included with T1 in the same ultrasound staging category – U1.

Tumors with superficial muscular infiltration (T2), deep muscular infiltration (T3a) and extravesical extension (T3b) are included in the same category – U2.

U3 category includes T4a and T4b tumors according to TNM classification of bladder tumors.

The distuinguishing between tumors with or without muscle infiltration should lead to adequate treatment.

Results

Intravesical ultrasonography

Table 1. demonstrates the correlation between

Table 1. Correlation of transurethral ultrasonography and histologically determinated T-category.

	U1	U2	U3	TOTAL
pT1	32	9	–	41
pT2/3	7	23	–	30
pT4	–	3	12	15

In pT1 category with transurethral ultrasonography 78,0 % tumors are correctly staged and 21,9 % are overstaged.

In pT2/3 category with transurethral ultrasonography 76,6 % tumors are correctly staged and 23,3 % are understaged.

In pT4 category 80,0 % are correctly staged and 20,0 % are understaged.

Table 2. Correlation of transabdinominal ultrasonography and histologically determinated T-category.

	U1	U2	U3	TOTAL
pT1	30	11	–	41
pT2/3	10	20	–	30
pT4	–	5	10	15

In PT1 category with transabdominal ultrasonography 73,1 % tumors are correctly staged and 26,8 % are overstaged.

In pT2/3 category with transabdominal ultrasonography 66,6 % tumors are correctly staged and 33,3 % are understaged.

In pT4 category 66,6 % are correctly staged and 33,3 % are understaged.

the transurethral ultrasonography (indicated by U) and the histological pT category. Bladder findings were subdivided in three groups with reference to the extent of diffusion of the bladder tumor.

There were 41 tumors of pT1 pathological stage and in 32 in tumors we found conformity between transurethral ultrasound and histological findings.

30 tumors of pT2 and pT3 categories showed confirmity in 23 cases.

15 tumors of pT4 showed conformity in 12 cases.

We have calculated the test sensitivity and test specifity of transurethral ultrasonography in distinguishing muscle infiltration from muscle non infiltrating tumors. In 38 out of 45 tumors in the pT2 to pT4 categories, we correctly identified the infiltrative growth wiht sonography. This indicates the specifity test of 0,82. With tranusrethral probe we were able to rule out muscle infiltration in 32 out of 41 carcinoma which had been determined as non infiltrative by histology. This indicates a sensitivity of 0,78.

Transabdominal ultrasonography

Table 2. demonstrates the correlation between the transabdominal ultrasound T category (U) and the histological pT category.

In 35 out of 45 tumors in the pT2 to pT4 categories, we correctly identified the infiltrative growth with transabdominal ultrasonography. This indicates test specifity of 0,80.

We were able to rule out muscle infiltration in 30 out of 41 carcinomas which had been determined as non infiltrative by histology. This indicates a sensitivity of 0,73.

Transrectal ultrasonography

Table 3. demonstrates the correlation between the transrectal ultrasound T category (U) and the histological pT category. In 34 of out 45 tumors in the pT2 to pT4 categories, we correct-

Table 3. Correlation of transrectal ultrasonography and histologically determinated T-category.

	U1	U2	U3	TOTAL
pT1/	31	10	–	41
pT2/3	11	17	2	30
pT4	–	4	11	15

In pT1 category with transrectal ultrasonography 75,6 % tumors are correctly staged and 24,3 % are overstaged.

In pT2/3 category with transrectal ultrasonography 56,6 % tumors are correctly staged, 36,6 % are understaged and 6,6 % are overstaged.

In pT4 category 73,3 % are correctly staged and 26,6 % are understaged.

ly identified the infiltrative growth with transrectal probe. This indicates the specifity of 0,74. We were able to rule out muscle infiltration in 3 out of 41 carcinomas which had been determined as non infiltrative by histology. This indicates a sensitivity of 0,75.

Computed tomography

Table 4. demonstrates the correlation between the computed tomography category (non-invasi-

Table 4. Correlation of computed tomography and histologically determinated T-category.

CT	non infiltrativ tm	infiltrativ tm	advanced tm	TOTAL
pT1	30	11	–	41
pT2/3	5	23	2	30
pT4	–	2	13	15

In pT1 category with computed tomography 73,1 % tumors are correctly staged and 26,8 % are overstaged.

In pT2/3 category with computed tomography 76,6 % tumors are correctly staged, 16,6 % are understaged and 6,6 % are overstaged.

In pT4 category 86,6 % are correctly staged and 13,3 % are understaged.

ve, invasive, perivesical infiltration) and the histological pT category. In 40 out of 45 tumors in the pT2 to pT4 categories, we correctly identified the infiltrative growth with CT. This indicates the specifity test of 0,88. We were able to rule out muscle infiltration in 30 out of 41 carcinomas which had been determined out as non infiltrative by histology. This indicates a sensitivity of 0,73.

Discussion

According to our investigation, staging of pT1 category has a rate of overstaging, between 28 % and 37 % performed by three methods of ultrasound and CT.

pT2/3 category tumors were associated with an understaging error from 21 % to 64 %.

pT4 category tumors had the greatest staging accuracy which is in correlation with investigations of other authors.[3]

The overstaging observed in this study was mostly caused by difficulty in distinguishing submucosa from the muscularis, owing to contiguous normal extravesical structures, and because of the thickening of the bladder wall.

Sonographical overstaging can have different causes:

1. Sound-absorbing, especially calcied tumors can produce a sound-shadow that simultated a wall infiltration.

2. Scar tissue resulting transurethral operations sometimes possesses an echo structure similar to the tumor tissue.

3. Trabecule often give the impression of bladder tumors on ultrasound.

Most authors believe that transabdominal ultrasound is of great value in staging bladder tumors, especially those located on posterior or lateral walls.[4, 5]

In our investigation transabdominal ultrasound was performed before cystoscopy. The cystoscopic examination was carefully directed to the suspected sonographic area, reducing in this way the possibility of false-negative cystoscopic results.

Accuracy of detection of bladder tumors by transabdominal ultrasound depends on their position. When the pathological process affects the dome and/or neck of the bladder, suprapublic ultrasound has has lower accuracy of detection.

In our investigation transurethral ultrasound permits perfect differentiation between Ta-T1 and T2-T4 tumors. But transurethral ultrasound cannot be viewed as an isolated diagnostic technique and should be evaluated in its proper place in accordance with the established diagnostic work-up of bladder cancer.[6]

If transurethral ultrasound cannot clarify perivesical tumor growth in andvanced categories, then transrectal ultrasound can be used in addition to investigate the suspected infiltration.

CT fails to match the staging accuracy in early invasive tumors but is most common modality used to make lymph node assessment in the staging of bladder tumors.[7–9] Transurethral and transrectal ultrasound has proved to be of no value in the assessment of pelvic lymph nodes and its only role appears to be in the evaluation of the primary tumor. For the recognation of lymph nodal diffusion, information obtained from transabdominal ultrasound is unsatisfactory, and only CT can be proposed for such a role.[5, 10]

According to our protocol of bladder tumors diagnosis, we use cystoscopy with transurethral ultrasound as an integral method and transrectal

and transabdominal ultrasound as an additional examination.

Cystoscopy with transurethral ultrasound is also a possible method for following up endoscopic operated bladder tumors.

Ultrasound has established accuracy in assessment of the depth of infiltration of the bladder tumors but in evaluation of pelvic lymphs nodes we use CT as the most common modality for this purpose.

Current experience indicates that NMR has not been significantly better than CT in differentiating invasion of the bladder wall. NMR may be better in detecting tumor invasion of perivesical fat,[11, 12] but it does not appear to be any more helpful in staging of bladder tumors.[13, 14]

Recent investigation made by Tanimoto which were performed by gadolinium – enhanced Dynamic MR Imaging show that we can expect more accuracy in staging of bladder carcinoma by using this method.

Gadolinium – enhanced Dynamic MR Imaging has staging accuracy of bladder tumors 85% (73 of 86), which is significantly (better than CT in the same investigation: 55% (47 of 86).[15]

In conclusion, we can say that ultrasound used by all the three methods in staging of bladder carcinoma has nearly as good accuracy as CT and NMR but ultrasound methods have the advantage of low cost.

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Normal data base for quantitative salivary gland scintigraphy

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The purpose of this study was to establish a normal data base for quantitative salivary gland scintigraphy. Prior to routine thyroid scintigraphy 166, patients without any evidence of salivary gland malfunction underwent standardized salivary gland scintigraphy after intravenous injection of 31.0 – 83.8 MBq Tc-99m-pertechnetate. The uptake was calculated in percent of the dose injected (%ID) for parotid and submandibular glands at 13 min p.i.. After application of lemon juice p.o. as sialogogue, excretion fraction (EF) at 18 min p.i. was expressed as percent of the uptake. Data were analyzed separately for three age subsets. A somewhat higher uptake could be shown in patients aged > 60 yrs. No further age dependent differences could be detected as far as uptake and EF is concerned, therefore, all patients were pooled. Uptake was 0.42±0.16 %ID, and 0.36±0.13 %ID in parotid gland and submandibular gland, and EF of parotid gland and submandibular gland amounted to 47.4±11.7 % and 37.4±9.8 %, respectively. In conclusion, a reliable normal data base for quantitative salivary gland scintigraphy is now available.

Key words: salivary glands-radionuclide imaging; quantitative salivary gland scintigraphy; normal data base, uptake, excretion fraction

Introduction

Salivary gland scintigraphy has been an established method in clinical practice to investigate both parenchymatous and excretory function of parotid and of submandibular glands for almost 30 years.[1–12] Numerous investigators established normal values for the excretion fraction[13–19] in order to quantitatively describe impaired saliva flow due to obstruction. On the other hand, parenchymatous function is much more difficult to quantify. Therefore, various (semi)quantitative methods were described, i.e. scoring the shape of time-activity curves,[12, 20–23] time-to-maximum uptake,[24, 25] ratios of salivary gland uptake calculated either to background activity,[18, 26] to serum activity[27, 28] or to the uptake of the thyroid gland,[20] slope of the time-activity curves,[25, 29] or calculation of rate constants.[25] None of these methods gained relevance in routine salivary gland scintigraphy today possibly due to their sophisticated nature.

However, there are reports of a simple clinically feasable method in analogy to thyroid

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quantitative scintigraphy. Tracer uptake as a measure for parenchymatous function is expressed in percent of the injected dose.[13–17, 30–33] Unfortunately, neither inclusion nor exclusion criteria for patient selection are given in these papers. Moreover, their number of patients is rather limited.

Therefore, the purpose of this study was to quantitatively establish a normal data base regarding both uptake and excretion fraction in quantitative salivary gland scintigraphy in percent of injected dose form a large number of carefully selected normal patients. Parts of the results have been presented orally.[34]

Materials and methods

Patients

Prior to routine thyroid imaging, 485 patients underwent salivary gland scintigraphy. Informed written consent was obtained from all subjects. To rule out any influence on salivary gland function, patients were excluded for several reasons: xerostomia (n = 45), sialolithiasis (n = 78), history of either radioiodine therapy (n = 32), external radiation of the head/neck (n = 4), salivary gland tumour (n = 5), acute or chronic inflammation (n = 16), rheumatic disease (n = 58), perchlorate medication (n = 7), neuroleptic or antidepressant drugs with anticholinergic effects (n = 21), either sonographic (n = 46) or radiographic (n = 23) signs of obstruction or parenchymatous impairment. The accepted 166 patients were considered normal of which 39 were male, and 127 were female ranging from 18 to 81 years. Patients were divided into three age subsets. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics.

Group	age		n	f/m
	range	mean ± SD		
I	18–40	31.5±6.4	28	21/7
II	41–60	51.9±5.2	69	52/17
III	61–81	69.4±4.8	69	54/15
Total	18–81	55.8±14.5	166	127/39

Salivary gland scintigraphy

After intravenous injection of 53.9±10.5 MBq Tc-99m-pertechnetate, ranging from 31.0 to 83.8 MBq sequential images of 1 min each were acquired for 25 min with a conventional large field-of-view gamma camera (Searle Pho/Gamma, Nuclear Chicago Division, Chicago, USA) with a parallel hole LEAP collimator in anterior position as close as possible to the patients head, which was slightly reclined. Images were stored in a 128 × 128 matrix. Excretion of saliva was caused by 3 ml of diluted lemon juice given perorally 15 min p.i. from the patients left side. Five regions of interest (ROI) were used (Figure 1): one rectangular ROI in the brain, which served as backround ROI, and four irregular ROIs over the respective parotid and submandibular salivary glands. In each patient uptake of parotid and submandibular glands was calculated in percent of the dose injected (%ID), using a calibration factor between gamma camera (counts per minute) and activimeter (MBq). For compensation of noise and, thus for stabilization of data, uptake was calculated as mean of uptake from 12–14 min after

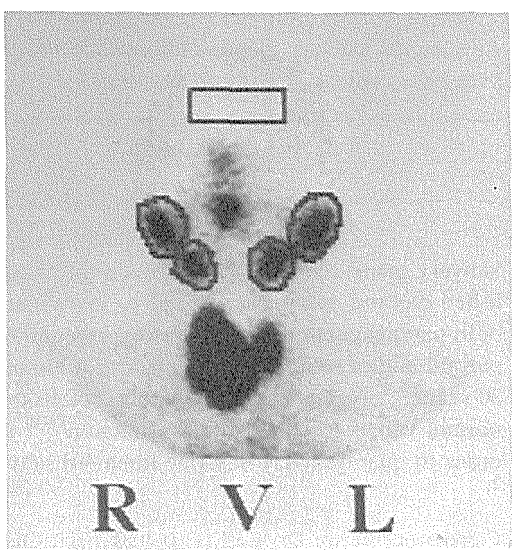

Figure 1. Illustration of the ROI technique used for quantitative salivary gland scintigraphy. Observe, four irregular salivary gland ROIs and a single, common rectangular background ROI over the brain.

subtraction of background activity from a ROI in the brain, and excretion fraction (EF) was calculated from mean activity at 17–19 min p.i., and was expressed as percent of the uptake measured. From both uptake and EF data left-to-right (L/R) ratio was calculated for each individual patient. Moreover, background-corrected time-activity curves were obtained from the salivary gland ROIs.

Statistics

All data were checked for Gaussian normal distribution using Kolmogoroff-Smirnoff test for $n > 50$ and Lilliefors modification of the Kolmogoroff-Smirnoff test for $n < 50$.[35] In all subsets normal distribution could be shown, consequently, results are given as mean ± one standard deviation. Two-tailed unpaired students t-test was used to evaluate statistical differences between subsets, with $p < 0.05$ considered to be statistical significant.

Results

Uptake

There was no sex difference in tracer uptake. Therefore, all patients were pooled. Original data of Tc-99m-pertechnetate uptake in major salivary glands is shown in Figure 2. After pooling data of all patients uptake was about 0.42 %ID and 0.36 %ID in parotid and submandibular glands, respectively. Visually, uptake seemed to be somewhat higher in elderly people. Therefore, uptake was calculated separately for three subsets as given in Table 2, and uptake data was tested for statistical significant differences. In fact, a significant difference in

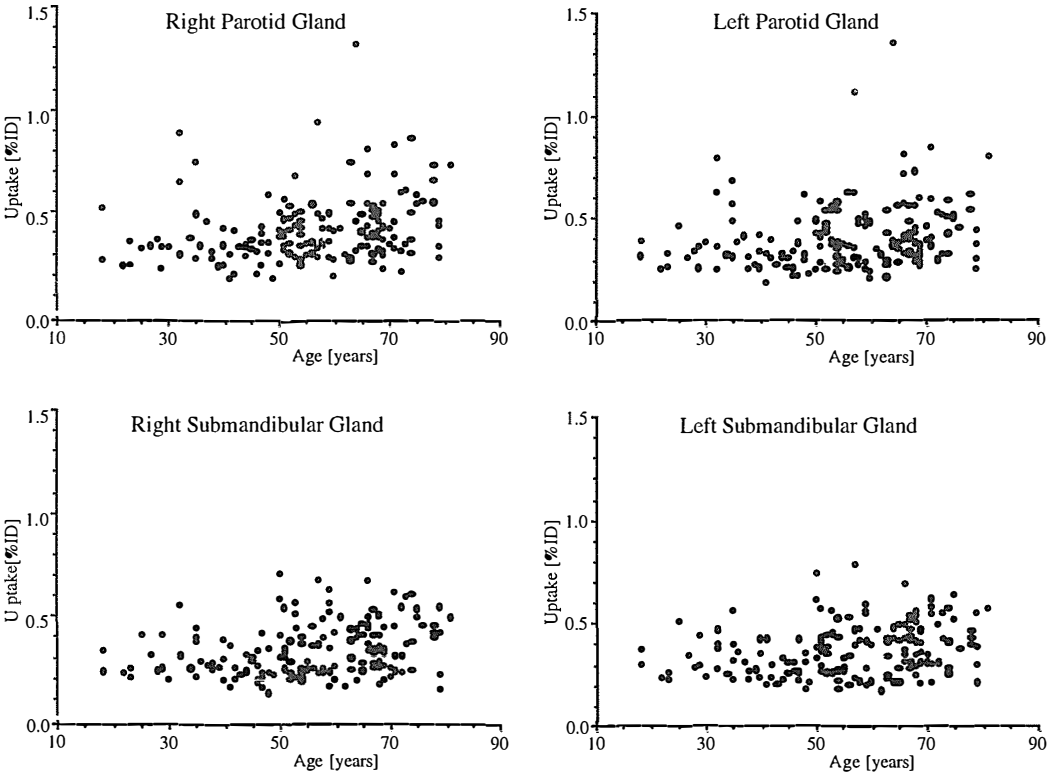

Figure 2. Original data of Tc-99m-pertechnetate uptake in major salivary glands expressed in percent of the activity applied. Pooled data of 166 patients.

Table 2. Normal values of pertechnetate uptake expressed as percent of injected dose in salivary glands. Data is given both for subsets and for all patients pooled (total). I: 18–40 yrs, II: 41–60 yrs, III: 61–81 yrs.

Group	Uptake [%ID]			
	RPG	LPG	RSG	LSG
I	0.40±0.15	0.38±0.14	0.32±0.09	0.32±0.09
II	0.40±0.12	0.38±0.15	0.34±0.13	0.34±0.14
III	0.48±0.18	0.45±0.18	0.40±0.12	0.40±0.12
Total	0.43±0.16	0.41±0.16	0.36±0.13	0.36±0.13

RPG, LPG: right, left parotid gland. RSG, LSG: right, left submandibular gland.

uptake could be shown between patients aged > 60 yrs. as compared to younger patients in age less than 60 yrs. (II vs. III). Patients being younger than 40 yrs. showed less pertechnetate uptake than patients aged > 60 yrs. (I vs. III) as well, but no significant differences could be detected between subsets I and II, their uptake values being almost identical.

Excretion fraction

Original data of excretion fraction in major salivary glands is shown in Figure 3. No differences could be detected between subsets as indicated by EF data given in Table 3. EF was about 47% in parotid glands, and 37% in submandibular glands when pooling all data.

Left-to-right ratio

Detailed data of L/R ratios of uptake and EF as calculated for the subsets and for all patients pooled is given in Table 4. In all subsets the marginally higher uptake in the right parotid glands was statistically insignificant. In contrast, L/R ratios of almost exact one were determined for the uptake in submandibular glands. As far as EF is concerned, L/R of parotid and subman-

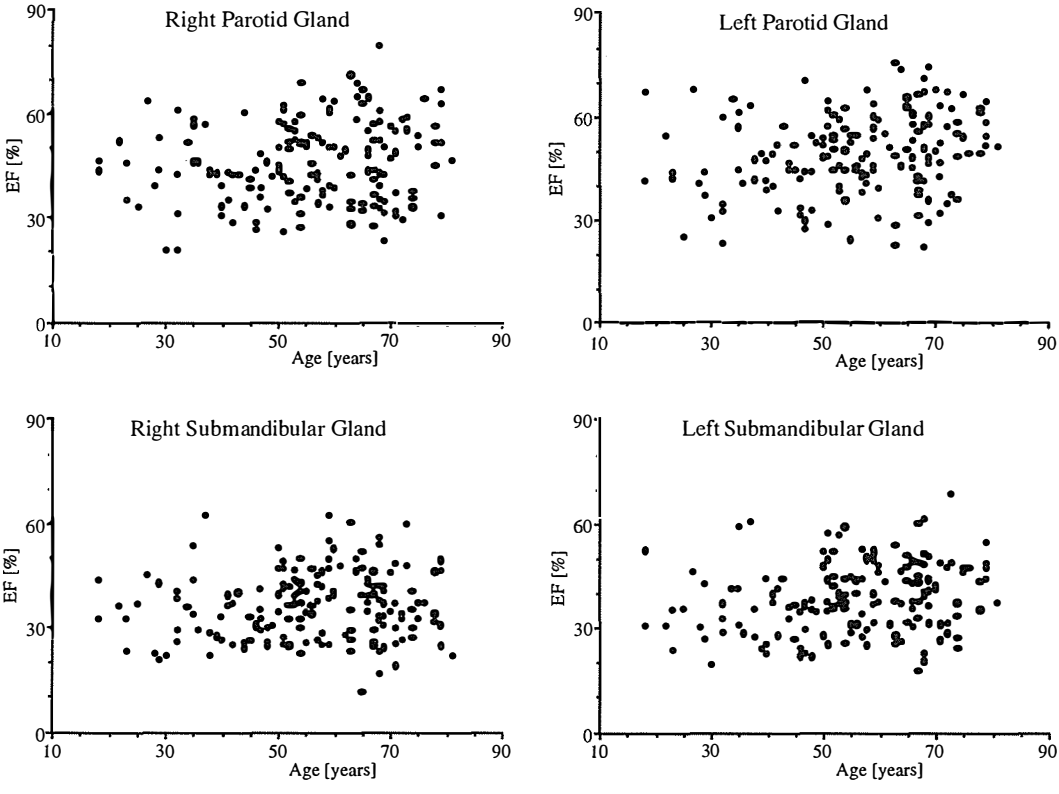

Figure 3. Original data of excretion fraction of major salivary glands expressed in percent as referred to the uptake. Pooled data of 166 patients.

Table 3. Normal values of excretion fraction expressed in percent as referred to the uptake in salivary glands. Data is given both for subsets and for all patients pooled (total). I: 18–40 yrs, II: 41–60 yrs, III: 61–81 yrs.

Group	Excretion fraction [%]			
	RPG	LPG	RSG	LSG
I	44.2±11.0	46.2±12.0	34.3± 9.7	35.3±10.3
II	45.6±10.3	47.1±10.0	36.9± 8.9	38.4± 9.1
III	46.9±12.7	51.5±12.6	36.9±10.1	39.2±10.4
Total	46.0±11.5	48.8±11.7	36.5± 9.6	38.3± 9.9

RPG, LPG: right, left parotid gland. RSG, LSG: right, left submandibular gland.

dibular glands was found to be above 1 in all subsets with a tendency to somewhat higher values both in elderly people and in parotid glands, i.e. L/R of EF was calculated as 1.15 in parotid glands of patients aged > 60 yrs., while L/R of EF in submandibular glands in patients less than 40 yrs. was about 1.04. However, statistical differences of EF in right and left parotid gland could be shown for EF in subgroup III (61–81 yrs.) only. In subgroup II (41–60 yrs.) we just failed to show a difference with $p = 0.053$. In no other subgroup statistical differences between right and left glands could be shown concerning EF.

Table 4. Left-to-right ratios (L/R) both of uptake and of excretion fraction given separately for parotid gland (PG) and submandibular gland (SG). Data is given both for subsets and for all patients pooled (total). I: 18–40 yrs, II: 41–60 yrs, III: 61–81 yrs.

Group	Uptake		Excretion fraction	
	L/R PG	L/R SG	L/R PG	L/R SG
I	0.95±0.12	1.01±0.13	1.06±0.21	1.04±0.18
II	0.96±0.15	1.00±0.16	1.06±0.23	1.06±0.18
III	0.94±0.14	1.00±0.16	1.15±0.38	1.10±0.29
Total	0.95±0.14	1.00±0.15	1.10±0.30	1.07±0.23

Time-activity-curves

Time activity curves of major salivary glands

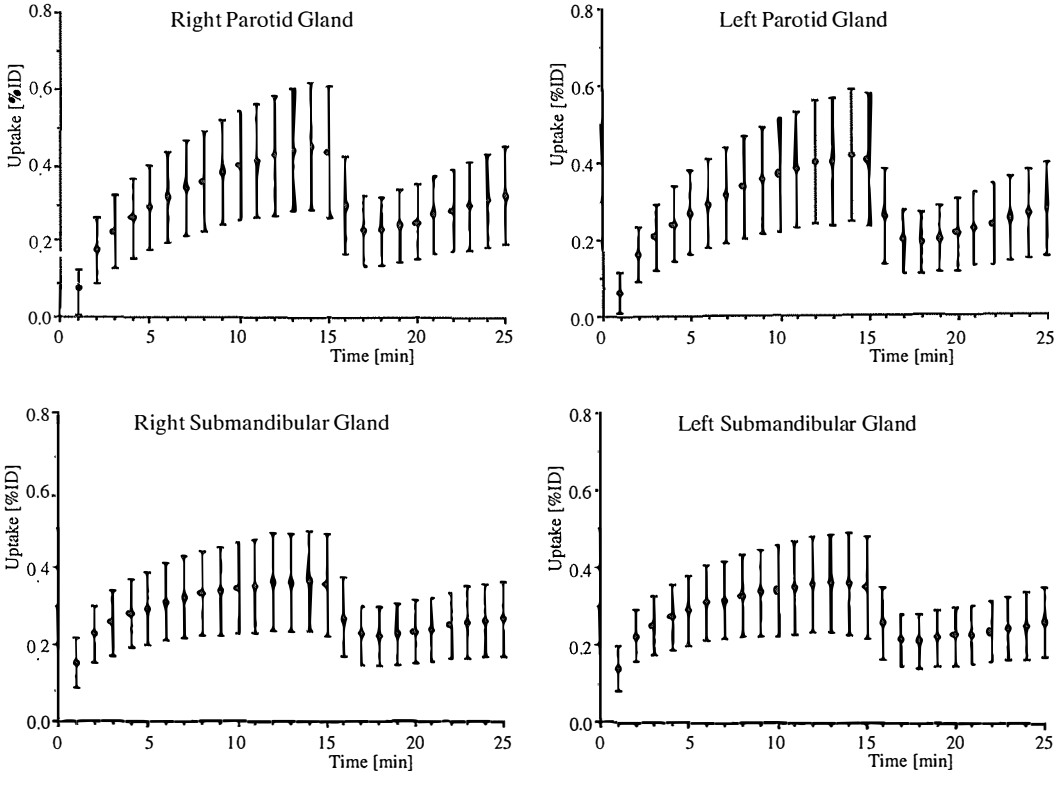

Figure 4. Time-activity-curves of Tc-99m-pertechnetate uptake of major salivary glands. Mean ± one standard deviation of 166 patients.

showing mean ± one standard deviation of all patients pooled are shown in Figure 4.

Discussion

Methodology

Basically, there are two methods to obtain normal values, i.e. the inductive and the deductive way.[36] When determining normal values in an inductive way, healthy normal subjects have to be selected for investigation out of the whole population. Both for ethical reasons and for reasons of radiation protection radioactive substances must not be injected in healthy subjects without thorough clinical indication. Therefore, in this study normal values were obtained in a deductive way. In patients who were referred for thyroid imaging salivary gland scintigraphy was performed prior to thyroid scintigraphy. However, all patients who were suspected to have impaired salivary gland function had to be excluded from statistical evaluation. This was done for following reasons: xerostomia,[2, 9, 12, 20, 22, 31, 37] sialolithiasis,[4, 11, 18, 37] history of either radioiodine therapy,[3] external radiation of head/neck,[10] salivary gland tumour,[4, 5, 8, 11, 38] acute or chronic inflammation,[7, 13] rheumatic disease,[2, 9, 12] perchlorate medication,[1, 37] either neuroleptic or antidepressant drugs with anticholinergic effects,[37, 39–41] either sonographic or radiographic signs of obstruction[4, 8, 18, 23] or parenchymatous impairment.[2, 8, 9, 12] Therefore, quantitative values obtained in this study reflect salivary gland function of normals, and thus, can be ascribed to be a reliable normal data base.

The background ROI was positioned close to the salivary glands by others.[16, 31] The advantage might be a more accurate estimation of the true background activity. However, this ROI technique is rather difficult to standardize during routine patient management. For simplicity, we selected a single, common background ROI for all four salivary glands (see Figure 1). In patients with complete destruction of parenchymatous salivary gland function the uptake values amounted to approximately zero, as shown elsewhere.[42] Thus, this ROI located in the brain seems to be appropriate for background estimation of the salivary glands.

Excretion of saliva can be stimulated by the application of several drugs, e.g. subcutaneous injection of carbamoylchloride,[18, 25] or by peroral application of either tartraic acid,[12] pilocarpin as a parasympathomimetic drug[14, 15] or even by sugar.[38] However, for patient's convenience and due to both its lack of undesired side effects and its equal efficacy as compared to parasympathomimetics we chose diluted lemon juice to increase excretion of saliva.[29]

L/R ratio of pertechnetate uptake in parotid and submandibular glands was calculated as of approximately one, whereas L/R ratio of EF was systematically above 1. This was more pronounced in elderly people as given in table 4. In case of sufficient patient selection a L/R ratio near unity is expected, however, L/R ratios of up to 2.5 were observed by others.[16] In our study, lemon juice was given by the technologist from the patient's left side. Patients were told to turn the lemon juice around in the oral cavity in order to reach a homogenous excretion in all four major salivary glands. However, this obviously depends on patient's compliance. Therefore, this artifact, observed especially in elderly people, should be kept in mind in routine salivary gland scintigraphy.

Normal data base

Quantitative measurement of parenchymatous function has been performed in various way, e.g. calculation of time-to-maximum uptake,[24, 25] ratios of salivary gland uptake calculated either to background activity,[18, 26] to serum activity[27, 28] or to the uptake of the thyroid gland,[20] obtaining the slope of the time-activity curves,[25, 29] or calculation of rate constants.[25] None of these methods is easy to handle, and in consequence none of them has become a relevant method in routine salivary gland scintigraphy today. Therefore, salivary gland scintigraphy in work-up of patients suffering from impaired parenchymatous function, e.g. Sjögren's syndrome is performed usually in a qualitative manner. However, a reliable quantita-

tive measure of parenchymatous function would be helpful for the clinician especially when impairment is just beginning. In addition, this measure should be easy to handle. In analogy to well established state-of-the-art quantitative thyroid scintigraphy[43, 45] some authors reported on quantitative salivary gland scintigraphy calculating the uptake of pertechnetate expressed in percent of the injected dose. Details of their data are given in Table 5. However, none of them reported in detail on their criteria of patient selection. This could be the reason for varying uptake values ranging from 0.30 %ID[16] up to 0.83 %ID.[14, 15] Most authors evaluated somewhat higher uptake values than calculated in this study. However, in these studies[13–15, 17, 32] salivary gland scintigraphy was performed in an one hour protocol, thus, uptake was calculated between 40 and 50 min post injection. It is known that uptake in salivary glands depends on the interval from injection to calculation. Therefore, their data is not quite comparable to the uptake values obtained in this study. In two studies a 30 min protocol was used, and uptake was calculated at 13 min post injection yielding uptake values of 0.30 %ID[16] and 0.31 %ID[31] for parotid glands and 0.17 %ID and 0.18 %ID for submandibular glands, respectively. These data were based on 36 and 25 patients, and no detail can be found whether their scatter data indicate standard error or – most probably – standard error of mean. In our study at 13 min post injection uptake values of 0.42 % ID and 0.36 %ID were obtained for parotid and submandibular gland, respectively, basing on data of 166 clearly defined normals.

Scatter of uptake data varied in the literature from 0.10 % ID up to 0.45 %ID with numbers of patients ranging from 8 to 45 as given in table 5. Nevertheless, after reducing systematic scatter by well defined selection of patients reliable uptake data with reduced standard deviation can be obtained by an increased number of patients only.[35] Scatter data of pertechnetate uptake expressed as one standard deviation in our study based on 166 normals and amounted to 0.16 %ID and 0.13 %ID for parotid and submandibular glands, respectively. As could be expected, standard deviation of our data is less than observed from other authors.[14–17, 30–32] The value of this reduced standard deviation of our normal data base has already been proven by the detection of mild parenchymatous impairment in early Sjögren's syndrome.[42]

Many authors reported normal values for the exctretion fraction. EF is an established measure of functional obstruction of the salivary gland ducts, which can be used conveniently in daily clinical nuclear medicine.[13–19] Therefore, even lithothriptic treatment of lithiasis can be

Table 5. Quantitative salivary gland scintigraphy, as reported in the literature. Data represent mean of left and right gland expressed as mean ± one SD. min: time after injection of measurement of tracer uptake given in minutes.

		Parotid glands		Submandibular glands		
Reference	n	Uptake [%ID]	EF [%]	Uptake [%ID]	EF [%]	min
[13]*	n.g.	0.70±0.10	≈50	n.g.	n.g.	50
[15]	11	0.83±0.40	≈20*	n.g.	n.g.	45
[16]	36	0.30±0.02§	≈50*	0.17±0. 01§	≈8*	13
[17]	45	0.56±0.29	81.7±15.9	0.36±0. 15	75.0±19.5	50
[30]	8	0.35±0.11§	0.34±0.1§	n.g.	n.g.	30–35
[31]	25	0.31±0.02¶	n.g.	0.18±0.02¶	n.g.	13
[32]	9	0.75±0.45*	n.g.	n.g.	n.g.	40
[33]	44	0.40±0.15*	≈75*	0.38±0.10*	≈50*	60
own data	166	0.42±0.16	47.4±11.7	0.36±0.13	37.4±9.8	13

* estimated from their curves, though data not given explicitely.
§ ± SEM.
¶ probably ± SEM.
n.g.: data not given

evaluated quantitatively by the measurement of EF using salivary gland scintigraphy.[45]

Both uptake and excretion fraction are derived from time-activity curves. Sugihara and Yoshimura[12] and Mita and co-worker[46] have defined several curve characteristics of which type N was described as normal. Our time-activity curves (see Figure 4) are of this type N.

Conclusions

A normal data base for quantitative salivary gland scintigraphy as presented in this study regarding both pertechnetate uptake and excretion fraction allows reliable evaluation of salivary gland function within 30 minutes by an easy-to-perform routine method.

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Bone scintigraphy as a diagnostic tool in chronic inflammation of paranasal sinuses

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Bone scintigraphy as a part of diagnostic procedure was carried out in 38 patients with atypical signs of chronic paranasal sinusitis. In 18 patients, positive bone scan findings were obtained, in 8 patients the scintigraphic display of sinuses was characterised by slight asymmetry, whereas in 12 patients the findings were negative. Twelve patients were treated surgically. In 9 of them, a marked correlation among the X – ray, scintigraphic and histologic findings of sinus mucosa was observed, making the method a reliable diagnostic procedure in selected patients. The method has not been routinely used to date.

Key words: paranasal sinus diseases – radionuclide imaging; sinusitis

Introduction

Acute inflammation of the naso-paranasal region, especially with inadequate therapy administered can progress into chronic paranasal sinusitis. Chronic sinusitis can also develop from several consecutive inflammatory events. As a rule, acute inflammation is caused by viruses that provide a favourable support on the respiratory mucosa, for a mixed bacterial superinfection leading to chronicity.[1, 2] Numerous exogenous and endogenous factors also play an important role in the genesis of chronic paranasal sinusitis.[2]

Chronic paranasal sinusitis is manifested by nasal obstruction, discharge from the nose and headache with diurnal oscillations in severity and acute exacerbation of chronic inflammation.

Chronic sinusitis is usually quite simple to diagnose. In most patients it can be diagnosed using classical methods of examination. In some patients though, a diagnosis is by no means easy to make. This is so because the clinical picture of chronic sinusitis may occasionally be altered, primarily due to abundant use of antibiotics, which has urged clinicians to search for new non-aggressive diagnostic methods that will ensure a high percentage of diagnostic accuracy. Patients are willing to accept such methods of examination. An accurate diagnosis is a precondition for a proper decision between the conservative or surgical treatment of the disease.

At present, a great variety of diagnostic procedures are available for the diagnosis of chronic sinusitis. Obviously, only some of them should be chosen in each particular case, as mentioned above. A proper choice of the me-

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thods depends on the clinician's experience and skill.[3, 4]

In one selected group of patients with diagnoses made by means of classical methods and which often saw recurrence of the inflammation regardless of adequate antibiotic therapy, we performed bone scintigraphy in order to make a decision whether to proceed with conservative therapy or surgical treatment.

The crucial factor to the choice of surgical treatment was the involvment of bone wall in the inflammatory process which could not be seen without the performance of bone scintigraphy.

We have described our own experience with the use of bone scintigraphy. In general, this diagnostic procedure is less frequently used and therefore only few data on it are available in literature.[5-7]

Material and methods

Clinical examination, sinus X – ray and bone scintigraphy of facial bones were performed in 38 patients aged 18 – 64 years; 20 males and 18 females, all with atypical signs of chronic sinusitis. The bone scintigraphy was performed 3 hours after the intravenous administration of 740 MBq 99 m Tc-MDP (methylene diphosphonate). The thyroid was blocked by Irenate. Gamma camera General Electric, equipped with low energy, high resolution and parallel-hole collimator was used.

The bone scintigraphy of facial bones was performed in 5 projections – anteroposterior, straight and flexioned, posteroanterior and lateral profiles.

Results

The X – ray was considered positive when the sinuses were shaded marginally or diffusely.

The bone scan was considered positive when intensive accumulation of the radiopharmaceutical was seen at the sites of chronic paranasal sinusitis.

Only slight asymmetry in intensity of accumulation in paranasal sinuses was regarded as doubtful.

All 38 patients had positive X – ray finding.

Eighteen patients had positive scan finding, 12 patients had negative scan finding while in 8 patients it was doubtful.

Twelve patients from the study group were surgically treated, 9 of them with positive scintigraphic findings, 2 with doubtful scintigraphic findings, and one patient with negative scintigraphic finding.

In the patients with positive bone scintigraphy, who were surgically treated, a marked correlation was found among the paranasal sinus X – ray, scintigraphic finding and histologic finding of the sinus mucosa. (Figures 1–4).

In patients with doubtful bone scintigraphy, a similar correlation of the finding was observed, but histologically determined chronic mucosal alterations were less prominent. Respiratory epithelium was only partly damaged whereas stroma was affected by inflammatory cells. In patients with negative bone scintigraphy, a sinus mucocele was detected. The patients with positive bone scintigraphy and who refused surgery have been regularly controlled for frequent occurrence of acute sinusitis exacerbations.

Discussion and conclusion

If the diagnosis of chronic sinusitis can most frequently be made by using classical methods, i. e. good case history, rhinoscopy, sinus X – rays, ultrasonography, etc., the question is when to use bone scintigraphy then?[3, 4]

It has already been emphasized that the clinical picture of chronic paranasal sinusitis may be altered in some patients, i. e. in patients who describe typical symptoms of chronic sinusitis but present no characteristic signs of chronic inflammation. In such patients bone scintigraphy may prove very useful. The method is very sensitive and can display the sinus wall alterations earlier than the X – ray visualization.[5, 8, 11]

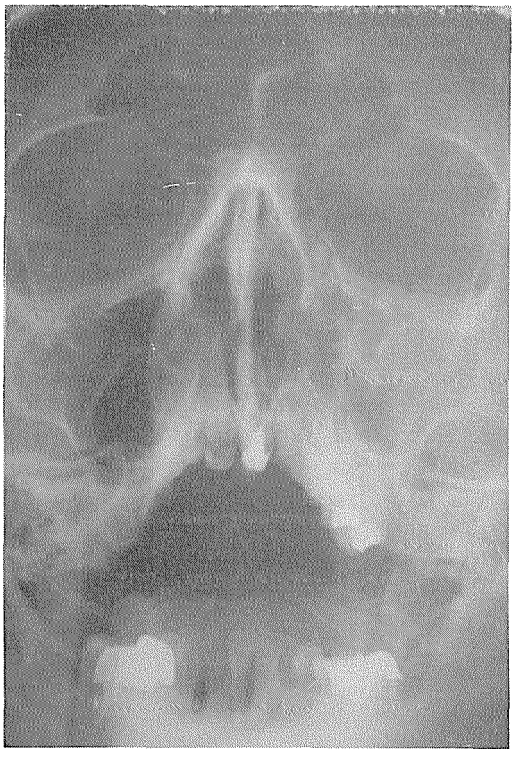

Figure 1. Intensively homogeneously shaded left maxillary sinus.

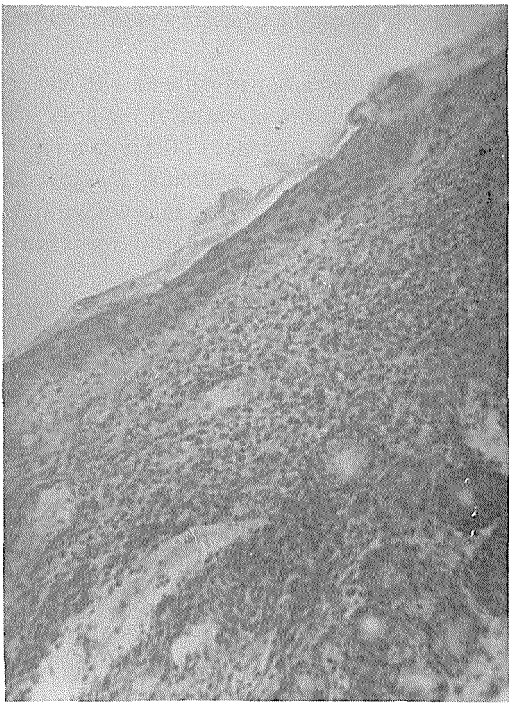

Figure 3. Histologic finding of sinus mucosa. Respiratory epithelium is damaged. Mucosa of edematous stroma pervaded with inflammatory cells. Visible seromucous glands and connective tissue. (H. E. 250x)

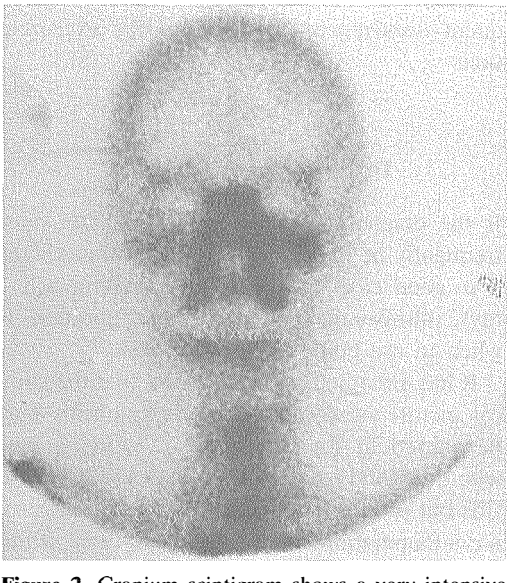

Figure 2. Cranium scintigram shows a very intensive and inhomogeneous accumulation of radioactive indicator in the left maxilla projection. The finding points to a dynamic remodelling in the region.

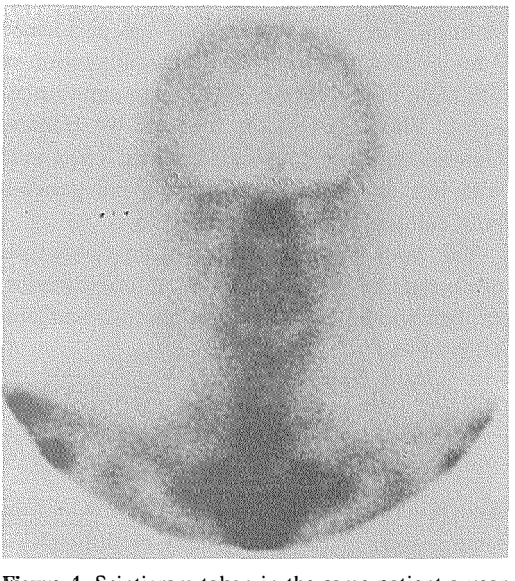

Figure 4. Scintigram taken in the same patient a year and a half after the surgery. A normal, symmetrical display of the maxillae can be seen.

Intensive accumulation of radioactive indicator suggests an intensive bone remodelling and, in part, enhanced perfusion, so that these data alone, appear to be of great importance for the determination of indicators for surgical treatment. These alterations cannot be seen on an X – rax.[10]

X – ray finding is a result of changes on the mucous membrane of the sinuses and only rarely can the co-existance of changes on the bone be perceived.

We analysed only the late static images of the bone scan which reflect bone remodelling.

The positive bone scan finding could be the result of the irritation of the chronic inflammatory process of the mucous membrane on the bone.

Sinusoscopy allows a direct observation of the sinus mucosa. A swab for bacteriological examination of a tiny fragment of mucosa for histology can also be taken, but a disadvantage of the method is that it is aggressive.[12] Apart from this, the extent to which the osseous sinus wall has been involved and whether it has been altered at all, cannot be assessed by sinusoscopy.

Sinus CT provides a very good insight into chronic alterations of the paranasal sinuses. 13 Magnetic resonance is certainly a method of choice in certain cases of chronic paranasal sinusitis, but is quite expensive and available only in large centers. Apart from the above mentioned, CT and MR are also morphological methods of examination. The positive bone scan is the result of metabolic changes which cause morphologic changes on X – ray, CT or MR a couple of weeks or months afterwards. Therefore, bone scintigraphy remains the method of choice in selected cases of chronic paranasal sinusitis. It is not routinely used but is well accepted by patients for it is a painless method.[6]

The only contraindications are pregnancy and the period of lactation. Breast feeding can be resumed 48 hours after the examination.

Therefore, considering our patients in whom a correlation among the paranasal sinus X – ray, bone scintigraphy and histology was observed, we are inclined to conclude that there are quite good reasons to single out bone scintigraphy with technetium from a variety of examinations available for the diagnosis of chronic paranasal sinusitis. It should be employed in those patients in whom other methodes have failed to reveal whether the sinus osseous wall has also been involved, or when no firm decision can be made between surgical treatment or further conservative therapy.

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Prognostic factors in breast cancer

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Prognostic factors in breast cancer comprise those characteristics of primary tumors on the basis of which we can predict the course of disease, and thus the prognosis of breast cancer patients. The established prognostic factors are tumor size, histological type and grade of malignancy, axillary lymph node involvement, and the presence of hormone receptors in the tumor. At present the primary treatment is planned with respect to these prognostic factors. Even though adjuvant therapy is accepted as standard care in primary breast cancer neither the particular therapeutic modalities involved nor the specific subset to which it should be directed are well defined. Therefore, we look for new prognostic factors the role of which in the prediction of recurrence and survival of breast cancer patients still needs to be confirmed. These include ploidy, tumor proliferation markers, growth factors and receptors, growth suppressor and antimetastatic genes, invasion markers, tumor angiogenesis and some others.

Key words: breast neoplasms; prognosis; established prognostic factors, putative prognostic factors

Introduction

Breast cancer is the most frequent cancer of females. In the last two decades, its incidence has been increasing throughout the world.[1, 2] According to the data of the Cancer Registry of Slovenia for 1991, it represented 19 % of all female cancers in Slovenia.[3] Breast cancer is also the leading cause of cancer-related death of females in the developed countries.[4] In the last decade, mortality due to breast cancer has decreased only by few percents so that almost a half of all patients still die from this disease. In the phase of distant dissemination, the disease becomes incurable.[5] Metastatic disease cannot be treated even by a high-dose chemotherapy combined with simultaneous bone-marrow transplantation or peripheral blood stem cell support, according to the schedule which was considered very promising a few years ago.[6] Therefore, research has been focused again on the search of a more effective primary treatment of breast cancer. Adjuvant systemic therapy has been found to improve the survival of patients with operable breast cancer.[5] Adjuvant therapy with cytotoxic drugs proved effective in patients with axillary lymph node involvement, while adjuvant hormonal therapy prolonged the survival of patients with hormone dependent tumors.[7]

The question remains, how to recognize the biologically more aggressive cancer at the time of diagnoses, and which are those properties of

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the primary tumor that help us to predict an unfavourable course of the disease, and select a more suitable treatment accordingly. We already know some of the primary tumor properties, the so-called established prognostic factors for breast cancer, according to which the primary treatment is planned in every patient.[8] The established prognostic factors, are as follows: tumor size, pathohistological type and grade of malignancy, axillary lymph node involvement, and the presence of hormone receptors in the tumor (Table 1).[9, 10] Axillary lymph node involvement is considered to be the prognostic factor with the highest predictive value. Already in the 60's, adjuvant chemotherapy was introduced into the primary treatment of patients with lymph node involvement. It has considerably improved the survival of these patients.[7] Nevertheless, in almost a half of the patients with axillary lymph node involvement metastatic disease will develop within few years following completed primary therapy. Furthermore, dissemination of the disease will also occur in a third of the patients without axillary lymph node involvement at the time of surgery.[7, 11]

Table 1. Established prognostic factors.

1. Tumor size
2. Axillary nodal status
3. Histopathology
4. Steroid hormone receptors

Table 2. Putative prognostic factors.

1. DNA-ploidy
2. Tumor proliferation markers
S-phase
Ki67
cyclin D_1
3. Growth factors and receptors
EGF (EGFR)
erb-B2 (p185)
4. Growth suppressor or antimetastatic genes
p53
nm23
5. Invasion markers
cathepsin D
μPA/PAI 1
stromelysin 3
6. Tumor angiogenesis

The need to better identify breast cancer patients who are at risk to develop a reccurrence and are likely to benefit from adjuvant therapy, and to spare others from treatment related side effects is spurring researchers to look for new prognostic indicators. Since their predictive value has not been exactly determined yet, these factors are called putative prognostic factors (Table 2).[12]

Established prognostic factors

Tumor size

Primary tumor size is an independent prognostic factor of operable breast cancer. The survival of patients with small tumors is better than the survival of those with large tumors.[13] Tumor size is also an important prognostic factor in patients with negative axillary lymph nodes, whose prognosis is generally better. Thus, the disease recurs in every tenth patient with a tumor smaller than 1 cm, and in every third with a tumor measuring approximately 2 cm.[14] Therefore, only the patients with negative axillary lymph nodes and small tumors have good prognosis while the same is less favourable in those with larger tumors, even when their lymph nodes are negative.

Axillary lymph node involvement

Axillary lymph node involvement is presently the most important prognostic factor for breast cancer. Within the first ten years after surgery the disease recurs in as many as 3/4 of patients with positive axillary lymph nodes, and in only 1/4 of those with negative axillary lymph nodes.[11, 13] The extent of lymph node involvement is important as well. The greater the number of affected lymph nodes, the worse is the survival of patients. While the 10-year survival of patients with 1–3 positive axillary lymph nodes is 60 %, the 10-year survival of those with more than 10 positive axillary lymph nodes is only about 20 %.[15]

Histological type and grade of malignancy

Invasive cancer is the most frequent type of

breast cancer. There are a few different histological types of invasive breast cancer. Prognostically most favourable among them are pure mucinous, tubullar, and papillary invasive breast cancer. Five-year survival of patients with these cancer types is over 80%. Lobular and medullary invasive breast cancers are considered somewhat less favourable, while ductal invasive breast cancer is prognostically the least favourable of all invasive breast cancers.[16] The latter type represents approximately 70% of all invasive cancers and is thus the most frequent breast cancer.

According to the grade of malignancy (G), ductal cancer is classified into three subgroups; the higher the grade of malignancy, the worse is the survival of patients. While 10-year survival rate of patients with tumors of low-grade malignancy (G1) is 56%, the relevant rate of those with high-grade malignancy (G3) is only 33%.[17] Also in patients with negative axillary lymph nodes the grade of malignancy is found to be an independent prognostic factor.[18] The predictive value of this factor is adversely affected by the subjectivity of assessment, and by differences in the methodology of sample processing. Nowadays, malignancy grade is most frequently assessed according to Scarf-Bloom-Richardson (SBR) system which is based on nuclear pleomorphism, mitotic activity and tubular formation in the tumor.[19]

Steroid hormone receptors

The presence of estrogen (ER) or progesterone (PR) receptors in the tumor tissue greatly influences the prognosis of breast cancer patients. Hormonal receptors can be found in approximately half of the primary tumors. They are present at a slightly higher percentage in postmenopausal women. The patients with hormone positive tumors have better prognosis.[13] Patients with axillary lymph node involvement are known to have worse prognosis than those with negative lymph nodes. However, there is no difference between the survival of the patients with axillary lymph node involvement and positive hormone receptors and the patients without axillary lymph node involvement and negative hormone receptors.[8] The presence of hormone receptors is not only a prognostic factor of survival, but it is also an predictor of the effectiveness of hormonal therapy. Patients with positive hormone receptors, both premenopausal and postmenopausal, respond to hormonal therapy at a much higher percentage than patients with negative hormone receptors.[8]

Putative prognostic factors

DNA-ploidy and the percentage of cells in S-phase

Flow-cytometry is a new method for quantitative determination of biological, chemical and physical cell properties.[20] The method makes possible the determination of tumor DNA-ploidy and the percentage of cells in S-phase. DNA-ploidy expresses the DNA content in tumor cells. Normal non-dividing cells contain an euploid quantity of DNA. Changes in tumor cell genome, however, can result in a changed, aneuploid DNA content. The rate of cells in S-phase is an indicator of the tumor's proliferative activity. Different authors have reported from 53 to 73% of aneuploid tumors among the breast cancers studied.[21] DNA-ploidy was found to be a relevant prognostic factor of survival by the majority of univariate analyses, whereas its predictive value as independent prognostic factor failed to be confirmed by most of the multivariate analyses.[22, 23, 24, 25, 26] Likewise, our study of 230 operable breast cancer patients did not confirm DNA ploidy to be an independent prognostic factor.[27] On the other hand, the percentage of cells in S-phase was undoubtedly found to be an independent prognostic factor.[26, 28, 29] The greater the rate of cells in S-phase, the worse is the patient's prognosis, regardless other prognostic factors. The prognostic value of DNA-ploidy and of the rate of cells in S-phase is increased when both these factors are considered together.[26, 29] Thus, patients with diploid as well as those with aneuploid tumors have worse prognosis in the case of higher percentage of cells in S-phase. Particularly in diploid tumors, the rate of cells

in S-phase significantly influences the patient's prognosis. Five-year disease-free survival of patients with diploid tumors and a low rate of cells in S-phase is 90 % whereas in the case that the same tumors are associated with a high percentage of cells in S-phase, the survival is 70 %.[26]

The percentage of cells in S-phase is also a predictive factor of the effectiveness of chemotherapy. In patients with a high percentage of tumor cells in S-phase chemotherapy is more effective than in those with a low percentage of tumor cells in S-phase.[30]

Cyclin D1

Cyclins are cell proteins which play an important role in controlling the speed of cell division. The most known among these is cyclin D1 which controls the transition of cells into the S-phase of the cell-cycle. Increased expression of cyclin D1 was established in a half of all breast cancer patients. Its prognostic value is still subject to extensive research.[12]

Growth factors and growth-factor receptors

Growth factors accelerate the growth of tumor cells. Several growth factors and their receptors have been detected in breast cancer tissue. One of the most important and widely studied ones is the epidermal growth factor receptor (EGFR). The presence of EGFR in breast tissue is associated with worse prognosis.[31] EGFR is a trans-membrane glycoprotein coded by erb-B1 gene. It is present in breast tissue in approximately 40 % of cases.[32] Different growth factors released either by tumor cells or other cells in the organism, which accelerate tumor growth, are bound to this receptor.

The group of epidermal growth factors also includes p-185 protein coded by erb-B2 gene, also known as neu or her-2. Increased expression of this gene was established in 20–25 % of breast cancer patients, particularly in those with tumors of high-grade malignancy and negative hormonal receptors.[12] It has not been confirmed yet whether an increased expression of this gene is an independent prognostic factor for breast cancer.[12]

Increased expression of both erb-B1 and erb-B2 in the primary tumor tissue is associated with a higher susceptibility to chemotherapy, and can thus be considered a prognostic factor of treatment response.

Suppressor genes

Suppressor genes prevent uncontrollable cell division. The most thoroughly studied one is p53-gene which controls cell division. Mutations of this gene, which cause uncontrollable cell division, are found in approximately a half of all breast cancer patients. Patients with tumors exhibiting p53-gene mutations have worse prognosis.[12, 33] Worse prognosis is also associated with lower expression of the antimetastatic gene nm23 in breast cancer tissue.[12]

Invasion markers

Tumor-cell invasion depends on the content of proteolytic enzymes in the tumor. These enzymes dissolve the basal membrane and extracellular matrix, thus accelerating local growth and metastasizing of the tumor. The proteolytic enzymes undoubtedly associated with greater invasiveness of breast cancer are as follows: cathepsins, metaloproteinases and serum proteinases. The most thoroughly studied among cathepsins is cathepsin D. Normal breast tissue contains little cathepsin D while its content in cancer tissue is increased.[34] Higher quantities of cathepsin D can be found in the tumor tissue of patients with positive axillary lymph nodes, although particularly in these patients the level of the enzyme is not found to be an independent prognostic factor. In contrast to that, the cathepsin D content in the tumor tissue of patients with negative axillary lymph nodes is lower but prognostically relevant for course of the disease.[18] The influence of other cathepsins such as cathepsins B, H and L, on the prognosis of breast cancer patients is under study.[35]

Recently, the presence of urokinase plasminogen activator (μPA) and plasminogen activator inhibitor type 1 (PAI 1) in breast tissue was found to be highly relevant. Urokinase plasminogen activator is involved in the transformation of plasminogen into the proteolytic enzyme

plasmin. An elevated level of μPA in breast cancer tissue is associated with a higher metastatic potential of particular cancer, and thus believed to greatly influence the prognosis of breast cancer patients. While the 10-year survival of patients with low μPA levels exceeds 60%, the survival of those with high levels of μPA is hardly over 20%. Elevated μPA levels in breast cancer tissue are generally accompanied by high PAI 1 values. PAI 1 is an inhibitor of plasminogen activator, and its increased content in the tissue is supposed to protect tumor cells against self-destruction. The presence of μPA and PAI 1 in breast cancer tissue is presently the most promising new prognostic factor for breast cancer.[12]

Metaloproteinase stromelysin 3 is also proteolytic enzyme. While stromelysin 3 is rarely present in benign tumors of the breast, it can be often found in breast cancer. In non-invasive breast cancers the presence of stromelysin 3 indicates the possibility of later invasive cancer development.[31] The prognostic value of stromelysin 3 in invasive breast cancer however has not been established yet. The proven correlation with other known prognostic factors, as well as the results of studies performed so far point out that it may play an important role.[37, 38]

Tumor angiogenesis

Weidener and co-workers[39] were the first to call attention to the prognostic value of tumor vascularization. He has proved that vascularization of the primary tumor is an independent prognostic factor for breast cancer. Breast cancer metastases were also found to grow faster when provided with rich blood supply. By inhibiting the proteins that stimulate endothelial cell growth, such as integrins, it is possible to slow-down angiogenesis in the tumor and thus inhibit its growth.

Conclusion

A number of primary tumor characteristics which indisputably influence the prognosis of breast cancer patients are known at present. These well established prognostic factors serve as a basis for primary treatment planning. Nevertheless new biological characteristics of primary tumors are being detected and studied in order to better predict the course of the disease. These studies are both difficult and time consuming since assessment of the reliability of prognostic factors requires long-term follow up of a large group of patients with comparable tumors and identical primary treatment. There is also a problem of the subjectivity of evaluation methods and their standardisation, as well as the cut-off values of new prognostic factors that should be taken into account. Daily determination of all prognostic factors is technically demanding and expensive. Therefore, identifying the most relevant ones among these factors is of utmost importance. Equally important is also the simplification and unification of the methods used. At this time only the established prognostic factors are routinely determined. Nevertheless, it seems that the determination of DNA ploidy, percentage of cells in S-phase, as well as of some proteolytic enzymes and oncogenes in breast cancer tissue, may soon become part of daily practice. It seems that at least some of these tumor characteristics may also predict the response to systemic treatment in individual patient.

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Clinical features as a predictor of laparotomy findings in supradiaphragmatic stage I and II Hodgkin's disease

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Clinical features (sex, age, histology, B-symptoms, the number of lymph node areas involved, supradiaphragmatic site of disease and laboratory findings) have been correlated with staging laparotomy (SL) findings in 95 adult patients with supradiaphragmatic Hodgkin's disease (HD), clinical stage I and II seen at the Institute of Oncology, Ljubljana in the years 1974–1989. Sex and age ware the only significant independent predictors of positive SL. On the basis of these observations, low risk (less than 15 %), intermediate risk (16–50 %) and high-risk (more than 50 %) groups for predicting positive SL can be defined. These observations could be considered for treatment planning as well as selection of patients for SL.

Key words: Hodgkin's disease; staging laparotomy; clinical predictors

Introduction

Although staging laparotomy (SL) is known to be the most accurate method for staging of Hodgkin's disease (HD) in the abdomen, it cannot be ignored that this relatively aggressive method is associated with certain morbidity and, albeit rare mortality, should therefore be avoided whenever possible. Despite the controversial opinion on the indications for this method, its value in the cases when ist outcome governs the choice of treatment is indisputable. It would be a great advantage if among patients with supradiaphragmatic clinical stage (CS) I and II those with low and high risk of occult abdominal disease could be recognised on the basis of clinical data. In these cases, the method of treatment could be chosen without SL. To address this question, we have analysed data from 95 patients and correlated the presenting features with laparotomy findings; the obtained results were compared with those reported by other authors.

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Patients and methods

In the period 1974–1989, 219 adult patients with supradiaphragmatic HD CS I and II were treated at the Institute of Oncology in Ljubljana. SL was performed in 43 % (95/219), i.e. in less than a half of them. Of these, 51 were

males and 44 females, aged 15–63 years (mean 32 yrs). All 95 laparotomized patients had histologically confirmed diagnosis.[1]

Preoperative evaluation included a complete history, physical examination, routine laboratory tests, chest X-ray, bone marrow biopsy, pedal lymphography, Gallium scintiscan of the body, and recently also computer tomography and/or ultrasonography of the abdomen.

Stage was determined according to the Ann Arbor classification.[2] Five supradiaphragmatic lymph node areas were defined for the needs of this study: 1. left neck and/or supraclavicular; 2. right neck and/or supraclavicular; 3. left axillary and/or subclavicular; 4. right axillary and/or subclavicular; 5. mediastinal and/or left/right/bilateral hilar lymph nodes. Bulky mediastinal disease was defined as the largest transversal diameter exceeding one third of the trans-thoracic diameter at the level of the 5th/6th thoracic vertebral body.

SL consisted of splenectomy, liver biopsy, lymph node biopsy and bone-marrow sampling.

Laparotomy findings were correlated with age, sex, histology, B-symptoms, the number of lymph node areas involved, the localization of supradiaphragmatic disease, and some laboratory tests (sedimentation, hemoglobin, serum copper and albumins).

Chi-square and Yates' correction of Chi-square were used for statistical analysis. Logistic regression analysis (LRA) was used to test the effect of each variable independently, and to estimate the risk of positive laparotomy in various clinical subgroups. Statistics were calculated by means of BMDP program.[3]

Results

Laparotomy findings

Of the 95 supradiaphragmatic CS I–II patients who underwent pretreatment SL, 34% had occult abdominal HD (Table 1).

The percentage of positive SL was statistically significantly higher in male patients, aged 40 years or more, with mixed-cell HD type (Table 2.)

The outcome of SL was not found to be statistically significantly influenced by sedimentation rate nor by the values of serum hemoglobin, copper and albumins (Table 3).

Supradiaphragmatic localization of HD did not exert a statistically significant effect on the outcome of SL either in CS I (Table 4) or in CS II (Table 5).

Logistic regression analysis (LRA)

By LRA, sex ($p = 0.0001$) and age ($p = 0.05$) were the only independent significant predictors of positive laparotomy in CS I–II. On the basis of these factors the predicted risk estimates were shown (Tables 6 and 7).

Discussion

The objective of the present investigation was to define high- and low-risk CS I–II patients of occult abdominal disease on the basis of their clinical features on admission.

Males were shown to be at a significantly higher risk of occult subdiaphragmatic disease than women (Table 2). This observation in consistent with other reports.[4–9]

The findings one the influence of age on the outcome of SL are inconsistent. We have shown (Table 2) that the rate of positive SLs is increasing by age, being significantly higher in patients at an age of $\geq$40 years than in younger ones. Some authors[10] confirm this observation while others claim just the opposite,[4] or even report a higher rate of positive SLs in patients under 20 years of age.[6] It is not clear, however, whether the studies reporting findings different from ours also included children, which might be the cause of the observed difference.

Our patients with CS I–II and mixed cellularity histological type presented with a significantly higher percentage of HD in the abdomen than patients with nodular sclerosis type (Table 2), which has been also confirmed by some other authors.[5, 7, 8, 10] Those who have been investigating the influence of histology separately for CS I and II report interesting results: histological type correlates with SL outcome in

Table 1. Hodgkin's disease clinical stage I–II; Results of laparotomy.

CS	No. of pts	Unchanged stage		Upstaging		Upstaging %
		PS I No.	PS II No.	PS III No.	PS IV No.	
I	36	20	0	15	1	44
II	59	0	43	16	0	27
Total	95	20	43	31	1	34

CS = clinical stage

Table 2. Hodgkin's disease clinical stage I–II (n = 95): Laparotomy findings by clinical features.

Clinical features	CS I–II No.	Postlaparotomy stage PS I–II No.	PS III No.	PS IV No.	Stage change %	Chi^2	df	p
Age (yrs)								
≤19	12	10	2	0	17			
20–39	59	42	16	1	29	Trend		
40–59	21	11	10	0	47	3.810	1	0.0504
≥60	3	0	3	0	100			
Age (yrs)								
15–39	71	52	18	1	27			
≥40	24	11	13	0	54	4.8666	1	<0.05
Sex								
Males	51	26	24	1	49			
Females	44	37	7	0	16	10.1579	1	<0.01
*Histology								
LP/NS	55	43	12	0	22			
MC/LD	35	17	17	1	51	7.1591	1	<0.01
Symptoms								
A	86	58	27	1	33			
B	9	5	4	0	44	0.1206	1	>0.1
No.of lgl areas involved								
1	36	20	15	1	44			
2	34	23	11	0	32	Trend		
3	19	16	3	0	16	1.521	1	0.2175
≥4	6	4	2	0	30			
No.of lgl areas involved								
1	36	20	15	1	44			
≥2	59	43	16	0	27	2.2789	1	>0.1

*Histologically unclassified (5/95) are not included.

CS = clinical stage, PS = pathological stage, LP/ND = Lymphocyte predominant and Nodular sclerosis, MC/LD = Mixed cellularity and Lymphocyte depleted

CS I but not in CS II.[6] The lowest percentages of positive SLs were found in patients with CS I and LP histological type: 0%,[7] 5%[5] and 16%.[6]

Table 3. Hodgkin's disease clinical stage I–II (n = 95): Laparotomy findings by laboratory results.

Clinical features	CS I–II No.	Postlaparotomy stage PS I–II No.	PS III No.	PS IV No.	Stage change %	Chi^2	df	p
SR								
0–15	29	20	8	1	28			
16–30	15	9	6	0	27	Trend		
31–50	21	18	3	0	14	0.747	1	0.3873
51–70	15	10	5	0	33			
≥70	15	6	9	0	60			
Hb								
<100	4	3	1	0	25			
101–120	17	11	6	0	35	Trend		
121–140	42	31	11	0	26	0.4490	1	0.502
141–180	32	18	13	1	44			
Cooper								
normal	45	26	18	1	4			
increased	44	33	11	0	25	2.2330	1	0.1
Albumins								
normal	54	36	17	1	33			
decreased	36	23	13	0	36	0.0205	1	>0.1

SR: mm/hr; range 2–132; $\bar{X}$ = 38.5; Median = 33; SD = 29.3
Hb: g/l; range 97–169; $\bar{X}$ = 135; Median = 132; SD = 16.5
Copper (in 89/95 pts): μmol/l; normal 11–26.7; range 10–48; $\bar{X}$ = 27.9, Median = 26.8; SD = 7.82
Albumins (in 90/95 pts): g/l; normal 35; range 21–58; $\bar{X}$ = 35.8; Median = 36; SD = 6.4

CS = clinical stage, PS = pathological stage

Table 4. Hodgkin's disease clinical stage I (n = 36): Laparotomy findings by site.

Site		CS I No.	Stage change No.	%	Chi^2	df	p
Neck	L	12	6/12	50	0.3272	1	>0.1
	R	13	4/13	31			
Axilla	L	1	1/1	100	–	–	–
	R	2	1/2	50			
Neck or axilla	L	13	7/13	54	0.5056	1	>0.1
	R	15	5/15	33			
Mediastinum	yes	8	2/8	25	0.2526	1	>0.1
	no	28	12/28	43			
Neck	R + L	25	10/25	40			
Axilla	R + L	3	2/3	67	1.634	2	>0.1
Mediastinum		8	2/8	25			

Compared to patients with CS I, in those with CS II subdiaphragmatic disease is reported to be significantly more frequent;[4, 5, 8] moreover, the rate of positive SLs is increasing by the number of regions involved. Other authors[6] have not confirmed those findings, possibly due to the fact that only patients with less that three involved regions were included into the study.

Table 5. Hodgkin's disease clinical stage II (n = 59): Laparotomy findings by site.

Site		CS II No.	Stage change No.	%	Chi^2	df	p
Neck bilat.		2	1/2	50	–	–	–
Neck unilat. + mediastinum		26	8/26	31	0.0037	1	>0.1
Neck bilat. + mediastinum		9	2/9	22			
Mediastinum	no	14	4/14	29	0.0417	1	>0.1
	yes	45	12/45	27			
Mediastinum size	bulky	11	1/11	9	2.442	2	>0.1
	not bulky	29	8/26	31			
	undefined	8	3/8	37			

CS = clinical stage

Table 6. Hodgkin's disease clinical stage I–II (n = 95): Predicted risk of positive laparotomy, based on sex* and age*.

Sex	Age yrs	Stage change Observed No.	%	Predicted %
Males:	≤20	2/6	33	28
	21–39	11/27	41	44
	40–59	10/16	63	62
	≥60	2/2	100	77
Females:	≤20	1/7	14	8
	21–39	5/31	16	15
	40–59	0/5	0	27
	≥60	1/1	100	43

* derived from logistic regression analysis.

positive SL (Table 2) than those with CS II, though the difference is insignificant. The reason may be in our definition of supradiaphragmatic lymph node areas (see Patients and Methods).

Opinions on the influence of B-symptoms on SL outcome are also controversial. We – as well as some other authors,[5] could not prove a significantly higher percentage of positive SL in patients with B-symptoms while others did.[4, 7, 8, 10] We also did not confirm the influence of sedimentation rate, serum hemoglobin, copper and albumins on the outcome of SL (Table 3). Only one such study[8] has been found in the available literature, which also

Table 7. Hodgkin's disease clinical stae I–II (n = 95): Predicted risk of positive laparotomy, based on sex* and age.*

Risk degree	Risk factor	Stage change Observed No.	%	Predicted %
High	male + ≥40 yrs	12/18	67	62–77 (69.5)
Medium	male + <40 yrs or female + ≥40 yrs	13/33 1/6	36	28–44 (36) 27–43 (35)
Low	female + <40 yrs	6/38	16	8–15 (11.5)

* derived from logistic regression analysis

Our results also fail to confirm the above cited findings; on the contrary, we have found that patients with CS I have higher percentage of

failed to prove any influence of sedimentation rate, serum copper and LDH values on the outcome of SL.

The results of some investigations[4–6] reveal an interesting observation that none of the patients with a single localization of HD in the mediastinum (CS I) had positive SL (in one of the previously mentioned studies[4] this applies only to females). Therefore, in Stanford (U.S.A.) SL has not been performed in such patients since 1973. Ours (Table 4) as well as the findings of other investigators[8, 10, 11] support this observation since the percentage of positive SLs was lower in patients with a single mediastinal HD site than in those without mediastinal involvement, though in our case the difference was not statistically significant. In patients with CS I the side of localization, i.e. either left of right, did not influence the outcome of SL (Table 4) which is in accordance with the results of other studies.[4-6] We did not evaluate the influence of the size and localization of cervical lymph nodes on the outcome of SL since these data were not available. The results of some studies[6–8] lead to an interesting conclusion that patients with CS I and lymph node involvement above the hyoid cartilage have statistically significantly less positive SLs than those with localizations under the hyoid cartilage, and that patients with lymph nodes >5 cm in diameter have subdiaphragmatic disease more frequently than those with smaller lymph nodes;[6] the latter observation, however, has not been confirmed by other authors.[8]

In patients with CS II the situation is different. As evident from our study (Table 5) and those of others,[6] the outcome of SL is neither influenced by the size of lymph nodes[6, 8] nor by the presence or absence of HD in the mediastinum.

By LRA, sex and age were the only independent significant predictors of positive laparotomy in our CS I–II patients. On the basis of these factors the predicted risk estimates for positive SL are shown (Tables 6 and 7). The higher risk in males is particularly evident in those exceeding 40 years of age, with a predicted chance of positive laparotomy of 69.5 %. At the other end of the spectrum, females under 40 years of age have a predicted risk of 11.5 %.

To our knowledge, there are only four studies[4–6, 8] where the predictors of positive laparotomy have been analysed by means of multivariate analysis. On the basis of these factors some authors predicted risk estimates for positive SL.

Summarising ours and the above four studies, we can draw the following two conclusions:

1) Clinical features predicting a low risk of positive SL in CS I are as follows: female sex, and irrespective of sex: mediastinal site, nonbulky upper neck nodes, and LP histological type.

2) Clinical features associated with a high risk of positive SL in CS I–II are as follows: male sex (confirmed by all studies), age (the evidence for that is controversial: <20 years,[6] >27 years,[5] ≥40 years[our results]), a greater number of involved regions (inconsistent evidence: 2 or more,[4] 3 or more,[8] 4 or more[5]), mixed cellularity and lymphocite depleted histological type,[8] and B-symptoms.[4, 8]

Conclusion

Our study and the review of existing literature were aimed to identify the patients who do not require SL, i.e. those in whom the selection of treatment metod can be based solely on the evaluation of risk of abdominal HD involvement. Patients with low risk would require radiotherapy alone, and high-risk patients chemotherapy. The objective to define high- and low- risk patients on the basis of clinical features has been only partly realized.

The above findings have shown that the definitions of risk groups are unreliable due to incomplete agreement between different studies, which could be attributed to the following reasons:

1) Most of the studies were done on a small number of patients.

2) In some studies, CS I and CS II were analysed separately, which is correct, while in others CS I–II were pooled together owing to the small number of patients in a particular center.

3) The clinical features analysed were not always the same.

Nevertheless, the most reliably definable is the group of patients at a low risk of positive SL. A prospective multicentric study on a larger number of patients would be required to allow more rigorous statistical analysis, which however seems hardly feasible as SL has been mostly abandoned nowadays.

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Conservative surgery and irradiation in early lung cancer: Local control and survival

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1041 patients underwent complete resection for peripheral lung cancer prior to 1990. In 230 (22 %) cases tumor was less or equal to 30 mm and metastases were absent (pT1N0M0). Tumorectomy was carried out in 7 cases, wedge resection in 57, segmentectomy in 40, standard curative operations in 126. In 5 cases microinvasion at the specimen margin or malignant complexes in lymphatic (blood) vessels of adjoining lung structures was detected. In 63 cases (from 1983) prospective randomization was used. Preoperative (59 patients) and postoperative (123) radiation therapy completed according to 4 protocols. After tumorectomy 5-year survival was 60,0 %, after wedge resection – 69,1 %, after segmentectomy – 72,5 % ($p>0.05$). Local relapse after lung-preserving resections were proved in 7,7 % patients and correlated with type of operation and regimen of radiation therapy.

Key words: lung neoplasms-surgery; radiotherapy; survival rate

Introduction

Radiation therapy was added to organ-preserving operations in order to reduce the risk of local recurrences. In lung oncology this adjuvant method is not desirable for it compensates the curability but disturbs the lung function. So the profit of lobe conservation becomes dubious. However, the advantage of lung irradiation has been proven in some institutions. Suppression of occult regional metastases and creation of unfavorable conditions for malignant elements growth in adjoining structures had been shown in the course of experience.

In the year 1982 we retrospectively studied the results of occasional conservative resections with postoperative irradiation and found that combined treatment provides the best survival.[1]

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Material and methods

Pilot study of lung-preserving resection and radiation therapy began in 1980. 1041 patients underwent complete resection for peripheral lung cancer prior to 1990. In 230 (22 %) cases tumor was less or equal to 30 mm and metastases were absent (pT1N0M0).

Before the year 1980 no more than one organ-preserving resection had been experienced annually. In the years 1986–1988 the treatment in association with irradiation was

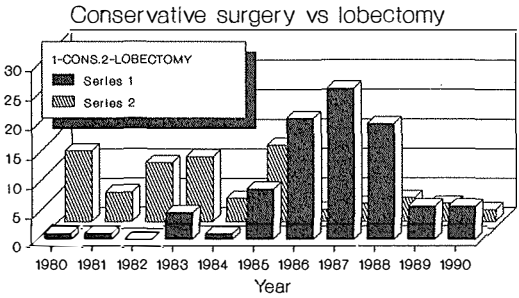

Figure 1. Annual number of conservative and radical resections of T1N0 lung cancer.

executed on more than 20 patients in a year (Figure 1). Diagnosis of primitive lung lesion was verified histologically. Tumor localization and other prognostic factors were essentially similar.

Wedge resection was carried out with staplers that applied on the lung tissue at distance more than 2 cm from tumor margin. Segmentectomy technique with original automatic suture was presented elsewhere.[2] Following surgery 98 patients were observed more than 3 years, 71–5 years and 11-ten years after treatment. Survival was according Kaplan-Meier and Fisher methods with the use of computerized data base (FoxPro).

Tumorectomy was carried out in 7 cases, wedge resection in 57, segmentectomy in 40, lobectomy or pneumonectomy in 126. In 63 cases (from the year 1983) prospective randomization was used.

Conservative surgery seemed to be curative but after careful histologic inspection of the resected tissues in 5 cases microinvasion at the specimen margin or malignant complexes in lymphatic (blood) vessels of adjoining lung structures was detected. Agressive tumor growth was found in 3 (5,25 %) cases of wedge resection, in 1 (14,2 %) case of tumorectomy and in 1 (2,5 %) case of segmentectomy. All patients survived conservative resections. Following lobectomy or pneumonectomy 4 (3,2 %) patients died.

Preoperative radiation therapy (PreRT) with betatrone 25 MeV or telecobaltherapy was completed in 59 cases according to 3 protocols: TD = 40–45 Gy (2–2,5 Gy daily fractions); TD = 36 Gy (3 Gy in 12 fractions); single dose 7,5 Gy with thoracotomy on the next day. The irradiated volume included hilus, bifurcation and paratracheal zone on the side of the lesion. Following multiple fractionation of PreRT lung resection was practiced in 3–4 weeks at completion of radiation therapy. Methods of treatment are given in Table 1.

Postoperative radiation therapy (PostRT) in 123 cases. In 18 cases PreRT (single dose 7,5 Gy) and PostRT (30 Gy in 3 Gy fractions) were utilized.

Results

Risk of surgical complications increased with excised lung parenchyma volume. However, the lowest morbidity registered after segmentectomy – 12 %. Following tumorectomies minor complications were seen in one patient (14 %); the difference was not significant ($p > 0.05$). Following lob-, pneumonectomy complications were observed in 33 % of cases ($p < 0.005$). There were no lethal complications connected with conservative resections.

Actuarial 5-year survival following conservative surgery – 73,1 %, lobectomy or pneumonectomy – 63,4 % ($p > 0.05$; Figure 2). The rate in females was 82,1 % in male – 71,6 % (after radical operations respectively 71.0 and

Table 1. Peripheral T1N0 lung cancer. Methods of resection and irradiation.

Type of resection	Radiation therapy				Total
	none	preRT	PostRT	Pre + PostRT	
Tumorectomy	–	–	4	3	7
Wedge resection	10	5	32	10	57
Segmentectomy	10	10	17	3	40
Lob-Pneumonectomy	46	26	52	2	124

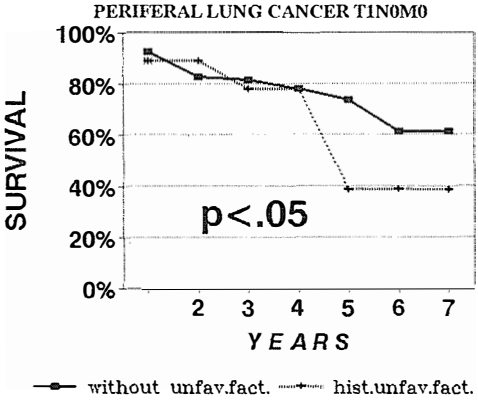

Figure 2. Survival after conservative surgery and adjuvant radiation therapy in peripheral T1N0M0 lung cancer.

61.7%). The difference was statistically insignificant. The trend for better prognosis in women we could trace in all groups of patients that underwent different methods of surgery.

Long-term results of organ-preserving surgery correlated with size of primary tumor. All the patients who had the primary lesion diameter less then 1.5 cm were alive for 5 years. If the diameter of the tumor was 1.5 cm or more 5-year survival was 71.5–74.1% depending of method of resection ($p < 0.005$). Lobectomy and pneumonectomy long term results were not significantly correlated with the size of the lesion.

The best prognosis observed in adenocarcinoma and adenosquamous cancer, 5 years after organ-preserving treatment respectively 85.7 and 73.8% patients were alive. We cannot properly explain good long term results of conservative resections in T1N0 adenosquamous carcinoma. Following lobectomy 5-year survival was 54.7% ($p < 0.005$). Some other important factors are to be included into analysis. On the other hand, one can appreciate rather good results of conservative resections in early scar cancer, 3 years 91.7% patients were alive, 5 and 10 years – 80.3%.

The most important long term results we got in monitoring of 9 patients with histologically disclosed tumor growth near resection margin (5 cases) or malignant cell complexes in lymphatic (blood) vessels in the excised preparation. After such a "relatively curative" resections in two cases developed local recurrences and in 2 – early distant metastases, 3-year survival in this group of patients was 77.8%, 5-year survival – 38.9% ($p < 0.001$; Figure 3).

Five-year survival following tumorectomy was 60%, wedge resection – 69.1% and segmentectomy – 72.5%. However, inspite of an apparent trend in prognosis, statistical difference is not significant. The reason for that is insufficient number of patients. But we cut down on tumorectomy after experience in the years 1985–1986. Neither PreRT nor PostRT improved in long-term results. It is not worth to repeat this reduced operation even with adjuvant therapy in early primary lung cancer.

Three years following 20 conservative resections lived 77.3% of patients, 5 year – 68.7%. Radiation therapy improved long term results: these rates were respectively 81 and 70.5%. The most effective method appeared to be PostRT. In the group of patients that were subjected to lobectomy 5-year survival was 63%, after combined treatment depending of the method – 59.5–65.3 ($p > 0.05$). With PostRT the results are somewhat better but the difference is not significant.

We studied the effect of radiation therapy depending on local doses. In 8 of 68 cases PreRT was completed in single dose of 7.5 Gy the day before conservative surgery. In 60 cases the equivalent dose attained 44 Gy. In 1st group

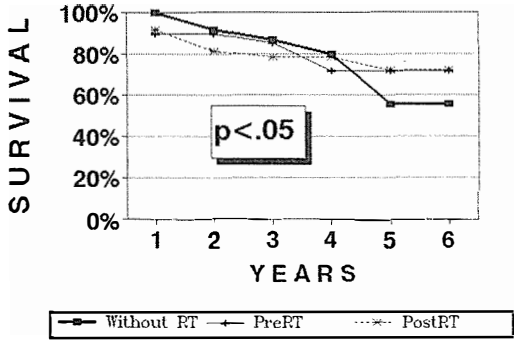

Figure 3. Survival after combined radiotheray and conservative surgery of T1N0 patients following "relatively curative" conservative resections.

Table 3. Type of resection and survival in T1N0 lung cancer.

Type of resection	Number of patients	5-year survival (%)			
		NoRT	PreRT	PostRT	Random
Tumorectomy	7	–	50	75	60
Wedge resection	57	66.7	25	73.1	69.1
Segmentectomy	40	67.5	80	76.5	72.5
Lob-, Pneumonectomy	124	66.9	57.9	65.3	63.7

local recurrences developed in 25 % cases (2 in 8 patients), in 2nd – 8.3 % (5 in 60). When the dose of PreRT was 36 or 44 Gy, the rate of recurrences decreased to 7.7 %. The same results were observed following "sandwich" use of both PreRT and PostRT.

So radiation therapy with low level of local doses in association with conservative surgery proved to be ineffective. Total doses of 44 Gy reduced the risk of local recurrences. Decreasing of the irradiated volume of the lung have not influenced the effect of local treatment. It is important to state that equivalent doses PreRT and PostRT produced the similar local effect.

In 7 (5.5 %) cases following lobectomy and in 4 (3.8 %) after conservative surgery patients developed severe radiation pneumonitis with clinical symptoms ($p > 0.05$). In all of them in zone of radiation included a large volume of lung parenchyma, lymph nodes of hilus and mediastinum. Total dose was not les than 44 Gy. Single dose of PreRT 7.5 Gy or decreased zone of irradiation have not developed symptomatic pneumonitis. Asymptomatic radiological changes in lung tissue were observed more frequently either after conservative or radical resections. But the impairments of general lung function following combined organ-preserving treatment were less significant than after lobectomy with adjuvant irradiation.

Discussion

It is rather a problem to compare our data with published reports. Sometimes complete conditions and important prognostic factors are lacking, other authors do not properly compare the results of conservative and radical resections. Some of them use the former versions of TNM. In the Table 4 we compare the rates of the most relevant reports. However, there are some significant differences, one can find the trend to better results of conservative surgery in early (T1N0) and stage I peripheral lung cancer. We presume that combined organ-preserving treatment of the tumor will be the alternative method of treatment at least in some groups of patients with favorable prognostic factors.

Special importance was attached to quality of life after combined organ-preserving treatment of lung cancer. Usually the main objections to combined organ-preserving treatment was radiation pneumonitis that brings to naught all the efforts to save the functioning lung tissue. The same point of view expressed some authors in opposition to radiation therapy be-

Table 4. Conservative and standard resections in T1N0 lung cancer.

Reference	Number of conservative resections	5-year survival (%)	
		Conserv. surg.	Lobectomy
Menne W.[4]	95	56.3	53.6
Windheim K.[5]	88	40	39
Jensik R.[6]	274	55	–
Dobrovolsky S.[7]	41	67.5	64.5
Khartchenko V.	104	74.8	68.1

fore of after bronchoplastic procedures. The problem of adjuvant therapy complications is real but seems to be exaggerated.[3]

The results of this study are preliminary findings but the analysis of immediate and delayed data offers the possibility to suggest the acceptable organ-preserving method in early (T1N0) lung cancer. The combined treatment of peripheral lesion must be an alternative method not only in elderly patients with limited lung function but in all T1N0 cases with favorable prognostic factors (tumor diameter less than 1.5 cm, scar cancer). It is preferable to carry out segmentectomy and PostRT in total dose 40–44 Gy.

Conclusion

1. Conservative resections with radiation therapy are justified in peripheral T1N0 lung cancer, 5 year following combined organ-preserving treatment 70.5% patients, after standard radical resections – 63.4% ($p > 0.05$) survived.

2. The less the volume of excised lung tissue, the greater becomes the risk of local recurrences, but limited experience is not enough to make a significant conclusion.

3. The best remote results of organ-preserving treatment were observed after segmentectomy with PostRT: 5-year survival – 77.2%.

4. Unlike standard resection in conservative surgery, size and histologic type of the tumor influenced the survival. The best prognosis is observed in scar carcinoma and early adenocarcinoma. Organ-preserving treatment is definitely justified when the diameter of primary lesion is less than 1.5 cm.

5. Tumorectomy in patients with early lung carcinoma is not an adequate procedure even with adjuvant therapy. Wedge resection is admissible only in cases of favorable prognosis and subpleural minute lesions.

6. PreRT in association with conservative surgery does not seem to be sufficient to provide the stabilization of malignant cells in primary lesion and to prevent the dissemination of distant metastases during surgery. The possible mechanism is connected with immune suppression.

7. Changes of lung tissue following irradiation and conservative surgery are not frequent and grave in comparison with standard combined treatment. In 5.5% lobectomy cases and in 3.8% organ-preserving resections severe radiation pneumonitis that demands repeated hospitalizations and unspecified treatment is to be found.

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Standardized immunohistochemistry of estrogen receptors in human breast carcinoma in routinely processed tissue

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The aim of this study was to determine the optimal method for estrogen receptor (ER) staining on routinely processed breast tumors. We tested different commercially available primary antibodies, different methods for tissue digestion and several detection systems on formalin-fixed, paraffin embedded tissue under conditions of our laboratory. All antibodies to ER tested (H222, ER1D5, D75, NCL-ER-P31, and 1D5), gave positive results at least under some conditions of retrieval and/or heavy salt enhancement. Proteolytic enzyme pretreatment, microwave irradiation and heavy metal ions had varions influence on intensity of final color products depending mostly on primary antibody tested. We have found that immunohistochemical assessment of estrogen receptor status using Dako 1D5 primary antibody, microwave heat induced epitope retrieval, and Streptavidin-peroxidase protocol, performed by an automatic immunostainer has many advantages over other antibodies and methods tested.

Key words: breast neoplasms; receptors, estrogen; immunohistochemistry

Introduction

The value of the estrogen receptor (ER) assay to predict breast cancer response to therapy and overall survival has been established by an extensive literature on the subject over last few decades (1,2,3). The widely used biochemical assay is based on the ligand binding, dextran-coated charcoal (DCC) using tissue homogenates. This method is generally regarded as the standard against which new methods are measured (4,5). Unfortunately, biochemical methods require substantial amount of fresh tissue, that has to be collected immediately after surgery and transported on ice. As the method is destructive of the tissue, the assessment of actual tumor content of the specimen is not possible (6). Furthermore, biochemical assay in very small tumors and retrospective analyses of fixed material are impossible.

The first step to solve these problems was the development of monoclonal antibodies to ER that has allowed the use of immunohistochemical techniques to visualize the receptors in tissue sections. It should now be possible to perform the study on scant material that otherwise would be insufficient for biochemical assay and to evaluate the degree of intratumoral heterogeneity.

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Among the well defined antibodies, the rat monoclonal antibody H222 raised by Greene and coworkers and commercially available as a kit by Abbott Laboratories was recommend initially for use on frozen sections (7). As frozen section has its drawbacks, in second step, efforts have subsequently been made to make this antibody effective on paraffin-embedded tissue (8,9). So far, the Abbott H222 antibody is well characterized and immunohistochemical results have been found repeatedly to correlate well with biochemical methods of assessing ER status. However, this antibody requires an overnight incubation and in different laboratories the results of staining were not reproducible. With the advent of new antibodies to ER, different techniques used, and diverse cut-off points established for evaluating the results, standardization of ER immunostaining protocol has been strongly advocated (4).

The aim of this study was to test different approaches to ER immunostaining on routinely processed breast tumors and to determine the optimal method under conditions of our laboratory.

Material and methods

Breast tumor tissue

As routine fixation and processing are by definition heterogeneous and may have unpredictable effects on the immunohistochemical results (4) we tried to avoid this variability. In our institution, all breast specimens were received fresh on the ice immediately after surgical removal, and examined by surgical pathologist.

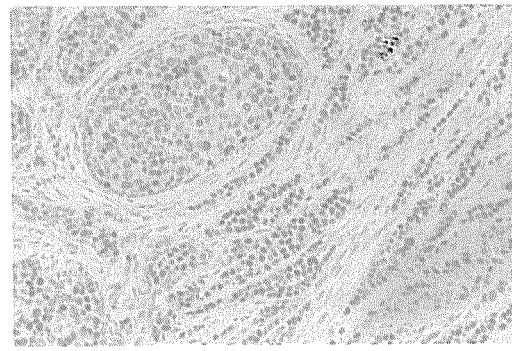

Figure 1. Immunostaining for estrogen receptors with Dako 1D5. Note the intense nuclear staining in cells of both, infiltrating and intraductal component of ductal carcinoma and the absence of cytoplasmic staining. Microwave pretreatment, automatic stainer.

Routinely, and for the purpose of this study, a portion of tumor tissue was snap frozen in liquid nitrogen and submitted for DCC assay. At the same time, an additional piece of tumor was fixed for period not exceeding 24 hours, using 10% neutral-buffered formalin at room temperature. In the tissue processor (Hypercenter, Shandon), the material underwent dehydration, clearing and paraffin infiltration. The tissue was then embedded in blocks, and 3-micron sections were cut and mounted on Silane (Sigma) coated slides.

ER staining procedure

Monoclonal antibodies. Five different monoclonal antibodies to ER were tested (Table 1).

Preparation of paraffin-embedded sections. The slides were dried in a 56°C oven overnight; then they were deparaffinized and rehydrated in graded alcohols. After rehydration, endogenous

Table 1. ER primary antibodies tested

Clone	Source	Dilution	Incubation time	Temperature
H222	Abbot	Prediluted	Overnight	RT*
ER1D5	Immunotech	1 : 10	Overnight	4°C
D75	Courtesy of Dr GL Greene	1 : 100	Overnight	4°C
NCL-ER-P31	Novocastra	1 : 20	Overnight	RT
1D5	Dako	1 : 100	Overnight	4°C

RT – room temperature

* reincubation at 37°C, 2 hours

peroxidases were blocked by immersing the slides in 1 % H_2O_2 in methanol for 15 minutes and washed well with phosphate buffer solution (PBS) before enzymatic, and in distilled water before microwave pretreatment.

Antigen retrieval The most controversial step in ER immunohistochemistry of paraffin-embedded tissue is, no doubt, the pretreatment of the sections. It is well known that many epitopes are sensitive to formalin fixation, often proportionally related to the duration of fixation, thus potentially causing unsuspected false-negative immunostains (10).

For the purpose of this study we applied two different methods of antigen retrieval. The first one, proteolytic enzyme treatment of formalin-fixed tissue sections was found to enhance immunoreactivity (11,12). In this study a series of enzymes was tested for enzymatic digestion (Tab 2).

As enzymatic digestion is effective with only limited fraction of currently used diagnostic antibodies, the second method using microwave radiation of sections has been stated to improve immunostaining in a broader group of antigens (13). To this end, we have used a microwave oven (M752, Miele, 850 W). Slides in the citrate buffer, pH 6.0, were exposed to heating at power setting of 750 W in three intervals of 5 minutes.

Completion of staining procedure. The remainder of the staining procedure followed our routine procedure for different detection systems or a method supplied by manufacturer (Abbott) for ERICA kit.

In this study, three immunohistochemical detection systems were tested in combination with different antibodies (Tab 3).

As heavy metal ions have long been proposed as a means to increase intensity of final color products (12,14), we also tested the influence of copper, nickel, cobalt, and osmium salts on ER staining intensity.

In the first part of the study, all procedures tested were performed manually. Ideally, a single method should be adopted and standardized for routine day-to-day staining within a laboratory. The chosen method should then be performed in identical fashion on every run. This is best achieved by automation, which offers levels of quality and consistency far better than that achievable by manual methods (15).

Table 2. Tissue enzymatic digestions tested

Enzyme	Source	Dilution	Time, min	Temperature
Protease XIV	Sigma	0.1 %	30	37°C
Protease 1	Sigma	0.1 %	30	37°C
Protease K	Sigma	0.25 mg/ml	5	RT
+ DNase	Sigma	5 mg/ml	15	RT
Ficin	Sigma	Undiluted	30	37°C

RT – room temperature

Table 3. Detection systems tested

System	Primary antibody	Secondary antibody	Chromogen
PAP	H 222	Goat anti-mouse	DAB
ABC	H 222	Biotinylated rabbit anti-mouse	DAB
	D 75		
	ER 1 D5		
	I D5		
	NCL-ER-P31		
StrAP	I D5	Biotinylated rabbit anti-mouse	DAB

PAP – peroxidase-antiperoxidase
ABC – avidin-biotin complex
StrAP – streptavidin-peroxidase
DAB – 3,3'-diaminobenzidine tetrahydrochloride

Table 4. ER Streptavidin-peroxidase protocol (Dako, modified)

Step No.	Step name	Duration min:sec
1	Buf 1	00:10
2	Pad 1	00:29
3	Buf 1	00:10
4	Pad 1	00:29
5	Buf 1	00:10
6	Pad 1	00:29
7	Buf 1	00:10
8	Pad 1	00:45
9	AB 1	25:00
10	Pad 1	00:29
11	Buf 1	00:10
12	Pad 1	00:29
13	Buf 1	00:10
14	Pad 1	00:29
15	Buf 1	00:10
16	Pad 1	00:29
17	Buf 1	00:10
18	Pad 1	00:29
19	Buf 1	00:10
20	Pad 2	00:45
21	AB 2	25:00
22	Pad 2	00:29
23	Buf 1	00:10
24	Pad 2	00:29
25	Buf 2	00:10
26	Pad 2	00:29
27	HP block	02:30
28	Pad 2	00:29
29	HP block	02:30
30	Pad 2	00:29
31	HP block	02:30
32	Pad 2	00:29
33	Buf 2	00:10
34	Pad 2	00:29
35	Buf 2	00:10
36	Pad 2	00:29
37	Buf 2	00:10
38	Pad 2	00:45
39	StrAP	25:00
40	Pad 3	00:29
41	Buf 2	00:10
42	Pad 3	00:29
43	Buf 2	00:10
44	Pad 3	00:29
45	Buf 3	00:10
46	Pad 3	00:29
47	Buf 3	00:10
48	Pad 3	00:29
49	Buf 3	00:10
50	Pad 3	00:45
51	Chrom	05:00
52	Pad 3	00:29
53	Buf 3	00:10
54	Pad 3	00:45
55	Chrom	05:00
56	Pad 3	00:29
57	Buf 3	00:10
58	Pad 3	00:45
59	Chrom	05:00
60	Pad 3	00:29
61	Buf 3	00:10
62	Pad 4	00:29
63	Buf 3	00:10
64	Pad 4	00:29
65	Buf 3	01:00
66	Pad 4	00:29
67	Buf 3	00:10
68	Pad 4	00:29
69	Buf 3	01:00
70	Pad 4	00:29
71	Buf 2	01:00
72	Pad 4	00:29
73	Buf 2	00:10
74	Pad 4	00:29
75	H_2O	00:10
76	Pad 4	00:29
77	H_2O	00:10
78	Pad 4	00:29
79	H_2O	00:29

Buf – buffer
Chrom – chromogen (DAB)
StrAP – streptavidin-peroxidase

Thus, in the second part of the study, ER immunostaining was performed on the DAKO TechMate 500 immunostainer. This system uses the capillary reaction to draw up reagents to cover the specimens on the specially prepared slides. Prior to staining, routinely fixed paraffin-embedded tissue sections were subjected to antigen retrieval in microwave oven. For the staining of ER, both the original DAKO reagent kit and Streptavidin-peroxidase protocol were used. The step names, number of steps, reagents and incubation times for the individual step are listed on Table 4. However, instead of the original prediluted primary antibody, the antibody used was DAKO 1D5, 1 : 150. Additionally, in the step 65, originally prescribed hematoxylin was substituted by buffer 3. Final counterstaining with hematoxylin was performed manually.

Controls. Only nuclear immunostaining was interpreted as positive result. Cytoplasmic reactivity, if any, was ignored. As a positive control,

a case of invasive breast carcinoma of known positive ER reactivity determined by DCC assay was included in all batches of paraffin-embedded material to ensure consistency of staining between batches. Cells in the same section, not expected to give positive reactivity with the antibody in question (stromal cells, lymphocytes, etc.), served as intrinsic negative controls.

A specimen was considered "ER positive" by biochemical assay if the result was more than 10 pmol/g protein. For the purpose of this study, a series of "ER positive" tumors from different patients was tested.

Scoring. The staining results were assessed semiquantitatively according to the percentage of stained tumor cells and the intensity of the staining, using a scale of 1-3 for each of these two components (16). The resulting two figures were multiplied by each other, and the final result expressed as follows: negative (no staining or only an occasional positive cell); weakly positive (+ , total score = 1-3); positive (+ + , score 4-6); strongly positive (+ + + , score more than 6).

Results

Positive immunostaining of nuclei was seen in both malignant and benign epithelial cells. Most cases show mild variation in staining intensity, but in few cases there was considerable heterogeneity of staining both in tumor and in normal breast epithelium.

All five antibodies to ER tested, gave positive results at least under some conditions of retrieval and/or heavy salt enhancement. The intensity of nuclear staining, however, showed great variations depending on the antibody applied (Table 5).

Analysis of our results confirmed the superiority of monoclonal antibody 1D5 for immunohistochemical determination of ER. In comparison to other antibodies, clone 1D5 not only produced the greatest intensity of staining, that was most extensive, but also gave no background or any cytoplasmic staining. The results were even better when staining had been performed automatically (Fit. 1). The second best results were achieved by ER1D5 and H222. The staining with the latter was acceptable only after protease K + DNase pretreatment. Generally, unsatisfactory stainings showed negative or weak staining of nuclei and extensive background staining of collagen and fat.

Proteolytic enzyme pretreatment gave different results. Protease K and DNase pretreatment resulted in notable enhancement of immunostaining with the antibody H222, whereas ER1D5, and NCL-ER-P31 proved to be less sensitive to this enzyme. Parallel to that, ficin pretreatment gave better staining with H222 compared to ER1D5 and D75. On the other hand, the staining with NCL-ER-P31 and ficin

Table 5: Results of ER staining in formalin-paraffin sections

Antibody	H222	ER1D5	D75	NCL-ER-P31	1D5*	1D5**
Protease K + DNase	+ +	+	ND	+	ND	ND
Protease K + DNase + Os	+ + +	ND	neg	+	ND	ND
Protease K + DNase + Ni	+ +	ND	neg	+	ND	ND
Protease K + DNase + Cu	ND	ND	neg	+	ND	ND
Ficin	+ +	+	ND	neg	ND	ND
Ficin + Os	+ + +	ND	neg	neg	ND	ND
Ficin + Ni	+ +	ND	neg	neg	ND	ND
Ficin + Cu	+ +	ND	neg	neg	ND	ND
MW	+	+ + +	ND	+ +	+ +	+ + +
MW + Os	+ +	ND	+	+ +	+ + +	ND
MW + Ni	ND	ND	+	+ +	+ + +	ND
MW + Cu	ND	ND	+	+ +	+ + +	ND

* manually; ** automatically; Os – Osmium; Ni – Nickel; Cu –Copper; MW – microwave; ND – not done

pretreatment proved to be completely negative.

In our experiment, microwave irradiation produced intense staining with the ER1D5 and 1D5 antibody. However, it only enhanced staining with NCL-ER-P31 and H222. Contrary to that, staining with D75 after microwave pretreatment remained negative.

Copper, nickel, cobalt, and osmium had various influence on intensity of final color products. Among them, the nickel-DAB product provided the highest detection efficiency. Copper-DAB product resulted an indistinct gray black color of nuclei thus providing insufficient contrast after subsequent hematoxylin counterstaining.

Discussion

The application of a suitable immunohistochemical method for assessing of ER in breast cancer on formalin-fixed tissue, contrary to more traditional method based on biochemical assay of estradiol binding in tissue homogenates, has been strongly advocated. The latter method has the disadvantage of being costly, requiring a fairly large amount of tissue homogenate, and being affected by bound estrogen receptor from high endogenous levels of estradiol in premenopausal women.

Immunohistochemistry, on the other hand, would eliminate the need for fresh tissue and has several other advantages. This method is applicable to formalin-fixed, routinely processed tissue and allows ER status to be assessed on the same blocks as those used for histopathological assessment of tumor without preselection of tissue for separate frozen section. This is particularly important in increasingly more frequent small tumors where separate samples for tissue diagnosis and biochemical assessment of ER cannot be taken, as well as in impalpable mammographically detected or unexpected malignancy cases where the carcinoma may be grossly invisible and the only source for ER determination remains paraffin block with microscopically identified tumor tissue. This method also allows improved morphology and better representation of the tumor, its use in archival material, not to mention the inclination of practicing pathologists to interpret the immunohistochemical findings on paraffin slides.

As immunohistochemistry is extremely technique-dependent, consistent quality can be significantly more difficult to achieve than with other staining techniques. The immunohistochemical ability to stain for cellular proteins is equally dependent on two factors: preservation of the proteins in tissue sections after fixation and processing and quality of the reagents, mainly antibodies, chosen for immunostaining. Pathologists are faced with the decision to expend valuable time and resources on in-house testing of different antibodies, processings and optimizing the procedures. The same holds for ER immunostaining, where the standardization of quality is still a problem even within individual laboratories and reproducibility in general practice is poor.

In this study we decided to compare different commercially available ER antiboies, different methods for tissue digestion, and different detection systems to determine the optimal method for ER immunostaining on formalin-fixed, paraffin-embedded tumor tissue. The comparison of our results showed that the best and most reproducible staining for ER can be achieved using standardized formalin fixation, together with Dako 1D5 primary antibody, microwave antigen retrieval, and Streptavidin-peroxidase protocol performed by an automatic immunostainer. The method we have described is technically easy and rapid to perform, not requiring overnight incubation procedure and gives reproducible results. Indeed, at our Department this method has now been adopted for all cases of primary breast carcinoma, allowing inclusion of ER status as a part of surgical pathology report.

It is beyond the scope of this study to identify a valid cut-off for positivity od ER status using Dako 1D5. Goulding et al found a good correlation in an assessment of ER using Dako 1D5 and Abbott H222 monoclonal antibody. However, in some cases a marked discrepancy was

observed between the scores obtained. This may be attributed to the recognition of different epitopes by the two antibodies (17,18). Similar discrepancies have been observed by others. With the use of the 1D5 antibody a significant increase in the sensitivity of ER determination has been noted together with a more significant correlation with overall survival and disease-free survival than showed previous results with Abbott H222 (19,20).

Moreover, recent data by Battifora and his group indicate that ER staining by Dako 1D5 on archival tumor samples followed by quantification of ER positivity by computerized image analyzer can give even stronger correlation with overall and disease-free survival in breast cancer patients (21).

With the present study we show again that reproducible results in immunohistochemistry are based on controlled conditions and can be achieved mainly on trial and error basis in an individual laboratory, and that no golden rules can be offered.

In conclusion, we have found that assessment of ER status using Dako 1D5 antibody, microwave antigen retrieval, and Streptavidin-peroxidase protocol performed by an automatic immunostainer has many advantages over other antibodies and methods tested.

Acknowledgment

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Radiol Oncol 1995; 29: 338–41.

Sixth World Congress of the International Society for Diseases of the Esophagus

Milan, August 23–26, 1995

The Congress was held in the building of the old University of Milano; its organization was entrusted to Prof. Peracchia. The audience consisted of some 600 participants from 50 different countries. There were five halls available for lectures and video presentations; 150 authors displayed their poster presentations. The scientific program comprised the following sessions: Cancer of the Esophagus: Epidemiology, Biology, Staging and Choice of Treatment; Surgical Treatment; Motility Disorders; Benign Diseases; Achalasia and Diffuse Spasm; Thoracoscopic and Laparoscopic Surgery; Progress in Enteral and Parenteral Nutrition; Extent of Lymphadenectomy; Multimodality Treatment; Palliation; Surgical Treatment; Progress in Diagnosis of Gastroesophageal Reflux Diseases. Barrett's Esophagus; Vagotomy and Reflux Disease; Pediatric Esophageal Surgery, etc. Invited lectures and meetings of ISDE work groups were organized separately. Some conclusions (e.g. those concerning TNM staging) will be accepted upon their confirmation by national societies.

Contributions on the epidemiological and biological properties of esophageal cancer were met with great interest. While the incidence of this disease in Europe was reported to be decreasing in Switzerland and Finland, the relevant trends for Hungary and Check Republic are on the increase. In Europa the etiology of esophageal cancer is associated with smoking and alcohol abuse while in the countries of Far East (China, Japan) relatively high incidence rates are recorded also among nonsmokers and non-alcoholics. The etiology of esophageal cancer is further associated with poor (inadequate) nutrition, heat-related damage, infection (HPV virus?) and genetic factors. In Brasilia a population of persons without cancer, who were at the same time smokers and consumers of *mate**, were found to present with statistically significantly higher content of micronucleoli (DNA fragments) in mucosa cells, as compared to non-smokers and non-users of *mate*, which may point out a population at risk of esophageal cancer. The study on possible association between esophageal cancer and a previous gastric surgery (partial gastrectomy for benign conditions) has failed to identify an increased number of esophageal cancer cases, although there were statistically significantly more cases of low squamous carcinoma of the esophagus among those who had undergone gastrectomy. These patients also presented with higher surgery-related mortality rates than patients without gastrectomy. Achalasia, which is a frequent esophageal motility disorder, is not associated with an increase in the incidence of cancer, and the absolute risk remains low.

Methallothionine (MT) as a prognostic factor and a product of squamous cell carcinoma of the esophagus was reported to inhibit the effect of cytotoxic drugs (cisplatinum) on cancer cells. The presence of MT together with operability significantly influenced the survival of patients treated by irradiation, cisplatin-based chemotherapy and surgery. Thus, MT-negative patients had longer postoperative survivals while MT-positive patients presented with cancers of higher TNM stage.

p53 gene product was not found to be a

relevant prognostic factor. It did not correlate with the survival in uni- or multivariate analyses based on clinical and histological parameters. Although p53 is found to be elevated in approximately 50 % of patients with higher stages of squamous-cell carcinomas, patients with stage N1 exhibit the same 5-year survival results as those without lymph node involvement. It appears that other factors such as hematogenous, lymphatic and neural invasion are prognostically relevant for survival.

Some authors from India reported on the influence of sex hormones on cancer growth. The longer survivals of premenopausal female patients as compared to males was associated with the inhibitory effect of estrogen on metastatic potential, i.e. invasive ability of micrometastases.

The Japanese reported on hematogenous spread of cancer. Blood samples were drawn from various veins (v.azygos, left gastric vein, v.cava superior, cubital vein) during esophageal surgery, and the presence of cancer cells was confirmed in 37.5 % of the studied patients. Although no correlation could be established between a positive blood finding and cancer stage, the presence of cancer cells in blood should be regarded as the initial stage of dissemination.

The reliability of esophageal ultrasonography (EUS) depends on the endoscopist's experience (over a 100 investigations should be performed for obtaining competence credentials) as well as on the technology used. While the reliability of this investigation is indisputable in large cancers, early changes (Tis) set a limit on its usefulness since inflammatory cells or lymph follicle can be misjudged as cancer invasion. After correlation with pathohistological findings, EUS cancer assessment yielded an overall accuracy of 79 %. For the evaluation of lymph node involvement, 86 % sensitivity, 89 % specificity and 88 % overall accuracy were established; the possibility of incorrect staging in cases with EUS undetected lymph node metastases was pointed out. For the needs of accurate staging of esophageal cancer bronchoscopy is possible subgrouping of patients.

Hungarian authors reported on the use of toluidin blue solution in endoscopies. In the past year this method was used in 64 patients with esophageal cancer: superficial beside the advanced disease was detected in 23 % of the patients. In a six-month period, endoscopies performed in asymptomatic patients helped to reveal 4 esophageal cancers. For the evaluation of central or low esophageal cancer and cardiac cancer spread, many authors suggested the use of laparoscopic ultrasonography because of its ability to image peritoneal involvement, which is more common than hepatic one in these cases. EUS is superior to CT, particularly in determining the depth of invasion and in enlarged lymph nodes. Stenosed esophagus due to cancer growth occurring in over 30 % of patients, as well as metastases inaccessible to US probe represent a limitation to EUS. Understaging and overstaging can be expected in approximately 10 % of cases, either due to failure at micrometastases detection or misinterpretation of an inflammatory process for cancer.

The reports on esophageal surgery were centred on interventions in benign and malignant conditions. The issues were discussed from different aspects which upgraded and completed each other.

When comparing mucosal and submucosal cancers, the former had better prognosis although the latter were free of nodal invasion. The type of surgical technique used (transthoracal, transhiatal and total thoracic esophagectomy) does not influence the survival. Surgery remains the treatment of choice for stages 0, I and II as well as for individual stage III patients. Adjuvant and neoadjuvant treatment of randomized groups of patients was not found to have influenced their survival, despite some other studies reporting prolonged survivals after such therapy.

The results of five-year or longer postoperative survival were reported by French authors. Of 733 patients, 76 % underwent curative resections. Not taking into account the 10 % perioperative mortality rate, their overall 5 – year survival was 25.7 %. The distribution by stages

was as follows: 0 – 100%, I – 51%, IIA – 25%, IIB – 13.6%, III – 6%, and IV – 0%. Authors from Hong Kong reported on postoperative recurrence. It occurs in about 50% of patients within 20 months (median) from surgery. Mediastinal recurrences, which are observed in 26% of patients are as frequent as distant metastases. Cervical lymph node (CLN) metastases occurred in 11% of patients; their survival did not differ from the survival of those with recurrences in other sites and no CLN metastases. Patients with neo-adjuvant therapy presented with a significantly lower recurrence rate (30%) than patients who did not receive such therapy (60%). Considering the relatively small number of patients with CLN metastases (also among patients without cervical lymphadenectomy), some authors suggest that indications for cervical lymphadenectomy be restricted accordingly. Unlike the Japanese data, a Chinese study of postoperative survival did not confirm any advantage of extended lymphadenectomy over a minor surgical intervention, with regard to morbidity, mortality, recurrent nerve paralysis and 5-year survival.

In a study of 48 surgically treated patients, the review of pathohistological findings from autopsy reports showed lymph node metastases to present in 87% of those operated on with curative intent and in 78% of palliatively treated patients (the latter had more localized disease and more distant metastases). The reported findings as well as the results of some other authors suggest adjuvant chemotherapy together with extended lymphadenectomy (3 field – 3F – lymphadenectomy), however with the possibility of a minor intervention (2F) to be used in both high and low esophageal cancers.

There were 24 reports on the combined therapy of esophageal cancer by means of surgery, irradiation and chemotherapy. Despite the fact that neoadjuvant therapy has not been accepted as routine therapy, some authors reported on favourable survival results obtained by neoadjuvant chemoradiotherapy, the most frequently used combination containing cisplatinum (70–100 mg/sqm) on Day 1 and 5-FU (800–1000 mg/sqm) on Days 1-4, as well as irradiation (30–40 Gy at different daily fractions). Such combined therapy resulted in better resectability and longer survivals, as compared to surgery alone. However, this applies only to the responders (approximately 30% of patients). Neoadjuvant chemoradiotherapy results in a lower TNM stage and is more effective in earlier stages of cancer. Postoperative ChT also influenced the survival and proved to be more effective in patients with less than 3 positive lymph nodes. In vitro testing of the sensitivity of cancer tissue to cytotoxic drugs correlated with histological findings. Treatment by intracavitary irradiation with TD 25 Gy to 1 cm depth (following percutaneous irradiation with TD 50 Gy) and/or 5-FU was reported. A better effect (local control) was achieved in patients receiving 5-FU. A higher dose rate was associated with more complications. The regimen was also considered suitable for palliative therapy. Intraoperative irradiation was found to effectively control metastasizing to the mediastinum (TD 15 Gy); the treatment was followed by postoperative irradiation.

Among different palliative interventions, gastrostomy is indicated in advanced and upper cancers. The success of laser recanalization depends on the localization (worse results in high situated cancers) and length of involvement. Improved swallowing ability can be achieved in approximately 78% of patients. The duration of treatment response depends mainly on the length of cancer involvement. The authors presenting the use of fine-mesh stents to overcome stenosis have pointed out the clinical and economic advantages of this method over the use of a plastic tube. In the treatment of esophageal fistula (which occurs in about 1–13% of patients) by-pass is considered superior to other methods (median survival 8.6 months vs. 2.1 months following intubation or gastrostomy). High-dose chemotherapy was mentioned as well, though the comparison with other treatment modalities showed only a minor difference in the survival (approximately 4 months).

The present report covers only a part of the topics, conclusions and research studies pres-

ented at the Congress. The great number of contributions is not surprising in view of the fact that esophageal cancer is the 7th most frequent cancer in the world. The relatively poor survival results obtained so far render esophageal cancer subject to extensive basic and clinical research. The Congress offered a good insight into the state of the art, and enabled our results to be compared with those of other authors, thus indicating the direction of our further research. Reflecting the state of the art in clinical practice, the prevailing majority of congress topics were dedicated to surgery. It would be sensible that in the future chemo- and radiotherapy as neo- and adjuvant treatment methods are dealt with in a separate section. Thus, a few issues pertinent to dosage and fractionation regimens in chemo- and radiotherapy have remained unanswered. The results would be easier understandable if all the authors consistently used standard units and abbreviations; further, survival should be expressed in set time intervals (e.g. after 1, 2, 3, and 5 years) and the survival of a small number of patients (around 30) in median value instead of percentages; all this would contribute towards standardization of the results presented in the text and graphic material.

Slovenian authors contributed a paper entitled "Fifteen Years Experience with Esophageal Atresia" (Eržen J. et al.), and a poster "Five-Year Survival of Esophageal Cancer Patients in Slovenia – 1960–1989" (Benulič T. et al.).

The next, i.e. 7th Congress will take place from 1-4 September 1998 in Montreal.

Tomaž Benulič, MD

* *mate:* a local alcoholic drink

Radiol Oncol 1995; 29: 342–3.

News of the EAR

Report on the Meeting of the EAR Executive Bureau held in Remscheid-Lennep on 26 March 1995

M. Bléry

Secretary General EAR, Centre Hospitalier Universitaire de Bicêtre, Department of Radiology, 78 rue du Général Leclerc, F-94275 Le Kremlin-Bicêtre, France

The meeting was held in Roentgen's birthplace, Remscheid-Lennep, upon special invitation from *Prof. P. Peters* and relating to the celebrations organized in honour of Roentgen's 150th birthday.

1. New members of the Executive were elected after ECR'95. The Executive Bureau comprises:

President:	Albert L. Baert
Vice-President:	H. Ringertz
Immediate Past-President:	L. Dalla Palma
Secretary General:	M. Bléry
Treasurer:	W. M. Ross
Members:	H. Pettersson
	P. Rossi

The President welcomed the new members and recalled the methods and means of the Association for attaining its aims and objectives and the goals of the EAR which are:

– to bring people close together on the European level and especially in radiology, and to promote personal and human relationships.

– to improve scientific integration in all fields of radiology. The relationship with the UEMS, the ECR and *European Radiology* and with the European Societies of Subspecialities will implement these policies.

2. Radiology in Eastern European Countries

The PHARE Programe on Health is a project of the European Union. Its aim is to help the countries of central and eastern Europe rejoin the mainstream of European development. PHARE provides grant finance to support the process of economic transformation, to strengthen newly created democratic societies and to help countries with Europe Agreements integrate with the European Union. The support could be obtained especially for restructuring hospital services and developing maintenance, standardisation of medical equipment and quality assurance methods.

The demands should comprise a global overview taking into account strategy for investment, timing execution, plan of amortization and an overview of the existing situation emphasising the present deficiencies. Further information is available from the office of the Secretary General.

3. Contacts with the European Union

The idea is to involve the EAR in the role of an expert or adviser at an early stage of the evaluation of projects such as Telematics, Phare or G7-projects that are devoted to the Health Care Sector. Meetings are planned with the heads of Directorate General I (External Eco-

nomic Relations), DG V (Social Affairs), DG XII (Science, Research, Development), DG XIII (Telecommunications, Information Market, Exploitation of Research).

4. Continuing Medical Education (CME)

Prof. P. Peters has drafted a paper on matters. This draft is based on the document laid down by the Royal College of Radiologists and the main purpose for its presentation was to compare it to the charter of CME that was approved by the UEMS (Union Européenne des Médecins Spécialistes). The following main points were taken in consideration: – the definition, – voluntary or mandatory character, responsible body, sanctions, financing credit, European Board of Radiology. The EAR draft on CME will be tabled at the EAR Working Group and the Joint Commission UEMS-EAR.

5. "European Radiology"

Since January 1995 the Journal is indexed in Current Contents.

6. Committee for Computer Science in Radiology

A Working Group of the Committee has decided to organize a "EAR Database". This initiative will be taken to set up a database of radiological teaching files, scientific and administrative information which would give access to the radiological community of Europe through Internet.

7. Cost Effectiveness

A Working Group has been set up. headed by *Dr. Saxton.* The members of the group will act as advisers to the Executive Bureau. Its final objective is to address guidelines in health care to be submitted to the European Union.

8. Project on Education of Management Concepts in Radiology

The project is directed towards a common education background in Europe, for the organization of all activities that academic departments deal with, such as clinical activites, research and teaching. The main target group for the project are European academic radiologists in advanced stages of their career. The project will be carried out under the auspices of the EAR.

Notices

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

Clinical Services

The "Advanced Program for Chiefs of Clinical Services" will be held in Boston, USA. *February 4–9, 1996.*

Contact HSPH, Office of Cont. Educ., 677 Huntington Ave., LL-23, Dept. B, Boston, MA 02115-6023, USA; or call +1 617 432 1171.

Gastroenterology

The symposium "VI Gastroenterology Week" will be offered in Titisee, Germany. *February 10–15, 1996.*

Contact FF e.V., P.O. Box 6529, D-79041 Freiburg/Br., Germany; or call +49 761 130 3425.

Radiation Oncology

The "26th Annual University of Florida Radiation Oncology Clinical Research Seminar" will be held in Gainesville, FL, USA. *February 22–24, 1996.*

Contact William M. Mendenhall, M. D., 1996 Seminar Coordinator, P.O. Box 100385, Gainesville, FL 32610-0385, USA; or call +1 904 395 0287; Fax: +1 904 395 0546.

Hepatobiliary diseases

The symposium "Update on Hepatobiliary Diseases 1996" will be held in Hong Kong. *February 29–March 1, 1996.*

Contact FF e.V., P.O. Box 6529, D-79041 Freiburg/Br., Germany; or call +49 761 130 3425.

As a service to our readers, notices of meetings or courses will be inserted free of charge.
Please sent information to the Editorial office, Radiology and Oncology, Vrazov trg 4, 61105 Ljubljana, Slovenia.

Oncology

The "9th NCI–EORTC Symposium on New Drugs in Cancer Therapy" wil be held in Amsterdam, The Netherlands. *March 12–15, 1996.*

EORTC, New Drug Development Office, Free University Hospital, P.O. Box 7057, NL-1007 MB Amsterdam, The Netherlands; +31 20 444 2795; Fax: +31 20 444 2767.

Gastroenterology

The symposim "Inflammatory Bowel Diseases in Aisa" will be offered in Hong Kong. *March 2, 1996.*

Contact FF e.V., P.O. Box 6529, D–79041 Freiburg/Br., Germany; or call +49 761 130 3425.

Radiotherapy

The Ibero Latin American Circle of Radiation Oncologists "CRILA Meeting" will be offered in Panama, Republic of Panama. *March 17–20, 1996.*

Contact Luis Delclos, Department of Radiotherapy, MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA; or call +1 713 792 3404; Fax: +1 713 792 3642.

Gastroenterology

The "III Pediatric Gastroenterology Symposium: Inflammatory Bowel Diseases and Chronic Recurrent Abdominal Pain" will take place in Basel Switzerland. *March 22–23, 1996.*

Contact FF e.V., P.O. Box 6529, D–79041 Freiburg/Br., Germany; or call +49 761 130 3425.

Clinical Oncology

The intensive course of clinical oncology will be held in Edinburg, U.K. *April 1–4, 1996.*

Contact Dr. Ian Kunkler, Western General Hospital, Crewf Road, Edinburg, U.K.; or call +44 31 3322525.

Hyperthermic Oncology

The "7th International Congress on Hyperthermic Oncology" will take place in Rome, Italy, *April 9–12, 1995.*

Contact Prof. C. Franconi, Internal Medicine Dept., Tor Vergata, Univ. of Rome, Via O. Raimondo, 00173 Rome, Italy; or call +39 6 723 5170; Fax: +39 6 725 92821.

Information systems

The seminar "Information Systems for Managed Care and Integrated Delivery Networks" will be held in Boston, USA. *April 9–12, 1996.*

Contact HSPH, Office of Cont. Educ., 677 Huntington Ave., LL-23, Dept. B., Boston, MA 02115-6023, USA; or call +1 617 432 1171.

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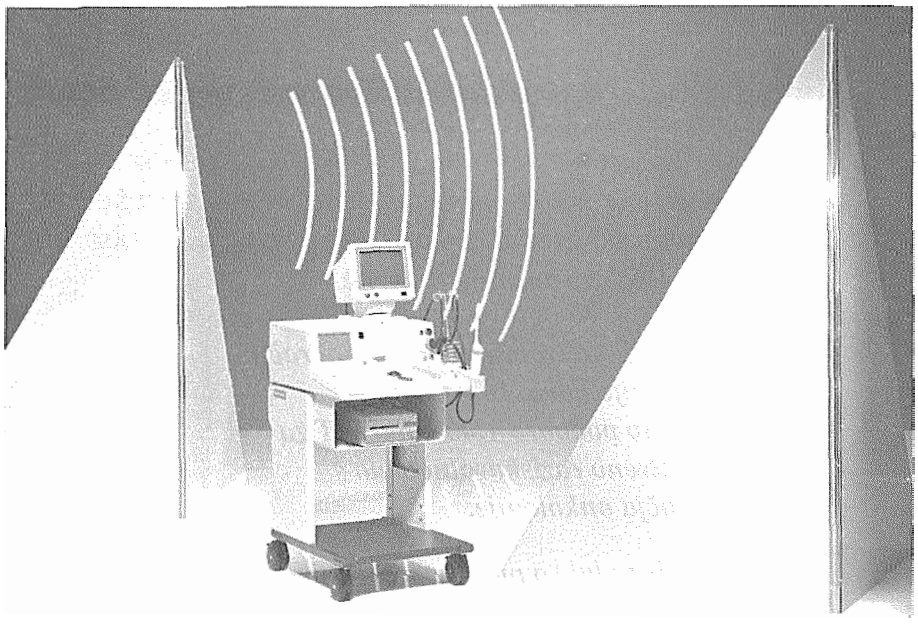

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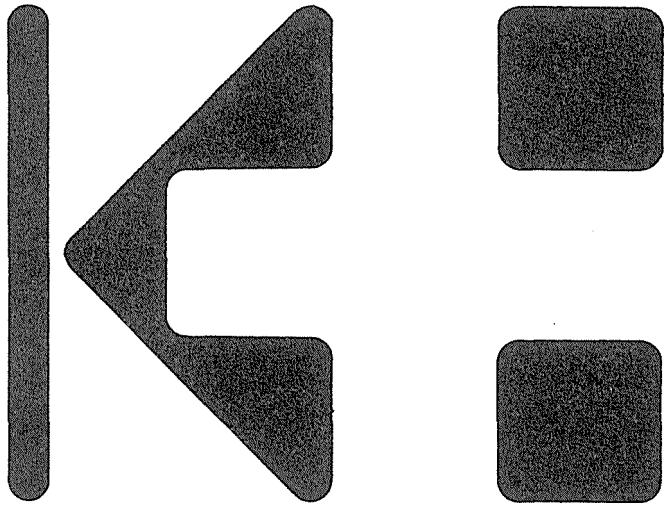

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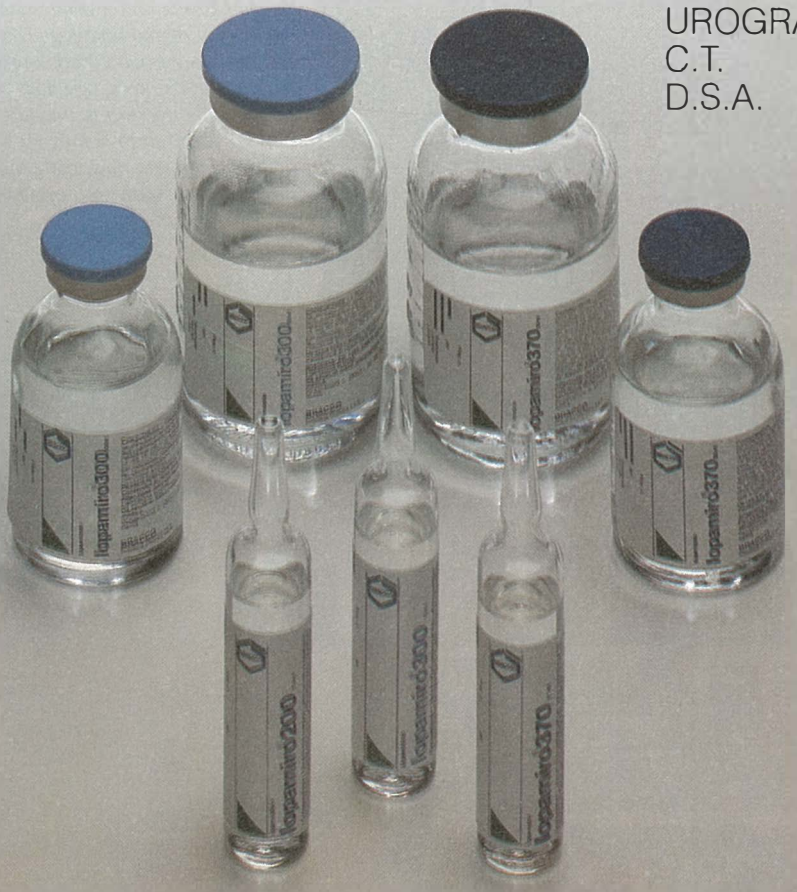

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1. Dent RG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.

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

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

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