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Endoscopic retrograde pancreatography in the diagnosis of chronic pancreatitis

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The importance of endoscopic cholangiopancreatography (ERCP) in the diagnosis of chronic pancreatitis is the basic topic of the paper. The method is considerably more sensitive than any other radiological, especially noninvasive method used in diagnostics. Especially thanks to this combined endoscopis radiological method, chronic pancreatitis is at present classified in three groups. Thus, it is possible to make exact plans for the further treatment, which may be either medical (endoscopical), or surgical. An analysis is here made of 370 patients with whom chronic pancreatitis was established by this method. Of this number 286 (77 %) were men, and 84 (23 %) women. Most of the patients were between 40 and 50 years of age, their number being 204 (55 %). Here they appear classified into three groups according to the mentioned classification method. The group of mild chronic pancreatitis includes 154 (42 %) patients, 123 (33 %) patients show moderate changes, and 93 (25 %) patients have marked changes. It is important to point out that 211 (74 %) of 286 patients in their case history mentioned the consumption of alcohol and nicotine for more than five years.

Key words: pancreatitis-diagnosis, cholangiopancreatography, endoscopic retrograde; chronic disease

Introduction

Endoscopic retrograde Cholangiopancreatography (ERCP), a combined radiological method, was introduced into clinical practice 25 years ago and became a routine procedure in the diagnostics of biliopancreatic system complaints.[1-4] It has since taken a special place in the diagnostics of chronic pancreatitis, where it is much more sensitive than any other noninvasive radiological method such as ultrasound and computerized tomography.[5-8]

Except in the appraisal of the severity of chronic pancreatitis on the basis of changes in its ductal system, it also serves to the planning of any further treatment, which may be either medical (endoscopical), or surgical.[9-10] The aim of the paper is to illustrate: the value of ERCP in the diagnostics of chronic pancreatitis and to make an analysis of the results obtained.

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Material and methods

An analysis of 370 successful ERCPs in which chronic pancreatitis had been established was made. The indication was made on the basis of the patients' case history, clinical picture, lab reports, and the pancreas ultrasound examination of all patients was carried out as well. ERCP was made a technique as it was described and adopted by a great number of authors. In this case the special attention was given to the pre-ERCP control to detect prefilling changes of parenchima, such as calcification before the central film examination.[2-5, 7, 11]

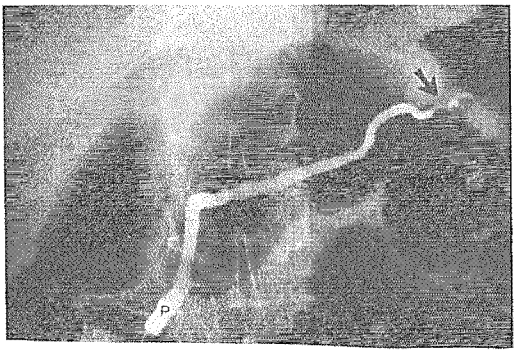

Figure 1. Mild changes chronic pancreatitis. Normal ductus pancreaticus (P) and > 3 changes lateral duct (arrow).

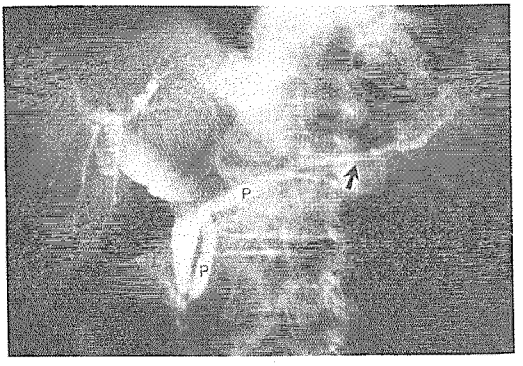

Figure 2. Moderate changes chronic pancreatitis. Dilatation of ductus pancreaticus (P) and 3 changes lateral duct (arrow).

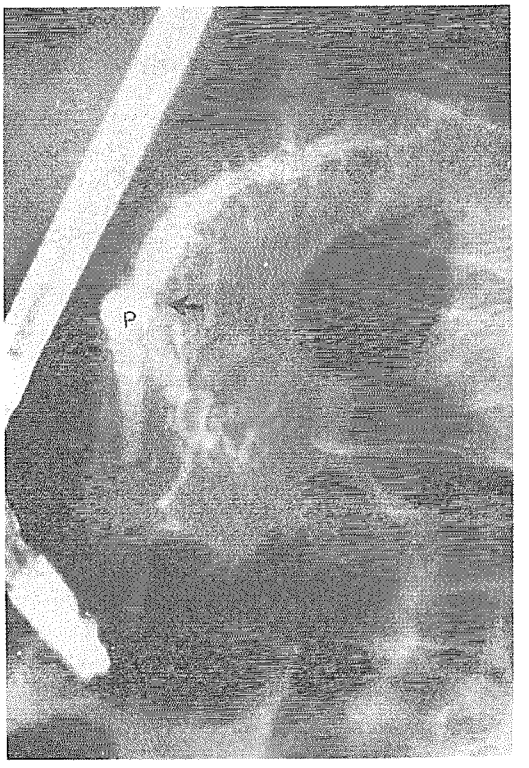

Figure 3. Marked changes chronic pancreatitis. The same as Figure 2 with extremly dilatation of ductus pancreaticus (P and arrow).

All ERCP findings have been classified by using the international system of 1984 (Table 1)[12] which is ilustrated at Figures 1, 2, 3.

Results

Of 370 successfully made ERCPs, where chronic pancreatitis had been found, 286 (77 %) were men, and 84 (23 %) women. The average age of all patients analysed was under 40, 93 (25 %); between 40 and 50 were 204 (55 %) patients, and 73 (20 %) patients were above 50. By using the above mentioned classification the group of mild changes comprised 154 (42 %) patients, the group of moderate changes 123 (33 %) patients, and the most severely affected group of marked changes 93 (25 %) patients. In this last group it is of interest to mention that it comprised 81 (87 %) men, and only 12 (13 %) women, all of them alcohol and nicotine consumers for five years of more. And of all the 286 men analysed, the case history of 211 (74 %) included a record of the consumption of these harmful agents.

Discussion

Chronic pancreatitis in its mild form presents a difficult diagnostic problem.[8, 13-14] In its severe form, with or without complications, the diffilculty is increased by a very serious therapeutic problem. But it is exactly through the ERCP that today we have also numerous nonsurgical possibilities in the treatment of this disease at our disposal.[14-18] Another important fact to be pointed out is, thanks to this method, that the classification of chronic pancreatitis has been effected into three forms, which in turn is important for the treatment of this disease.[11, 12]

To make the endoscopic treatment of this disease easier, there exist today also other classifications at our disposal, although they are rarely used.[16] This paper deals with the analysis of 370 ERCPs in

Table 1. Classification of chronic pancreatitis.[12]

Terminology	Main pancreatic duct	Number of dameged branches of pancreatic duct
Normal finding	unchanged	none
Border pathological finding	unchanged	< 3
Mild changes	unchanged	3 or > 3
Moderate changes	pathologicaly changed	> 3
Marked changes	pathologicaly changed*	> 3

* With one, or more than one criteria: big cyst, obstruction, marked dilatation or marked changes of organ shape.

which chronic pancreatitis has been established. It is evident that in 77 % of the cases men are predominant, which is the result of the more frequent use of noxious agents such as alcohol and nicotine. It has been further noticed that the disease occurs at the most reproducible stage, and that is between 40 and 50 years of age. Similar data have been established also by other authors.[19]

The internationally accepted classification has been used also in this paper, in which 42 % cases of mild, 33 % cases of medium, and 25 % cases of severe chronic pancreatitis have been found. It is not possible to compare these data with the pertinent literature, as the severity of the disease is dependent upon the duration of the period of time during which the noxious agents have been consumed, the type of alcohol and nicotine, and a number of other external and internal factors.[20-22] It is sometimes difficult to make or solve the differential diagnosis of pancreas carcinoma regardless the series of methods used, noninvasive radiological or invasive endoscopic ones.[23-25] And to conclude with, it is exactly thanks to the ERCP combined endoscopic radiological method that chronic inflamatory pancreas diseases can be established at an early stage, to differentiate this method from other radiological non-invasive examinations. In severe cases of the disease, besides for making a strictly correct diagnosis, the method offers also at present wide therapeutic possibilities.

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Radiol Oncol 1997; 31: 277-8.

Active bleeding due to pancreatitis diagnosed by contrast enhanced CT

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The authors present the case of a 55 - year - old male patient in whom an active bleeding developed in to pancreatitis, which was diagnosed by the contrast enhancement CT. So the verification of the process is rare but, the necessity and the advantage of contrast material administration during CT is emphasized. Finally, they summarize the special CT appearances of active bleeding which is definitive enhancement of contrast developed in the centre of the lesion.

Key words: pancreatitis-diagnosis; gastrointestinal hemorrhage-diagnosis; tomography, x-ray computed; radiographic image enhancement

Introduction

The course of acute pancreatitis can be mild, medium, and severe. The history, physical and laboratory findings are primary in setting up the diagnosis. Among the imaging systems CT is the most appropriate method in defining severity and complications of the acute phase.[1] Follow up examinations of chronic pancreatitis can be performed by the ultrasound (US). When clinical and laboratory data suggest bleeding, Doppler US and angiography are needed.

Case report

A 55-year-old male patient was admitted to the surgical department of Markusovszky Hospital because of the abdominal pain and vomitting. In his previous history the medical treatment for chronic pancreatitis and laparotomy for a pseudocyst were mentioned. His physical and laboratory findings were all normal: Hb: 7,7 mmol/l., HCT: 0,36, WBC: 7,4 G/l., serum amylase: 233 U/l., serum lipase: 160 U/l., but the elevated serum bilirubin: 23 mmol/l. The chest and the abdominal radiography were negative. A Levin tube was introduced to the stomach, and the patient received infusion. His condition improved so much that he was able to walk to the department of radiology where the abdominal US was carried out: a 7 cm diameter low echogenity, well circumscribed mass was seen behind the stomach. For the better visualisation a CT examination was performed: the head and body of the pancreas were swollen, but the tail could not be well discerned. In the lesser sac, a high, mixed density mass appeared, similar to that found by the US (Fig-

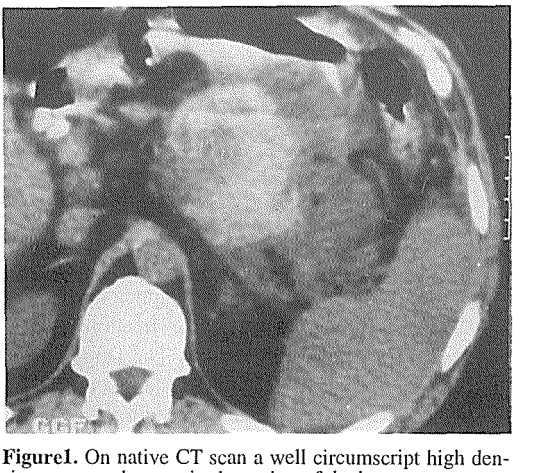

Figure1. On native CT scan a well circumscript high density mass can be seen in the region of the lesser sac.

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ure 1). After the administration of contrast material a definitive enhancement developed in the centre of the lesion (Figure 2). These US and CT findings prompted us to diagnose pancreatitis caused by the active bleeding from the ruptured pseudoaneurysm of the lienal artery. Unfortunately, we were not able to perform angiography and the needed embolization because our equipment did not actually work, being under repair. Next day the patient's condition worsened dramatically. He went into shock, and vomitted blood. Emergency laparotomy revealed that the stomach was filled with blood, and that a 3 cm long rupture appeared on the posterior wall. A large, bloody, necrotic cavity was found in the region of the pancreatic tail. The source of the bleeding was the artery lienalis arroded in the bottom of this cavity. Splenectomy and ligature of the lienal artery were performed. The patient was treated in the intensive care unit, but he died after a few days.

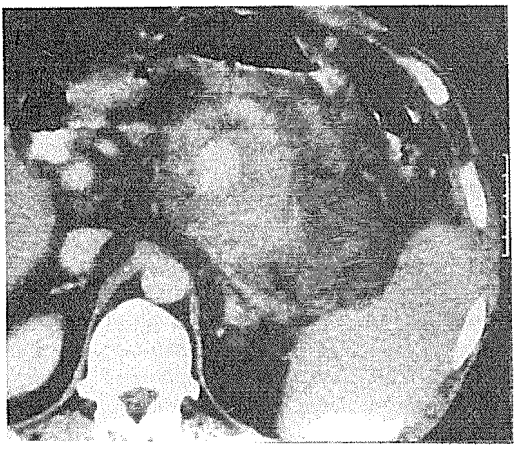

Figure 2. After contrast material administration a definitive enhancement developed clearly showing the rupture of the lienal artery pseudoaneurysm.

Discussion

Enzymes released as a consequence of pancreatitis may cause the formation of peripancreatic vessels. Pseudoaneurysm formation or, in rare cases, active bleeding can develop. In case of the suspected active bleeding, a life-threatening complication, a rapid correct diagnosis, and the verification of the source of bleeding are imperative. The Doppler US and the selective angiography are the examinations of choice in these cases. When bleeding is proved, the percutaneous embolization is a possible therapeutic approach.[2]

The symptom-free active abdominal bleeding is rare. It may be incidentally revealed by CT after the blunt abdominal trauma.[4-7] In the acute phase of pancreatitis a contrast, enhanced dynamic CT examination can exactly define the boundaries of intact and damaged parenchyma. In addition, the active bleeding causes characteristic changes observable by a contrast enhancement. Jeffrey et al. summarized the CT features of active bleeding, not due to pancreatitis but based on their own experience and literature data.[8,9]

Circumscript form: On native scans the density of haematoma is higher /70-80HU/ than the surrounding organs' density. After the contrast material administration, a definitive enhancement can be seen within the haematoma (130-150HU).

Diffuse form: The high density area in the peritoneal cavity or the extraperitoneal space with massive enhancement after the contrast material. It is important to mention that the degree of contrast enhancement is similar to the enhancement of the neighbouring vessels in both forms.

When bleeding invades into a preformed pseudocyst, and the patient is free of symptoms, the high density of the pseudocyst content on native scans may call our attention to bleeding, and the degree of contrast enhancement can verify its presence.

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Radiol Oncol 1997; 31: 279-85.

Radioprotection of salivary glands by amifostine in high-dose radioiodine therapy investigated in a new rabbit animal model

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Salivary gland damage following high-dose radioiodine treatment (HD-RIT) is a well known side effect. Since differentiated thyroid cancer (DTC) has a very good prognosis, the reduction of long-term side effect is of major interest. Therefore, the radioprotective effect of amifostine was investigated in a rabbit animal model. Quantitative salivary gland scintigraphy was performed on 5 rabbits prior to and up to 3 months after HD-RIT applying 1 GBq I-131. The uptake of Tc-99m-pertechnetate was calculated as a measure of parenchymal function. Three animals received 200 mg/kg amifostine prior to HD-RIT, and two served as controls. Salivary glands were examined histopathologically. In two control rabbits HD-RIT significantly ($p<0.001$) reduced pertechnetate uptake by 63 % and 46 % in parotid and submandibular glands, respectively, and lipomatosis was found histopathologically. In contrast, in three rabbits treated with amifostine parenchymal function was not decreased significantly ($p = 0.953$), and lipomatosis was negligible. In conclusion, salivary gland impairment induced by HD-RIT can be evaluated quantitatively by salivary gland scintigraphy in rabbits, and amifostine significantly reduced salivary gland damage induced by HD-RIT. These encouraging results need further evaluation in patients since it may help to increase the quality of life of patients with diffentiated thyroid cancer.

Key words: Salivary glands – radiation effects; radiation-protective agents; – amifostine; radiotherapy-adverse effects; rabbits

Introduction

A standard therapy in differentiated thyroid cancer requires a total thyroidectomy and a high-dose radioiodine therapy in order to completely ablate thyroid remnants.[1] Apart from thyroid tissue the β-emitting iodine isotope I-131 used for radioiodine therapy is accumulated actively by an ATP dependent $Na^+/K^+/2Cl^-$-cotransport due to its similar atomic diameter and its comparable electric charge.[2-6] This causes an undesired accumulation of I-131 in parietal cells of the stomach as well as in acinar cells of salivary glands.[6-9] Consequently, well recognized side effects of high-dose radioiodine therapy are transient gastritis and long-lasting xerostomia.[10-16] Therefore, a radioiodine therapy is performed under salivary gland stimulation in order to decrease the impairment of salivary gland function.[17-23] However, even under salivary gland stimulating conditions, a parenchymal damage could be shown after high-dose radiodiodine therapy using quantitative salivary gland scintigraphy.[13, 24-27] Since

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differentiated thyroid cancer has very good prognosis, reduction of long-term side effects following high-dose radioiodine therapy is important for the patients' quality of life.[1]

In the last few years various reports dealt with radioprotective effects of amifostine,[28–33] a phosphorylated aminothiol chemically described as S-2-[3-aminopropylamino]-ethylphosphorotioic acid (Figure 1). Since amifostine accumulates markedly in salivary glands,[34] it has been used successfully in external radiotherapy in patients with head and neck tumors in order to prevent xerostomia.[35–40]

$$H_2N–CH_2–CH_2–CH_2–NH–CH_2–CH_2–S–PO(OH)_2$$
$$\downarrow \text{[Alkaline Phosphatase]}$$
$$H_2N–CH_2–CH_2–CH_2–NH–CH_2–CH_2–SH$$

Figure 1. Chemical structure of amifostin (above) and its active metabolite WR–1065 (below).

Therefore, it looked worthwhile to transfer the radioprotection of salivary glands by amifostine to high-dose radioiodine therapy in order to prevent patients from xerostomia, and, thus, to increase the tolerance of high-dose radioiodine therapy.

As a first step we established a rabbit animal model and report on first results.

Materials and methods

In order to investigate the cytoprotective effect of amifostine an animal model was established. Five male New Zealand white rabbits aged three months, weighing 2.5±0.1 kg, were treated with 1 GBq I-131 intravenously in order to ablate the thyroid and to destruct salivary gland parenchyma. Prior to the application of radioiodine all animals received 4 mg Dexamethason (Fortecortin®, Merck, Darmstadt) and 0.5 mg Tropisetron (Navoban®, Sandoz, Nürnberg) as antiemetic treatment. In addition, three out of five rabbits received 200 mg/kg amifostine (Ethyol®, Essex, München), and two rabbits served as controls, receiving physiological saline solution.

To quantify parenchymal function, salivary gland scintigraphy was performed prior to as well as four weeks, eight weeks and twelve weeks after the application of I-131. Rabbits were put in prone position directly onto a low energy high resolution collimator of a large field – of – view gamma camera (Bodyscan, Siemens, Erlangen). After injection of 100–140 MBq Tc-99m-pertechnetate sequential images of one minute each were acquired up to 25 minutes. Images were stored digitally in a 256 × 256 matrix. For quantification one rectangular background ROI was positioned caudally to the left parotid gland, and five oval ROIs were drawn over both parotid and submanidbular glands and the thyroid gland, respectively. ROIs were copied from the study performed prior to radioiodine treatment to the studies obtained after radioiodine treatment. As a measure for parenchymal function the uptake of Tc-99m-pertechnetate was calculated in percent of the injected activity. For compensation of noise and, thus for stabilisation of data, uptake was averaged from 21.–23. minute post injection. Whole body distribution of Tc-99m-pertechnetate in a rabbit is shown in Figure 2A and ROIs used for quantification are depicted in Figure 2B.

Twelve weeks after radioiodine therapy all animals were sacrificed to remove salivary glands for histopathological examination. Salivary glands were stained with Hematoxilin/Eosin in conventional manner.

Animal studies were approved by the local government (XI 330a 72241.11-17).

Data are given as mean ± one standard deviation. Two-tailed U-test according to Wilcoxon, Mann and Whitney was used to evaluate statistical differences between animal subsets.[41] For $p<0.05$ data were considered to be statistically significant.

Results

Controls

Details of Tc-99m-pertechnetate uptake in salivary glands of controls and amifostine rabbits are given in Table 1. Salivary gland scintigrams of a control rabbit are given in Figure 3 (upper row). In controls thyroid uptake declined to almost zero as early as four weeks after radioiodine treatment, thus documenting a thyroid ablative dose of radioiodine. In parallel, parenchymal function of salivary glands decreased. Twelve weeks after the injection of I-131 Tc-99m-pertechnetate uptake was reduced by 63 % and 46 % in parotid and submandibular glands, respectively, (Figure 4, open symbols).

Amifostine group

Rabbits treated with amifostine exhibited complete ablation of the thyroid four weeks after the application of I-131 as well. This is shown in Figure 3 (lower row). In contrast, in these animals parenchy-

Table 1. Uptake of Tc-99m-pertechnetate in percent of injected activity prior to, 4, 8, and 12 weeks after the application of 1 GBq Iod–131 in control rabbits and in rabbits treated with amifostine 200 mg/kg body weight. Numbers represent mean of right and left parotid and submandibular glands, respectively.

	Controls		Amifostine	
	Parotid glands	Submandibular glands	Parotid glands	Submandibular glands
prior to I-131	0.226 ± 0.042	0.295 ± 0.070	0.241 ± 0.030	0.230 ± 0.074
4 weeks after	0.140 ± 0.018	0.199 ± 0.046	0.215 ± 0.038	0.215 ± 0.060
8 weeks after	0.106 ± 0.019	0.187 ± 0.067	0.209 ± 0.032	0.210 ± 0.065
12 weeks after	0.080 ± 0.011	0.154 ± 0.057	0.208 ± 0.023	0.212 ± 0.057

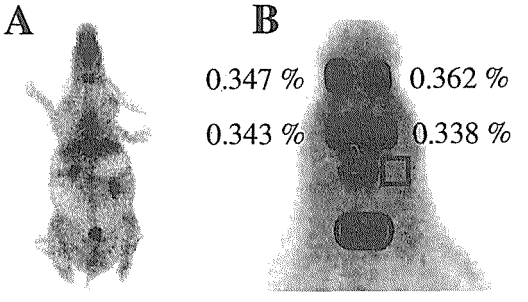

Figure 2. Whole body distribution of Tc-99m-pertechnetate (A) and the magnification of the head (B) visualizing the ROIs used for quantification. Numbers represent uptake of Tc-99m-pertechnetate in percent of the injected activity in parotid, submandibular glands, and thyroid gland, respectively.

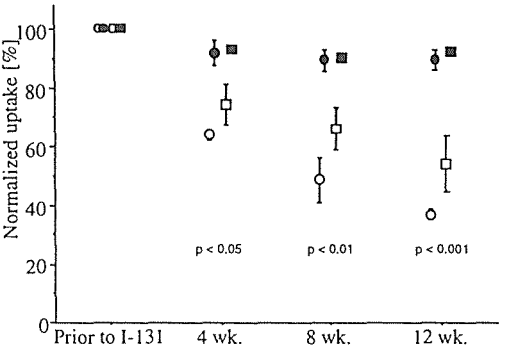

Figure 4. Normalized uptake of Tc-99m-pertechnetate in parotid (circles) and submandibular (squares) glands of control rabbits (open symbols) and of trabbits treated with amifostine (filled symbols) prior to, 4, 8 and 12 weeks after application of 1 GBq I-131.

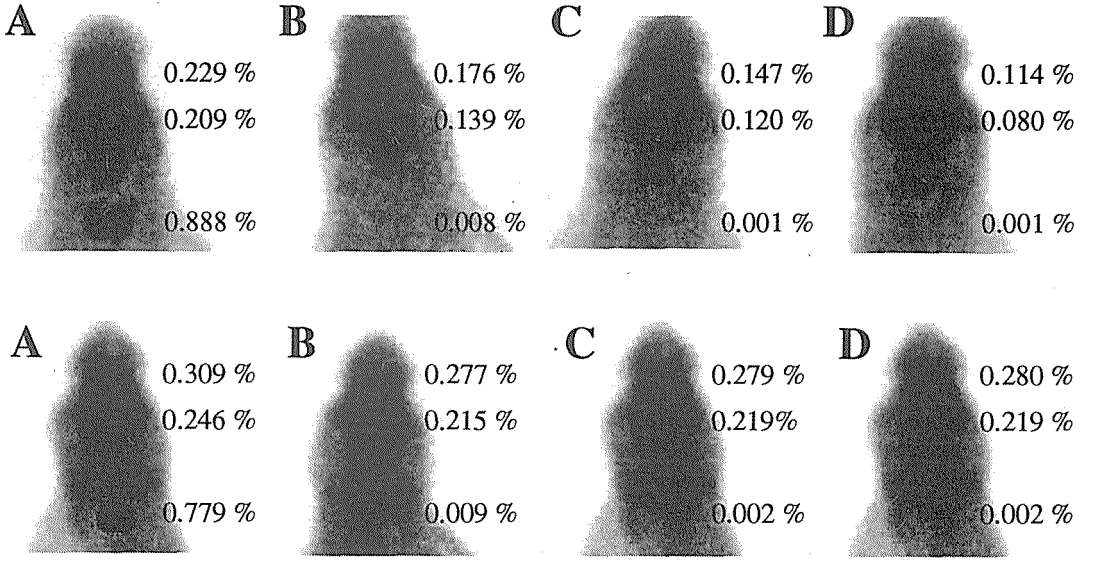

Figure 3. Salivary gland scintigraphy in the control group (upper row) and in the amifostine group (lower row) prior to (A), 4 (B), 8 (C), and 12 weeks (D) after the application of 1 GBq I-131. Numbers represent uptake of Tc-99m-pertechnetate in percent of the injected activity in parotid, submandibular glands, and thyroid gland, respectively.

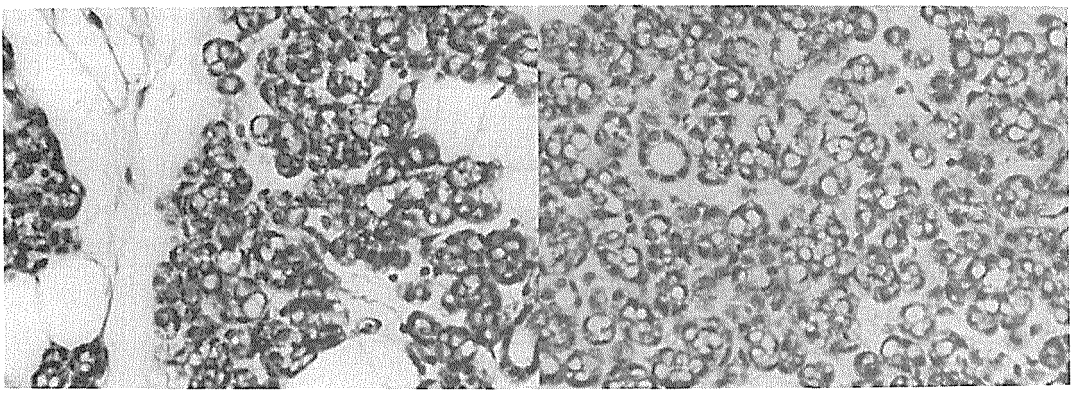

Figure 5. Hematoxilin/Eosin-stained slices of parotid glands of the control group (left), and of the amifostine group (right) twelve weeks after the application of 1 GBq I-131. Note a significantly more pronounced lipomatosis in the control animal. Magnification: 500 times.

mal function of salivary gland was decreased not significantly (p=0.953) by only 10 % and 7 % in parotid and submandibular glands, respectively (Figure 4, filled symbols).

Histopathology

Results of histopathological examinations are given in Figure 5. Salivary glands of control rabbits exhibited a marked lipomatosis as a typical sign of radiogenic damage, but no signs of inflammation (Figure 5, left), whereas lipomatosis was much less pronounced in animals treated with amifostine (Figure 5, right).

Discussion

Quantification of salivary gland function

Salivary gland scintigraphy performed in a standardized method as previously described[42, 43] facilitates the quantitative evaluation of salivary gland parenchymal function. It is characterized both by an excellent intraindividual observer variability and reproducibility which enables the detection of changes in parenchymal function in the range of about as less as 5–10 %.[26, 27] This enabled both the early detection of beginning Sjögrens syndrome by salivary gland scintigraphy as compared to other imaging modalities[44] and the detection of parenchymal impairment of salivary glands following low-dose radioiodine therapy.[26, 27] Therefore, quantitative salivary gland scintigraphy proved to be a suitable imaging modality for quantitative evaluation of salivary gland function.

Amifostine

Amifostine was originally developped as a radioprotective agent as a part of the Anti-Radiation Drug Development Program initiated by the United States Army at the Walter Reed Army Institute of Research (Washington) in the early 1950s.[29] Since numerous preclinical studies in cell culture and animal models showed that, following dephosphorilation to its active metabolite WR-1065, amifostine selectively protected normal tissue from damaging effects of irradiation, several clinical studies were initiated confirming its radioprotective potency in various publications.[35–40, 45] This resulted in an approval of amifostine in Germany in 1995 for the supportive therapy of patients with ovarian cancer being treated with cisplatin derivatives in order to minimize myelotoxic side-effects of cisplatin.[30]

The selective radioprotection of normal tissue by amifostine as compared to tumor tissue is mainly caused by two effects. First, amifostine is accumulated much more in normal tissue, and, second, the alkaline phosphatase necessary for dephosphorilation of amifostine and thereby activating amifostine is more active in the alkaline environment of normal tissue than in the acid tumoral tissue.[29, 46–48]

Since amifostin is known to be accumulated extensively in salivary glands[29, 34, 48–51] it seemed reasonable to use amifostine as protecting agent in patients with head and neck tumors receiving external radiation therapy. Takahashi and coworkers[37] studied Ga-67 uptake as an indicator for irradiation-induced damage in salivary glands of patients with head and neck cancer and showed that pretreatment with amifostine resulted in a significantly increased number of Ga-67 negative salivary glands following irradiation. Some studies have been undertaken so far in

head and neck tumors yielding very promising results concerning the reduction of radiation induced salivary gland damage.[35-40]

Since radiation effects of external radiation and radioiodine therapy are in general caused by the same mechanisms,[10] i.e. the production of free radicals, it seemed promising to transfer the radioprotective effect on salivary glands by amifostine to high-dose radioiodine therapy.

Animal studies

In this study 1 GBq I-131 was applied for complete ablation of the thyroid and for concomittant parenchymal impairment of salivary glands. In fact, the activity applied caused a complete thyroid ablation in the animals of the control group as well as in animals treated with amifostine as early as four weeks after application of I-131. Thus, amifostine did not protect thyroid tissue from I-131. This is in accordance with the observation that amifostine is accumulated to an only marginal amount in the thyroid of several specimen.[47, 52-56] This observation yields the prerequisite for the application in differentiated thyroid cancer since protection of thyroid tissue or metastases of differentiated thyroid cancer has to be excluted.

In our animal studies we could show a clear radioprotective effect of amifostine in salivary glands of rabbits treated with-dose radioiodine. This was demonstrated scintigraphically by a significantly reduced parenchymal impairment of salivary glands after pretreatment with 200 mg/kg amifostine. Moreover, in rabbits treated with amifostine we histologically observed a markedly reduced lipomatosis without evidence of an inflammation. This is in accordance with several papers in which lipomatosis is described as a typical late effect of radioiodine treatment.[57-59] Thus, animal studies showed an encouraging radioprotection of salivary glands by amifostine in high-dose radioiodine therapy.

Conclusion

Parenchymal damage in salivary glands induced by high-dose radioiodine therapy can be evaluated quantitatively by salivary gland scintigraphy in a new rabbit animal model introduced. Amifostine significantly reduced salivary gland damage induced by high-dose-radioiodine therapy. These encouraging results need further evaluation in patients since it may help to increase the quality of life in patients with diffentiated thyroid cancer by avoiding xerostomia.

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Diagnostic value of planar myocardial perfusion scintigraphy in patients with coronary artery disease

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Patients with suspected or proven coronary artery disease are investigated using noninvasive and invasive diagnostic methods. Noninvasive myocardial perfusion scintigraphy provides data on myocardial perfusion during stress and at rest. Coronary angiography is invasive morphologic method, performed before coronary artery dilatation or surgery. Aim of our retrograde analysis of planar thallium myocardial perfusion scintigrams and coronary angiograms was to assess sensitivity and specificity of myocardial perfusion planar scanning and to evaluate causes of possible disagreement. Original readings of myocardial perfusion scans and coronary angiograms of 156 patients with coronary artery disease were compared. When results of both investigations were partially concordant or discordant, the original studies were reviewed. Concordant results of both examinations were found in 62% of patients. In only 3% (5 patients) the results were discordant and the reason for disagreement of results of both studies could not be detected. Most of the remaining 55 patients had more pronounced myocardial perfusion defects than was the estimated severity of coronary artery stenosis, attributed to the different nature of both investigations. Anomalous coronary artery was found in 3% of all patients, tortuous coronary arteries with slow flow of contrast media in 9 patients (6% of all) and arterial hypertension with extreme left ventricular wall hypertrophy in one patient. Sensitivity of the myocardial perfusion scintigraphy was 100% and specificity 50%. Positive predictive value for coronary artery disease was 96% and negative predictive value was 100 %. We cconclude that myocardial perfusion scintigraphy has a definite role in diagnosis and follow-up of patients with suspected or proven coronary artery disease. New techniques and technetium labeled tracers improve reliability of myocardial perfusion scintigraphy and enable reasonable use of more aggressive diagnostic methods.

Key words: coronary disease-diagnosis; heart-radionuclide imaging

Introduction

Various diagnostic possibilities exist for patients with suspected or proven coronary artery disease. Clinical data are combined with electrocardiogram (ECG) and stress testing.[1] Myocardial perfusion scintigraphy is significantly more accurate for diagnosing coronary artery disease than the exercise ECG.[2,3,4]

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Additional invasive approaches are needed for evaluation of the disease extent, severity and before the therapeutic interventions. Coronary angiography detects morphological changes utilizing intracoronary injection of the contrast media.[5,6,7] Myocardial perfusion scintigraphy uses photon or positron emmitting substances to assess myocardial perfusion. Among first radiopharmaceuticals and until recently the most widely used was thallium 201.[3,4,8,9] Results of the myocardial perfusion imaging and the coronary angiography are usualy compared. Their concordance depends on the degree of coronary artery disease, previous myocardial infarction and technical factors.[3,10,11] As treatment of patients with coro-

nary artery disease depends on the results of diagnostic tests, they have to be accurate.

Our retrograde analysis of myocardial perfusion scintigrams and coronary angiograms in patients with coronary artery disease was performed to assess sensitivity and specificity of myocardial perfusion planar scanning and to evaluate causes of possible disagreament.

Patients and methods

Consecutive patients, referred for suspected or proven coronary artery disease to myocardial perfusion scintigraphy in two and a half years period were included. The time between perfusion scintigraphy and the coronary angiography had to be less than six months. No acute coronary event or therapeutic intervention between both examinations was allowed.

In the two and a half years' period more than 1000 patients had myocardial perfusion scintigraphy and 341 of them had coronary angiography. Only 156 of those had both investigations performed in up to 6 months period and both studies available in the archives. *Clinical data* (gender, age, previous myocardial infarction, possible fibrinolytic therapy, arterial hypertension and angina) were analysed. Left bundle branch block was searched for in ECG. Data are given in Table 1.

Table 1. Patients' data.

	Number	% of all
Men	133	85
Women	23	15
<40 years	2	1
40-50 years	43	28
>50-60 years	64	41
>60-70 years	42	27
>70 years	5	3
Time between investigations		
<1month	84	54
1-3months	46	29
4-6months	26	17
Hypertension	92	59
Angina pectoris		
Typical	125	80
Atypical	26	16
Myocardial infarction	92	59
Ventriculography		
anterior wall hypokinesia	87	56
inferior wall hypokinesia	47	30
Collateral arteries	77	49
Left bundle branch block	5	3
Thrombolytic therapy of myocardial infarction	24	15

Myocardial perfusion scintigraphy was performed using planar scintigraphy (General Electric 300 gamma camera, Macintosh II fx computer, LEAP collimator, 64 x 64 matrix, 7 minutes per view) in best septal (LAO 30 – 45 degrees), anterior and left lateral projection. Thallium (TICI – 201, 74 MBq) was injected during submaximal, simptome limited or during pharmacologic stress (dipyridamol 0,56 mg/kg body weight). Scintigrams were acquired immediately after stress (stress imaging) and three to four hours latter (rest imaging). Visual analysis of myocardial perfusion scintigrams was performed; perfusion was described as normal, diminished or absent for anteroseptal, posterobasal, apical, lateral and inferior regions in stress and rest.[2,3,10,12]

Left ventricular wall motion was observed on *contrast ventriculography* and described as normal, hypo-, a- or diskynetic for anterior or inferior wall.

Coronary artery narrowing was evaluated on *coronary angiograms* for left anterior descending artery (LAD), left circumflex artery (LCX), right coronary artery (RCA) and graded as less than 50%, 50-69%, 70-89%, 90-99% or as occluded.[5,6]

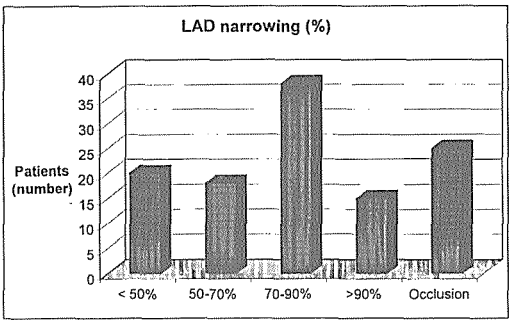
Data comparison: original readings of myocardial perfusion scans and coronary angiograms were compared for LAD, LCX and RCA perfusion territories. Results of comparison were either concordant (hypoperfused areas and stenosis in the same regions), partially concordant (not all areas concordant or differing degree of stenosis / tracer accumulation) or discordant (perfusion abnormality and coronary artery stenosis on different areas or not detected). When incompletely concordant and discordant results of both studies were found, original studies were reviewed by two experienced nuclear medicine specialists and the cardiologist.

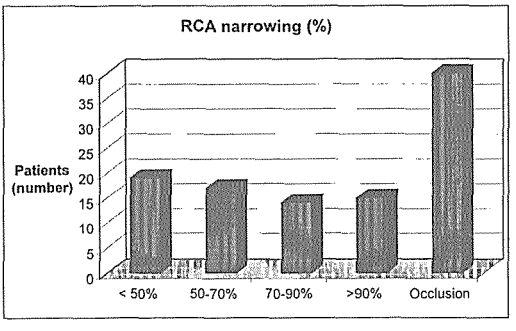
Statistical methods: patients' data were expressed in percent and average values. Sensitivity, specificity, positive and negative predictive value for myocardial perfusion scintigraphy were calculated.[13]

Results

Both examinations gave concordant results in 62% of patients. Only in 3% of all patients the results were discordant. In the remaining 35% concordance was only partial. Distribution of separate coronary artery narrowings is shown on Figures 1 a - c. Calculated sensitivity of the myocardial perfusion scintigraphy was 100% and specificity 50%. Positive predictive value for coronary artery disease

was 96% and negative predictive value was 100 %. Specificity and sensitivity for separate perfusion areas for men and women are given in Table 2.





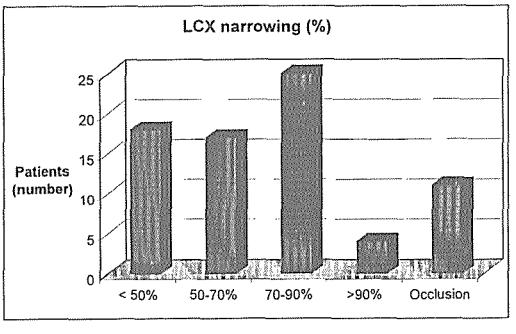


Figure 1. Distribution of coronary artery narrowings: a) left anterior descending artery - LAD, b) right coronary artery - RCA, c) left circumflex coronary artery - LCX.

Discussion

Myocardial perfusion scintigraphy is a common diagnostic method in evaluation of patients with suspected or proven coronary artery disease.[2, 3, 4] Coronary angiography is the golden standard in diagnostic evaluation of patients with coronary artery disease. It is a morphologic method, performed mostly in resting conditions; it has to be performed before coronary artery dilatation or surgery.[5, 6] Myocardial perfusion scintigraphy can not give anatomic details but provides data on myocardail perfusion during stress and at rest, thus detecting myocardial hypoperfusion before symptoms are evident at rest. It can therefore be used as a screening method in patients with intermediate pretest probability of coronary artery disease.[1, 4, 14, 15] Planar method was used until tomographic technique became available also at our institution. The data on sensitivity and specificity of myocardial perfusion scintigraphy vary largely and depend mostly on inclusion criteria used for separate study. The sensitivities from 79 to 96% and specificities from 85 to 91% are common; sensitivities from 20 to 80 % for separate coronary arteries in unselected patients are described.[2, 16] Evaluation of the method in separate institutions is therefore needed. Our study is a part of quality control process and helps to assess clinical impact of diagnostic procedures. Patients in our study were selected on basis of both investigations performed. Most of them had severe coronary artery disease with angina pectoris, previous myocardial infarction and wall motion abnormalities (Table 1).

Table 2. Sensitivity and specificity of myocardial perfusion scintigraphy for separate coronary artery perfusion areas in a) men, b) women.

2 a: Men	Sensitivity	Specificity
Left anterior descending coronary artery	96%	61%
Right coronary artery	100%	79%
Left circumflex artery	89%	94%

2 b: Women	Sensitivity	Specificity
Left anterior descending coronary artery	93%	38%
Right coronary artery	89%	100%
Left circumflex artery	86%	93%

"False positive" myocardial perfusion scintigrams were detected in 60 patients (38% of all) at the original first reading. The studies were reanayzed and underlying coronary pathology was detected in 55 patients. Most of them had more pronounced myocardial perfusion defects than was the estimated severity of coronary artery stenosis. This is a natural consequence of the different nature of both investigations. Other causes of "false positive" results were anomalous coronary artery in 5 patients (3% of all), tortuous coronary arteries with slow flow of contrast media in 9 patients (6% of

all) and arterial hypertension with extreme left ventricular wall hypertrophy in one patient.

Anterior wall hypoperfusion due to anomalous coronary artery can be present already at rest. Extensive additional patological findings on stress scan are detected.[3, 17] An example of coronary angiogram in patient with anomalous coronary artery is shown on Figure 2. Tortuous coronary arteries with slow

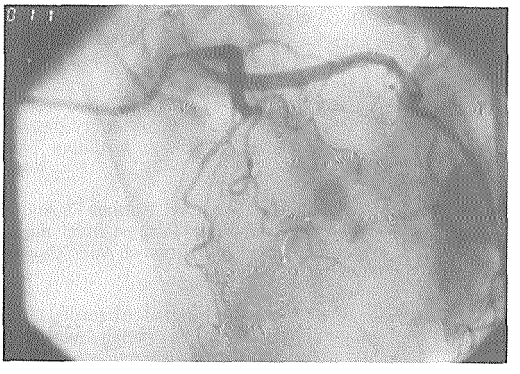


Figure 2. Coronary angiogram, left anterior oblique projection: anomalous left anterior descending coronary artery.

flow of contrast media cause inadequate myocardial perfusion without coronary artery stenosis.[3, 18] An example of coronary angiogram of our patient is shown on Figure 3. In patiens with arterial hyper-

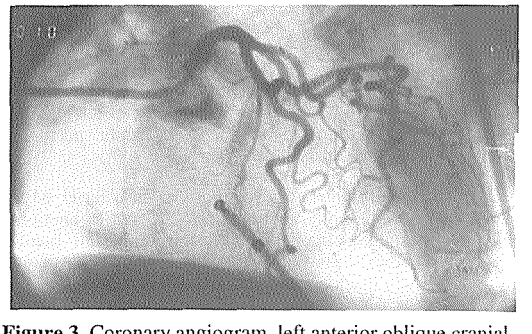
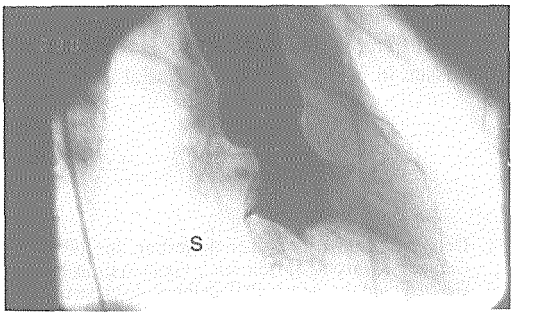


Figure 3. Coronary angiogram, left anterior oblique cranial projection: tortuous coronary artery.

tension, myocardial perfusion abnormalities are attributed to diminished coronary flow reserve.[19, 20] We detected evident perfusion defect in one patient with normal coronary arteries on angiography. Systolic and diastolic frames from contrast ventriculography of this patient are presented on Figure 4 (a, b); myocardial hypertophy with obliteration of myocardial cavity in systolic frame is evident.



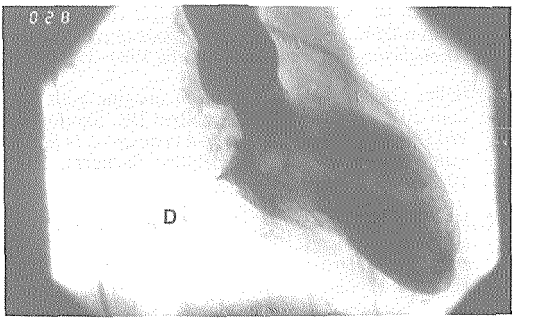


Figure 4. Contrast ventriculography, right anterior oblique projection: left ventricular hypertrophy. Left ventricle in a) systole, b) diastole.

False positive myocardial perfusion scans are possible in patiens with left bundle branch block.[22, 23] In 4 of our 5 patients with this conduction abnormality scintigraphic findings were concordant with angiographic findings, reflecting reliability of our nuclear medicine specialists.

The low specificity of myocardial perfusion scans for LAD perfusion territory in women can be due to the low number of women in our study and to the attenuation of thallium radioactivity in soft tissue.[8, 10, 11]

In 5 patients no evident reason for disagreement of results of both studies could be detected. Discordance could be due to the natural course of coronary artery disease[23] or episodes of silent ischaemia.[25]

In conclusion, myocardial perfusion scintigraphy has a definite role in diagnosis and follow-up of patients with suspected or proven coronary artery disease. New techniques and technetium labeled tracers improve reliability of myocardial perfusion scintigraphy and enable reasonable use of more aggressive diagnostic methods. Scintigraphy can evaluate the functional significance of coronary stenoses, detected by coronary angiography or magnetic resonance imaging. Development of positron

emission tomography and positron emission tracers allows differentiation of viable myocardium and scar tissue in patients after myocardial infarction.[4]

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Interstitial fluid pressure as an obstacle in treatment of solid tumors

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Over the past decades a development of different anticancer drugs has increased and brought many progressive agents that showed high level of efficiency in in vitro conditions. Unfortunately these drugs failed in solid tumor treatment in in vivo conditions because of inadequate uptake and nonoptimal distribution in tumors. Although tumors have higher permeability and hydraulic conductivity of the vessels than normal tissue, the extravasation of the drug molecules from vessels into the tumor interstitium is reduced due to elevated interstitial fluid pressure (IFP). This property also impedes the transport of the molecules through the interstitial space. Furthermore, IFP is uniformly high in the center of the tumor and declines to the value of the normal tissue at the rim of the tumor. Though, IFP gradient causes fluid flow which "washes" drugs out of the tumor to its periphery where it is reabsorbed by the lymphatic system or normal vasculature. Measurements of tumor IFP demonstrated that its values can reach 2600 Pa up to 6600 Pa whereas in the normal tissue it is below the atmospheric pressure (from -133 Pa to -798 Pa in s.c. and approximately -346 Pa in muscle). The most frequently used methods for instant and direct IFP measurement are: wick-in-needle technique (WIN) and micropuncture technique (MP). Since the reduction of the elevated tumor IFP could facilitate drug uptake and anti-tumor treatment, many approaches have been tested. In present paper we represent the results of two physical (hyperthermia, radiation) and one chemical (vasoactive agents) approach that other authors used for IFP reduction.

Key words: neoplasms-therapy; extracellular space; manometry

Introduction

A high level of drug development techniques, especially genetic engineering, has produced many novel drugs for cancer detection and treatment.[1,2,3] The first step in the development of such a drug is *in vitro* testing and many agents showed a very high degree of anti-cancer effectiveness. This stimulated the use of low-molecular-weight conventional drugs, monoclonal antibodies, growth factors, biological response modifiers, immunotoxins, lymphokine activated killer cells, tumor-infiltrating lymphocytes, and others in *in vitro* conditions.[2] Although they succeeded in the treatment of leukemias and lymphomas they had a minimal effect on solid tumors (breast, colon, lung, ...).[2,3] The main reason for their limited effectiveness is inadequate and nonuniform distribution of drug molecules or cells in tumors.[2-5] Since cellular factors, such as heterogeneity of tumor-associated antigens and inherent or acquired tumor resistance can not explain this problem, physiological factors have to be concerned.[2] To complete its mission, molecule of the blood-borne anticancer drug must travel via blood stream to the tumor. Further it must extravasate across the microvessel wall into tumor interstitium, where it must disperse uniformly in the tumor in order to reach each tumor cell. All of these steps

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are not present in *in vitro* experiments so each of these physiological factors could be the reason for the ineffectiveness of anticancer drug.[2,3]

The role of interstitial fluid pressure in transport of molecules through microvessel wall and tumor interstitial space

As tumor cells proliferate into the host tissue, tumor angiogenesis leads to the formation of a new, tumor vasculature.[2,6] Although the tumor microcirculation originates from the normal host vasculature, its organization may be completely different and vary from day to day and from one location to another. Vessels in tumor are, compared to vessels in normal tissue, more dilated, sacular and tortuous. They can also contain tumor cells within the endothelial lining of the vessel wall. Furthermore, tumor microvessels have wider intercellular junctions and discontinuous or absent basement membrane. Another difference between the normal and the tumor vasculature is that the latter has a large number of fenestrae and blood channels which are not lined with endothelial cells.[2,7]

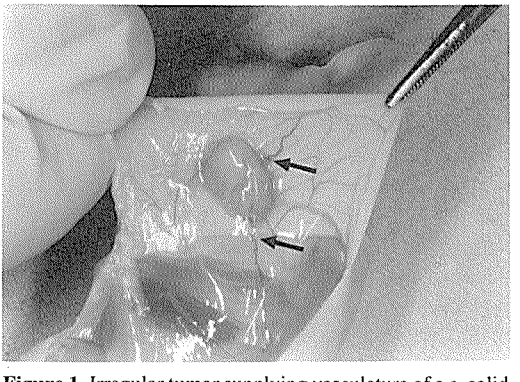

Figure 1. Irregular tumor supplying vasculature of s.c. solid LPB tumor in nude mice (arrows).

The extravasation of the blood-borne molecule that has reached the tumor vasculature is governed by diffusion and convection. The diffusion is a movement of the solute in the medium from an area with high concentration to an area with low concentration and is the primary way of transport for low-molecular-weight hydrophilic and lipophilic molecules. The diffusion is proportional to the concentration gradient and exchange vessel area. The proportionality constant that relates transluminal flux to the concentration gradient is the vascular permeability.[2,7] The convection on the other hand is a way of molecular transport by a stream of fluid. It is proportional to the difference between the vascular and the interstitial hydrostatic pressures minus the difference between the vascular and the interstitial osmotic pressures and also the exchange vessel area. Constants that relate fluid leakage to the pressure gradients are hydraulic conductivity for hydrostatic pressure difference and reflection coefficient for osmotic pressure difference. The equation that describes the solute flow across the vessel wall due to diffusion is:[7]

$$J_s = P \times A \times (c_v - c_i)$$

where: J_s is the flow of solute (moles/s or g/s); P is the vessel permeability (m/s); A is the surface area of the vessel (m^2); and c_v and c_i are the concentration within vessels and interstitial concentration of solute, respectively (moles/m^3 or g/m^3). The fluid flow across the vessel wall is given by:[7]

$$J_f = L_p \times A \times [\,(p_v - p_i) - \sigma \times (\pi_v - \pi_i)\,]$$

where: J_f is the volume flow of fluid (m^3/s); L_p is the hydraulic conductivity (filtration coefficient) of the vessel (m/Pa×s); A is the surface area (m^2); p_v and p_i are the vascular and interstitial fluid pessures (Pa); π_v and π_i are the colloid-osmotic pressures in vessel and interstitial fluid (Pa); and σ is the osmotic reflection coefficient. In the presence of convection and diffusion the total solute flow is given by the Staverman-Kadem-Katchalsky equation:[7]

$$J_s = P \times A \times (c_v - c_i) + J_f \times (1 - \sigma_F) \times \Delta c_{lm}$$

where: σ_F is the solvent-drag reflection coefficient; and Δc_{lm} is the log-mean concentration within the pore. For larger molecules the convection is the basic and a faster way of transport, although they also travel by diffusion.[2,3,7] Characteristics of tumor vessels described above suggest that they should have a relatively high vascular permeability and hydraulic conductivity. Various studies measuring tissue uptake confirmed that hypothesis.[2,7] Nevertheless, the extravasation of anticancer agents in solid tumors is poor. The main reasons are that, tumor does not create its own functioning lymphatic system, therefore, the excess fluid collects in the tumor interstitium and that tumor cells proliferate in the relatively limited, noncompliant space. These tumor properties cause increase of the interstitial fluid pressure (IFP). The elevated IFP hinders the convection across the vessel wall, because there is

no difference between the vascular and the interstitial pressure.[2-4,7] First it was assumed that the increased IFP causes the vessel occlusion in tumor, since IFP is higher than microvascular pressure (MVP). MVP relates to pressure in vessels with diameter 25 and 250 μm.[8,9] This hypothesis, however, failed to explain why a convection in the opposite way did not occur, i.e. fluid flow from interstitium into vessel. In addition, tumor vessels are very perfusive and though represent no resistance to the IFP.[7,8] Boucher and Jain demonstrated that MVP is increased and equal to IFP, furthermore, they assumed that MVP is the principal driving force for the elevated IFP.[8] The reasons for the observed increased MVP may be an increase in viscous and/or geometric resistance in the venous side of tumor circulation and that arterioles become less effective in controlling MVP.[8] Later they found out that the relationship between these two factors varies from one tumor to another.[9]

Another aspect in nonadequate anticancer agent uptake in tumor is the heterogeneity of the tumor vasculature. In general, solid tumors have three different regions: necrotic zone, semi-necrotic zone and well vascularized zone.[2] In necrotic and semi-necrotic zone there is no or very little blood supply and hence no extravasation of anticancer drug takes place. Tumor blood flow in these areas is also low compared to blood flow in normal tissue, whereas in well perfused zone (usually at the tumor periphery) tumor blood flow may be higher than that in normal tissue.[2] The increase of intercapillary distance and the decrease of vascular surface area also accompanies tumor vascular heterogeneity. In addition, the reduction of tumor blood flow restricts the extravasation of molecules even more.[2]

If the anticancer drug reaches tumor interstitium, it must uniformly distribute through it in order to reach and destroy each tumor cell.[1-3] The transport of the molecule in the tumor interstitium is also governed by diffusion and convection, only here the diffusive and the convective flow are proportional to gradients instead of differences in concentration and pressure, respectively. Proportional constants are the diffusion coefficient and the hydraulic conductivity. One-dimensional transport by the diffusion in a medium is given by Fick's law:[4]

$$J_D = -D \times (\partial C/\partial x)$$

where: J_D is the diffusive flow of the solute per unit area normal to the surface (moles/s×m^2 or g/s×m^2); D is the diffusion coefficient of the solute in the medium (m^2/s), and $\partial C/\partial x$ is the concentration gradient of solute (moles/m^4 or g/m^4) in x direction. Similary, the convective flow is given by:[4]

$$J_C = -C \times R_F \times K \times (\partial p/\partial x)$$

where: J_C is the convective flow of solute per unit area normal to the surface (moles/s×m^2 or g/s×m^2); R_F is the retardation factor (solute convective velocity/solvent convective velocity); C is the concentration of solute (moles/m^3 or g/m^3); K is the tissue hydraulic conductivity (m^2/Pa×s); and $\partial p/\partial x$ is the hydraulic pressure gradient (Pa/m) in x direction.

Their values in tumor are higher than in normal tissue, but the problem of the heterogeneous distribution of anticancer drug in tumor remains. Theoretical and practical researches of the IFP profile in solid tumor revealed that it is uniformly high over the center of the tumor and that it drops rapidly at the periphery of the tumor.[5,10-12] Unfortunately the convective interstitial fluid flux is created due to pressure gradient at periphery of the tumor. Considering that the time a large molecule needs to travel some distance by diffusion is proportional to the square of the distance and the time for a movement by convection is proportional to the distance alone, it is obvious that macromolecule that was washed out of the tumor with the convective flux has a hard time diffusing back into the tumor.[3,4]

Shortly said, due to heterogeneous tumor vasculature, the increased vascular permeability and hydraulic conductivity, elevated IFP, and IFP gradient in tumor very little drug gets in the tumor. Furthermore it is washed out rapidly.

Measurement of interstitial fluid pressure

Measurement techniques for IFP measuring are numerous, but a provocative question appears: which one is referential? Although a method seems to be reliable, accurate and repeatable, it is not necessary that it measures true IFP value. In 1971 Guyton *et al.* presented an extended study on IFP.[13] They classified tissue pressure into three categories: solid tissue pressure, IFP, and total tissue pressure, which is the sum of first two. Physiological structures that cause solid tissue pressure are two: I. solid elements in the tissue interstitium such as collagen, elastin, and other types of fibers; and II. interstitial gel composed primary by mucopolysaccharides possibly or probably cross-linked with collagen. IFP

on the other hand is the pressure of the free fluid in the tissue interstitium.[13] Nevertheless, other authors called interstitial free fluid phase an abstraction since interstitium may completely consist of a gel.[14] Guyton *et al.* also critically reviewed a number of measuring techniques which they divided into two groups: needle or capillary pipette techniques and fluid equilibration techniques.[13] They expose one of the fluid equilibration techniques (perforated-capsule method) as accurate and reliable technique for IFP measuring. In order to get IFP value with this technique a small hollow plastic sphere with little holes must be implanted into the tissue. It should be implanted for weeks so that interstitial fluid can fill it and creates pressure equilibrium. A needle connected to a pressure-measuring device is then inserted in the sphere through one of the holes.[13] However, this method does not enable instant measurements, which is important, when IFP in solid tumor is measured. Therefore, currently only two measuring methods, wick-in-needle and micropuncture techniques, are used in tumor IFP measurement. In this paper we describe both of them.

Wick-in-needle (WIN) technique

The method was first presented by Fadnes *et al.* in 1977.[15] They took benefits of needle and wick techniques and combined it into one. The main problem with the needle technique is the obstruction of needle tip. They solved it by creating a 2-4 mm sidehole cca. 5 mm from the tip of the 0.6mm hypodermic needle. The needle is then filled with strand of about 25 mm thick nylon fibers. The hole of the needle tip is not closed, yet densely filling of the wick, there represented a relative larger resistance to fluid comparing to the sidehole. Therefore, the sidehole has the role of the interface area. By inserting wick into the needle they reduced trauma that a fairly thick cannula, holding the wick in the wick technique, created to the tissue. A wick-filled needle is then connected to a pressure transducer via polyethylene tube and filled with physiologic saline. The whole system is air-proof so that tissue pressure is conducted through water column to the transducer where it is recorded. The calibration is performed by placing the needle in a saline-filled beaker, or in a saline drop, placed at the level of needle insertion. The method is simple and convenient way of measuring IFP. Pressure measurements are also reproducible and stable.[15] Compared to micropuncture method WIN technique provided comparable results when s.c. and hindlimb muscle IFP in rats were measured.[14] The major problem with WIN method is that it is still traumatic (23-26G needles) to the tissue and may change local IFP due to alterations in capillary pressure, permeability and effective surface area.[15] An effect of colloid osmotic pressure to IFP measurements with WIN technique should also be considered. The osmotic flow of fluid out of the wick, due to concentration difference of proteins between interstitial fluid and physiologic saline in wick, can lower the value of the measured pressure. However, Fadnes *et al.* proposed that small fluid volume contained in the wick prevents this artifact.[15] To minimize osmotic influence furthermore, heparinized (70 units / ml) physiologic saline can be used instead of pure physiologic saline.[8,16-21] In tumor IFP measurement the accurate position or depth (e.g. in steps of 0.1 mm) of the interface spot of the needle can not be determined, however, the evaluation of needle position in tumor can be done.[10]

Micropuncture (MP) technique

The method was first used by Wiederhielm *et al.* in 1964.[14] Sharpened glass capillary (micropipette) with tip diameter of 1-4 mm is connected to a servocontrolled counterpressure device. A micropipette is filed with 0.5M NaCl solution colored with Evans blue dye.[14] As in WIN technique, the water column is used to measure the pressure exerted by the interstitial fluid to pipette fluid. Servocontrolled counterpressure system responds to the changes in the electrical resistance in the pipette tip. The increasing of the fluid pressure surrounding the pipette tip causes the tendency of this fluid to enter the pipette. Therefore, the resistance increases and the servosystem applies a counterpressure to obtain the preset resistance (equilibrium of fluids).[14] Since micropipettes are very fragile, a micromanipulator is needed to maneuver it. This also requires the immobilization of the tissue, usually implying general anesthesia and that insertion of micropipette into the tissue is performed under a guidance of a microscope.[14] The calibration of MP method is the same as in WIN technique but can also be done in a saline test chamber.[5] Guyton *et al.* in their study characterized MP technique as a method which is only capable of measuring total tissue pressure since it needs larger free-fluid spaces that are those in usual normal tissue.[13] Later Wiig *et al.* suggested that the requirement for IFP measurement with MP

technique is not free fluid but the possibility of moving fractions of nanoliters of fluid into or out of the pipette.[14] They also proposed that the MP technique is the most reliable method for measuring IFP available today. Due to guidance of micropipette with micromanipulator very accurate positions (depths) of measurement points could be determined. Disadvantages of the method, however, are fragility of the micropipettes, urgent immobilization of the tissue, limited insertion range compared to WIN technique, and that the stretching or the compressing of the tissue, due to micropipette withdrawal or insertion, causes lower of higher pressures, respectively.[14]

Changes in IFP due to different treatment approaches

In 1950 Young *et al.* first demonstrated that IFP in solid tumors is increased.[22] Since it is known that increased IFP impedes the antitumor treatment many studies were performed to reduce it.

Hyperthermia

Hyperthermia is a cancer treatment where tumor is exposed to overheating with temperature up to 42-45°C or higher.[23] In their research Leunig *et al.* found out that local hyperthermia at 43°C for 60 min reduces IFP value in amelanotic melanoma A-Mel-3 from 1675.8 Pa to 106.4 Pa.[24] They assumed that the main reason for lowering IFP was the reduction of a local MVP to zero due to impaired tumor microvasculature. Their theory was that at the beginning of hyperthermia blood flow in tumor may increase, thus bringing more drug to the tumor. Later, when the reduction of blood flow begins, drug remains in tumor. Therefore, decreased IFP may increase the delivery of the drug to the tumor by facilitating the extravasation and by reducing the washing out of the drug.[24] On the other hand, Hauck *et al.* treated D-54MG glioma xenograft with the exposure to 41.8°C for 4h. They observed no changes in IFP after the tumor treatment.[25] Inconsistency of both studies could be a result of different treatment protocoles as well as different tumor models. Nevertheless, further studies are needed to determine whether hyperthermia has an effect on IFP.

Radiation

Radiation is one of the conventional antitumor treatments,[1] but the hypoxic nature of the tumor usually impedes the radiation effectiveness.[3,16] In this field of interest the question appears, how does the radiation affect IFP. Znati *et al.* investigated the effect of radiation on the IFP and determined the minimum dose required to affect IFP.[16] They used xenografts of LS174T human colon adenocarcinoma. The radiation dose below 10 Gy (2×2.5 Gy) did not significantly change IFP, whereas doses of 10 Gy and above (2×5 Gy and 2×10 Gy) decreased IFP value for 332.5 Pa (initial value was 1715.7 Pa). They also found out that the maximum reduction of IFP (35%) after the single-dose irradiation appeared 5 days after the radiation with 30 Gy and then started to increase again. The radiation of 10 and 20 Gy reduced IFP for 19 and 23% respectively, in both cases 3 days after the irradiation. They assumed that the observed decrease in IFP was the result of the reduction of microvascular pressure, due to the decreased venous vascular resistance. Roh *et al.* on the other hand measured IFP in carcinoma of the uterine cervix *in situ* after the irradiation.[18] They found out very high values of IFP (maximum value 5453 Pa) which exceeds that in many experimental tumors. They also measured IFP in normal uterine cervix and found it to be between 0 and 399 Pa. After the fractionated irradiation from 32 to 60 Gy they observed the decrease in IFP in 4 patients, whereas in 3 patients IFP remained unchanged or increased. The mechanism that causes the IFP reduction in some tumors and not in others remains unknown. They suggested however, that the correlation between changes in IFP and the tumor response to therapy, which they observed, could be useful in predicting a treatment outcome and in determining future strategies for treatment.[18]

Vasoactive agents

Based on a hypothesis that local MVP governs IFP, we can conclude that changes in MVP should result in IFP changes. To decrease (or increase) MVP two different approaches may be used: decrease (or increase) in mean arterial blood pressure (MABP) and increase (or decrease) in tumor venous resistance.[21] Both physiological factors can be manipulated with drugs that have the effect on vasculature (vasoactive drugs). Lee *et el.* studied the effects of the pentoxifylline (PTX) on IFP in FSaII murine tumors.[21] They found out 55% decrease in IFP which

reached its minimum 2 hours and remained up to 4 hours at this level after the injection of 100 mg/kg PTX. They suggested that the observed reduction of the IFP was due to decrease in the tumor venous resistance as described in the above hypothesis. In a similar comprehensive study Zlotecki *et al.* observed changes in IFP due to five different vasoactive drugs and compared it with mathematical model.[26] Three vasoconstricting agents angiotensin II, epinephrine, and norepinephrine increased IFP as well as MABP. However, the magnitude of increase in IFP (ΔIFP and IFP ratio post/pre) was significantly different for each agent whereas the increase in MABP was similar. Angiotensin II increased IFP for 838 Pa, epinephrine increased it for 386 Pa and norepinephrine for 186 Pa. Initial values were between 2394 and 2926 Pa. Two vasodilating agents (hydralazine and nitroglycerin) decreased IFP and MABP. Hydralazine which is a long-acting vasodilator causes 50% decrease in IFP (2261 Pa) over the first hour and nitroglycerin which is a short-acting vasodilator produced only small, transient 6% (173 Pa) decrease in IFP. Initial values of IFP before the hydralazine injection was 4389 Pa and before the nitroglycerin injection 2886 Pa. These results correlate with changes in MABP. In their study they also analysed the experimental results with a mathematical model. Briefly, they found out that changes in IFP are mainly due to the effect of vasoactive agents on tumor or on the surrounding tissue vasculature resistance.[26] In a similar study Tveit *et al.* measured IFP after the administration of norepinephrine. In contrast to the previous study of Zlotecki *et al.* they found out that IFP decreased form initial value of 1370 Pa to 931 Pa. This inconsistency of their results with results of Zlotecki *et al.* was not explained.[26]

In addition, other studies determining the effects of hemodilution and TNF-α on IFP were also performed.[20,27] In both of these studies authors report the decrease of IFP.

Conclusions

The elevated IFP together with the heterogeneous blood supply in solid tumors are the reasons for the inadequate uptake and nonuniform distribution of the anticancer drugs (especially macromolecules).[18] The main reasons for the increase in IFP are high vascular permeability and hydraulic conductivity, high tumor vascular resistance to blood flow, and lack of functioning lymphatic system.[16] It was demonstrated that IFP is mainly governed by the MVP which is also increased, due to high tumor venous resistance. Therefore, MVP values in tumors are the same as IFP values.[8] IFP in tumours is uniformly elevated throughout the tumor but drops rapidly in the periphery of the tissue-isolated tumors and at the tumor-normal tissue interface in tumors surrounded by normal tissue.[2,3,5,12] This property causes fluid to ooze out of tumor and thus create radial convection of macromolecules which are located into the tumor.[2,8,16,18]

Measurement techniques currently used to measure IFP in tumors are two: WIN technique and MP technique. Although MP technique is controlled by the counterpressure system and is though more accurate, WIN technique is, in spite of its simplicity, quite adequate to produce reliable and accurate results. Both techniques however, have their benefits and weaknesses.

Many methods were used to reduce IFP in tumors and thus optimize the anticancer drug uptake but none of them brought satisfactory results. Nevertheless, elevated IFP would present very few or no problems for the antitumor treatment with a molecule or cell which has nearly 100% specificity for tumor cells.[2] Meanwhile, novel treatment approaches must be found out that will eliminate these physiological barriers and will thus enable antitumor agents to complete their mission.[2] Only a complex antitumor treatment which will affect all carcinogenic mechanisms at the same time will be a successful one. Better understanding in IFP represents a step towards the effective antitumor treatment.

Appendix

All pressure units in this article are in SI system (Pascal - [Pa]) although pressure units used in references are in mmHg. Therefore we used transformation equation:[28]

$$101325 \text{ Pa} = 1 \text{ atm} = 760 \text{ mmHg}$$
$$1 \text{ mmHg} \cong 133 \text{ Pa}$$

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The urokinase-type plasminogen activator, its inhibitors and its receptor - the new prognostic factors in solid cancers

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The urokinase-type plasminogen activator (uPA), its inhibitors (PAI-1 and PAI-2) and its receptor (uPAR) play an important role in the degradation of the intercellular tissue, the process which affects the ability of cancer cells to invade to surrounding tissue and to metastasize. The results of clinical studies performed in the past few years point out a significant influence of uPA, PAI-1, PAI-2 and uPAR on the course of the disease and survival of patients with solid tumours, particularly breast cancer. Hopefully the categorization of patients according to the content of the serine proteases and its inhibitors in tumour tissues could provide a basis for more rational treatment planning and thus improving patients' survival.

Key words: neoplasms; prognosis; urokinase; plasminogen inactivators; serine proteinases

Introduction

The projection of the progression of the disease and hence the prognosis for each individual patient is of extreme importance in clinical oncology. The treatment strategy of solid tumours is nowadays based on the established prognostic factors, such as the patho-histological type, the size of the tumour, and the stage of the disease, but the survival statistics of individual groups of patients with the same values of these prognostic factors is still diversified. Therefore, the main objective of the research work is to find those tumour characteristics which would enable us to discern less biologically aggressive tumours from the more aggressive ones. In recent years, the methods of molecular biology have helped to identify a number of new factors associated with the differentiation and proliferation of cancer cells, such as: Ki67, cyclin D1, the proportion of cells in S phase of the cell cycle, various growth factors and oncogenes. Although these factors have been proven to influence the differentiation and proliferation of cancer cells, their value as prognostic factors is still questionable. It was found that the ability of cancer cells to invade the surrounding tissue and form distant metastases rather than the differentiation and proliferation of cancer cells is of vital importance for the prognosis of a particular patients. Therefore, an increasing number of investigations have been dedicated to the study of factors which define tumor invasiveness.

The research *in vitro* showed that the invasion of tumour cells in the neighboring tissue and the formation of metastases depend significantly on the content of proteases in the tumor tissue.[1,2,3] There are four recognized classes of proteases: cisteine proteases, (cathepsin B, H and L), aspartyl proteases (cathepsin D), metalloproteases (gelatinases, collagenases, stromelysins) and serine proteases (plasminogen activators and the product of their activation - plasmin). Metalloproteases play an important role in the invasion and metastatic growth of tumours in animals, but their significance for tumours in humans is still not totally clear.[4] Cysteine proteases and the cathepsin C have a proteolytic effect on the intercellular tissue and they are especially important for the activation of the urokinase-type plasminogen activator.[4,5,6]

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The research work carried out over the last few years revealed a most important prognostic relevance of serine proteases.[3] There are two types of serine proteases - plasminogen activators: the tissue plasminogen activator (tPA) and the urokinase-type plasminogen activator (uPA). The tPA is mostly present in the blood, where it participates in the intra vascular thrombolysis.[1,3] The uPA is found mostly in the tumour tissue, where it plays, together with its inhibitors and receptor, a most important part in the activation and regulation of the tumour associated proteolysis in man.[3]

Malignant cells, as well as macrophages and fibroblasts, present in tumours produce an inactive proenzyme (pro-uPA), which is bound to a specific receptor on the cellular membrane - to the uPAR. Through the activation of the cathepsin B and L, the cathepsin D and the plasmin transform the pro-uPA into the active form uPA. The uPA triggers off a cascade-like transformation of plasminogen into the active proteolytic enzyme plasmin, which disintegrates intercellular proteins (fibrin, fibronectin, proteoglycane and laminin) and which indirectly induces basement membranes degradation by the procollagenase IV activation (Figure 1).[1,3,5,6] At the same time, the proteolytic activity of the uPA produced by malignant cells and macrophages induces the formation of angiogenic factors and hence the neo-vascularization both in the primary tumours margins and in metastases. Apart from the presence of proteolytic enzymes, neovascularisation is the most important factor for the local growth and metastatic potential of tumours.[5]

Proteolysis is also strongly affected by the inhibitors of the plasminogen activator. The most relevant of the four known types are the plasminogen activator inhibitor type 1 (PAI-1) and the plasminogen activator inhibitor type 2 (PAI-2). The capacity of the PAI-2 as a pure plasminogen activator inhibitor is clear and straightforward. Contrary to what is known about the PAI-2, clinical research results display a stronger metastatic potential of tumours with high PAI-1 levels.[7,8,9] That may result from the PAI-1 protecting malignant cells against self-destruction or, another possible explanation, from the PAI-1 functioning as a biochemical marker of angiogenesis.[9] The activation of the uPA is possible only after its binding to the receptor. The uPAR presence in the membranes of tumour cells is much more pronounced than in normal tissues.[6] In some instances the presence of the uPAR in breast tissue was detected in the tumour itself but not in the normal tissue of the breast.[10] The blockade of the uPAR with monoclonal antibodies was found to prevent the invasion of tumour cells through the basement membrane.

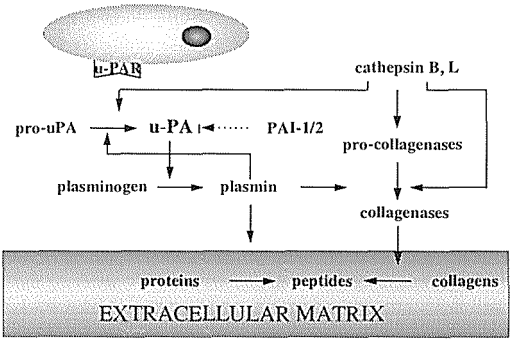

Figure 1. Scheme of the u-PA catalyzed plasminogen-plasmin cascade. Dashed line indicate inhibition. (u-PA - the urokinase type plasminogen activator, PAI-1/2 - plasminogen activator inhibitor type 1/2, u-PAR - specific receptor for u-PA).

The evaluation of the content of the uPA, PAI-1, PAI-2 and uPAR in tumours can be biochemical and immuno-histochemical. The biochemical method has been applied more frequently in the research performed so far. It involves the extraction of the urokinase system components with special puffers and detergents, and their evaluation with monoclonal antibodies. The referential values depend on the use and on the type of detergent. The best extraction can be obtained with the addition of the triton detergent.[12] The comparison of the values of the uPA content in the tissue of breast carcinoma obtained with biochemical and immuno-histological methods showed good correlation.[13]

The prognostic significance of uPA, PAI-1, PAI-2 and uPAR for different types of cancer

Breast cancer

By far the greatest number of studies on the prognostic significance of the uPA system components have been made for breast cancer, the most frequent type of cancer in women, the incidence of which has been on the increase.[14] The primary treatment of breast cancer is devised with respect to the established prognostic factors, such as the size of the tumour, the histological type and the gradus of the tumour, the axillary lymph nodes involvement and the presence of the hormone receptors in the

tumour.[15] Additional prognostic factors are being intensely investigated and the serine proteases being among the most promising ones.[16]

A number of studies proved that the levels of the uPA, PAI-1, PAI-2 and uPAR in the breast carcinoma tissue are considerably higher than in benign tumours and in normal breast tissues.[1,3,17,18] The content of the uPA can be 11 times,[13] the content of its inhibitor PAI-1 74 times and the content its inhibitor PAI-2 29 times higher in malignant that in benign breast tumours.[19] The level of the tPA is the same in malignant and in benign breast tumours.[3,20]

The uPA content in the tumour tissue does not correlate with other components of the uPA system and with common prognostic factors,[13,19] The PAI-1 correlates inversely with hormone receptors.[8] The PAI-2 correlates inversely with the size of the tumour and positive with the age of patients.[21] The uPAR correlates inversely with the estrogen receptors.[22]

Most of the clinical research has identified both the uPA and the PAI-1 as independent prognostic factors for breast cancer. Higher values of both uPA and PAI-1 in primary tumour are not only associated with higher risk of recurrence, but also significantly influence the overall survival rates. The question of a prognostic value of uPA and its inhibitor in prognostically different sub-groups of patients remains unsolved.[7,9,13,17,23,24,25] While they have both proved to be independent prognostic factors in the subgroup of patients with positive lymph nodes,[7,8,23] the uPA has not been established as an independent prognostic factor in the group of patients with negative axillary lymph nodes.[23] Only one study with small number of patients enrolled reports results supporting the uPA as an independent prognostic factor in this group of patients as well.[6] While a study involving over 600 patients revealed only the PAI-1 as an independent prognostic factor in patients with negative axillary lymph nodes.[7]

The prognostic value improves with the combination of individual system components. In patients with a high level of uPA content in primary tumours, the high level of PAI-2 is an independent prognostic factor while those with low PAI-2 levels have poor prognosis,[21] which is to be expected in the light of the function of the PAI-2 as a pure uPA inhibitor.

The uPAR has not proved to be such a strong prognostic factor as the uPA and the PAI-1 are. However, patients with a higher level of the uPAR in the breast tumour have significantly shorter relapse-free and overall survival[19] and the uPAR has proved to be an independent prognostic factor in the sub-group of post-menopausal patients with positive axillary lymph nodes.[22]

The components of the uPA system are not only prognostic but also predictive factors in breast cancer patients. In the study of 274 patients Foeckens *et al.* observed that the response to hormonal therapy with tamoxifen was better in patients with low levels of uPA, PAI-1 and uPAR and a high level of PAI-2 in tumour tissue.[26]

Ovarian cancer

The established prognostic factors for the ovarian cancer are the performance status, the stage of the disease, the histological type of cancer, the age of the patient, the tumour gradus, the size of the residual tumour after surgery and the presence or absence of ascites.[27]

The prognostic significance of the uPA system has been investigated for the ovarian cancer, too, but the studies are few and the number of patients involved is small.

The levels of the uPA, PAI-1 and uPAR were found to be significantly higher in the malignant tissue than in the benign tumours of ovaries,[28,4] which does not apply to the PAI-2.[4] The uPA was found to positively correlate with the number of metastatically involved lymph nodes, less differentiated tumours and excessive production of ascites.[28]

A study of 51 patients with advanced ovarian carcinoma (FIGOIII) revealed that the patients with lower levels of uPA and PAI-1 in the tumour had better prognosis.[28] In addition to the size of the residual tumour, the uPA and the PAI-1 levels proved to be the most reliable independent prognostic factors for patients with advanced ovarian carcinoma. The uPA and the PAI-1 levels were especially significant in the group of patients with no residual tumour.[28] These are the patients with relatively good prognoses, but their 5-year survival rate is still around 55%.[29] The evaluation of the components of the uPA system offers the possibility to find those with less favorable prognoses among these patients, and to adjust their treatment accordingly.[28]

A high content of the PAI-2 in the ascites of the patients with ovarian carcinoma proved to be an independent prognostic factor of the unfavorable outcome of the disease,[30] which is a surprising re-

sult in the light of the capacity of the PAI-2 as a pure uPA inhibitor. The level of the PAI-2 in the tumour was not measured in this study.[30]

Cervical cancer

The strongest prognostic factors of cervical cancer is the stage of the disease. Other prognostic factors are the size of the tumour, the amount of the cervical stroma involved, the involvement of lymphatic vessels and the presence of metastases in lymph nodes.[31]

There are few data in literature on the prognostic relevance of the levels of the uPA system components for cervical cancer. A clinical study involving 62 patients revealed a correlation between high levels of the uPA and/or PAI-1 in the tumour and the number of involved lymph nodes. High levels of the uPA significantly correlated with relapse free survival, and high levels of the PAI-1 with early relapses and shorter survival.[32]

The independent prognostic values of the uPA system components for the outcome of cervical cancer has not been studied yet.[32]

Lung cancer

The prognostic relevance of the uPA system components has been examined in three histological types of pulmonary carcinoma: adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[33,34]

A clinical study involving 106 patients with pulmonary adenocarcinoma showed that the level of the PAI-1 did not correlate with other prognostic factors, such as the age and sex of the patient, the stage of the disease, the size of the tumour, the number of the involed lymph nodes and the surgical radicality. However, the uPA levels were statistically significantly higher in old patients.[33] The uPA and PAI-1 values did not correlate with each other.[33] High levels of the PAI-1 in the tumour tissue of patients with pulmonary carcinoma significantly correlated with poor survival, which was not the case for the uPA.[33] The multi-variant analysis showed that the PAI-1 is an independent prognostic factor for the survival of patients in stages I-III of the disease. The PAI-1 proved to be an independent prognostic factor also for patients in a prognostically favorable stage I of the disease. This fact suggests a possible selection of patients qualifying for adjuvant treatment after the surgical removal of pulmonary carcinoma.[33]

A study of the squamous cell cancer of lungs in 84 patients showed positive correlation between the uPAR and the PAI-1.[34] None of the uPA system components correlated with other prognostic factors. The uPA and the PAI-1 did not have any impact on the outcome of the disease, but the uPAR correlated significantly with survival.[34] Besides the size of the tumour, the uPAR was the only additional prognostic factor in squamous cell pulmonary cancer.[34]

In half a smaller group of patients affected by the large cell cancer a correlation was found between the uPAR and PAI-1, and the uPAR and uPA.[34] None of the components of the uPA system correlated with other prognostic factors.[34] None of the components of the uPA system had any impact on the outcome of large cell cancer.[34]

Gastric cancer

A number of studies of the prognostic relevance of the uPA system components in gastric cancer patients have been made. Here, too, the content of the uPA was found significantly higher in the carcinoma tissue than in the normal mucosa of the stomach.[35] The uPA significantly correlated with the established prognostic factors of gastric cancer. Higher levels of the uPA were found in more advanced stages of the disease, positive lymph nodes and less differentiated tumours.[35]

The uPA, the uPAR and the PAI-1 were found to inversely correlate with the length of survival. The PAI-2 did not show any impact on the outcome of the disease.[36] Two clinical studies of 203 [36] and 97 [37,38] patients with resectable gastric cancer identified only the PAI-1 as an independent prognostic factor of survival in all patients, [37,38,39] as well as in subgroups of patients in pathological stage pT1/2 and pN1/2.[36]

Besides the PAI-1, the uPA and the uPAR proved to be independent prognostic factors in the subgroup of patients with diffuse type of gastric carcinoma.[36] None of the three was confirmed as such in the subgroup of patients with intestinal type of gastric carcinoma.[36]

Colorectal cancer

In addition to the established prognostic factors of colorectal cancer, such as the stage of the disease and surgical radicallity,[39,40] other prognostic factors have been examined, and among them serine proteases are the most promising ones.

Compared with normal mucosa, colon tumours have higher levels of the uPA [41,42] and its inhibitors PAI-1 and PAI-2, [42,43] and lower levels of the tPA.[42]

In the clinical study of 92 patients with colorectal cancer, Ganesh *et al.* report a positive correlation between the uPA content in the tumour and survival of patients, whereas the PAI-1 did not show any prognostic relevance. [42]

However the PAI-2 content in tumour inversely correlated with survival,[42] which is surprising and contrary to the results obtained on breast cancer, where high levels of the PAI-2 in tumours represent a favorable prognostic factor. A high level of the uPAR in the tumour was associated with shorter survival of patients.[44]

Brain tumours

The established prognostic factors for brain tumours are the age and the performance status, the radicality of tumour resection and the histological type of the tumour.[45] Patients with high levels of the uPA in malignant brain tumours or in metastases of lung cancer, breast cancer, colon cancer or of malignant melanoma, have significantly poorer prognosis.[46]

Two clinical studies involving a small number of patients showed that the uPA as well as PAI-1 levels are significantly higher in malignant astrocytoma, especially in glioblastoma, than in the low-gradus glioma and normal brain tissue.[46,47] Neither of the two studies examined the correlation between serine proteases and the usual prognostic factors. Independent prognostic values of the uPA system components for the outcome of brain tumours have not been examined in studies made so far.

Bladder cancer

Nowadays the depth of invasion and tumour grade are considered to be the most relevant prognostic factors of invasive bladder cancer.[48]

According to the data available, the possible role of uPA as a prognostic factor in bladder cancer has been reported only by Hasui *et al.* They found higher levels of the uPA in cancer tissue than in normal urinary bladder tissue and its content increased with the depth of the invasion and the gradus of the tumour.[49] A higher level of the uPA in the tumour was significantly associated with the local relapse and growth of non-invasive tumours and with the survival of patients with invasive cancer.[50,51]

The independent prognostic value of the uPA was not determined due to the small number of patients involved in this studies.

Conclusion

The urokinase type plasminogen activator, its inhibitors and receptors have proved to be independent prognostic factors in breast cancer patients. In breast cancer, serine proteases may also predict the response to hormonal therapy. According to the results of the research performed so far, the uPA and its inhibitors content in tumour tissue also affects the prognosis of patients with many other solid cancers such as ovarian, lung, gastric, bladder cancer etc .

Hopefully on the basis the serine proteases, their inhibitors and receptor determination in tumour tissue it will be possible to differentiate between biologically more and less aggressive tumours in the future. This would enable to select the most suitable treatment for individual patients and thus improve the patients survival.

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Interferon alpha (IFN-α) in treatment of malignant diseases

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There are several natural varieties of IFN-α in clinical use. Although IFNs were the first cytokines in use as a new treatment modality, we still know little about their mode of action in malignancies. IFN-α can inhibit cell growth, but it has been shown only recently, on malignant cells from patients with multiple myeloma, that IFN-α can exert a direct cytotoxic effect on tumor cells. The treatment with natural leucocyte IFN-α in doses used in the early clinical trials, are still most widely used. It has been shown that through a high local concentration by local application in malignant melanoma, basalioma, pleural carcinosis, glioblastoma, total local tumor control may be achieved. It is thus not known what the optimal doses of IFN-α are, and they may vary by the tumor type, as well as from patient to patient. The neccessary duration of treatment also remains an open question. IFNs are a tool for treatment of malignant tumors. Their cytotoxic effect, however, is not strong enough and does not last. At present, there is a vast field of investigative work still open - but in the meantime it seems necessary to proceed with clinical trials of different types of IFN, the natural IFN-α again beeing the most interesting one.

Key words: neoplasms-drug therapy; interferon-alpha

Introduction

The antiviral and antitumor efficacy of interferon alpha (IFN-α) has been established in the 1960's and 1970's.[1] During the 1970's it was demonstrated that IFN-α has an affects on benign and malignant tumors in man, but the question was whether this was due to the presence of IFN-α or contaminating substances in the preparations.[2-4] By 1979, recombinant human IFN-α had been produced in an almost pure form, thus the antitumor effect of IFN-α in man could be established.[5-7]

The natural IFN-α contains several species of IFN-α. Individual IFN-α subtypes have been isolated and they have specific activities according to the cell on which they are tested. Much effort has gone into attempts to isolate and purify single subtypes of IFN-α. The natural mixture of IFN-α, however, seems to be more active than any of its components: synergistic interactions might exist among IFN-α components. Consequently, new interest was aroused in the natural IFN-α.[8]

There are several natural varieties of IFN-α in clinical use. IFNs affect the organism and the tumor in a number of ways. They may act by altering the immune response, their antitumor action may be due to the effect on oncogenes, on the growth factor responses, on proliferation and differentiation, and on their cytostatic effect. Allthough IFN-s were the first cytokines in use as a new treatment modality, we still know little about their mode of action in malignancies. It is conceivable that their major mode of action varies with the disease and even among individuals. It is likely that the antitumor effects of IFN-α are due to different effects in interaction.[2]

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Laboratory and clinical studies

It is a well established fact that IFN-α can inhibit cell growth, but it has been shown only recently, on malignant cells from patients with multiple myeloma, that IFN-α can exert a direct cytotoxic effect on tumor cells.[9]

In several patients with different tumors such as Kaposi's sarcoma, lymphoma or renal cell carcinoma there has been no statistically significant correlation between the dose of IFN-α and the effect of treatment. The treatment with natural leucocyte IFN-α in doses (3×10^6, 3 times weekly) used in the early clinical trials, are still most widely used and regarded as the optimal treatment. They were introduced mostly for practical reasons such as: they produced a mesurable antiviral effect in monkeys which lasted about 3 days. Due to side effects, no higher doses could be given.[2, 10]

On the other hand, it has been shown that high local concentration by local application in malignant melanoma, basalioma, pleural carcinosis, glioblastoma, may achieve total local tumor control.[11-15] Systemic effect has been described in breast cancer patients some 20 years ago.[7] Some doubts have been expressed that IFN-α can be effective in solid tumors systemically, but in vitro experimental models showed that IFN-α may have effect on tumor cell metastasis. Furthermore, subcutaneous injections of IFN-α in combination with surgery and radiotherapy were effective in treatment of patients with skeletal metastases from renal cell carcinoma.[16-18]

Recently it has been shown that in breast cancer IFN-α is able to reduce cell proliferation, enhance steroid hormone receptors and sensitize breast cancer cells to tamoxifen treatment. It also increases the activity of medroxyprogesteron and restores hormone sensitivity in hormone resistant cells.[19]

Clinical application

It is thus not known what the optimal doses of IFN-α are, and they may vary by the tumor type, as well as from patient to patient. The neccessary duration of treatment also remains an open question. Most tumors recur when IFN-α treatment is discontinued. The doses may also vary when IFN-α is combined with chemotherapy or radiotherapy. Side effects should be dealt with to reduce symptoms, but the most efficacious way of deverting complication has been the reduction of the dosage. Moderate temperature rises should not be treated since some of the IFN-α effects are known to be enhanced by higher temperature.[1]

IFN-α has been effective against Kaposi's sarcoma. In certain groups of patients with HIV infection, IFN-α may enhance the CD 4 + cell count.[20, 21]

IFN-α has some advantages over other treatment modalities in patients with hairy cell leukemia: there is no enhanced risk for infections, as is with chemotherapy or corticosteroids. Complete remissions have been achieved in patients with hairy cell leukemia following low doses of IFN-α.[8] With low doses of IFN-α, the Philadelphia (Ph 1) positive cell clones could be suppressed in patients with chronic myelogenous leukemia. Approximately 70 % of patients with chronic myelogenous leukemia respond to IFN-α treatment and 20 % display complete cytogenetic remission. In hairy cell leukemia with continuous treatment, additional complete remissions were achieved. Therefore it was proposed that treatment of patients with chronic myelogenous leukemia should also be prolongued.[22]

IFN-α is used for treatment of T as well as B lymphomas. There is evidence that IFNs are natural regulators of various B cell functions including the induction of blast transformation and plasmacyto differentiation in malignant B cells. IFNs also inhibit the generation and function of T suppressor cells and some of the T-cell lymphomas may respond well to IFN-α treatment. Approximately 50% of cutaneous T cell lymphomas respond to high dose treatment with IFN-α. It has been reported that some patients with adult T cell leukemia respond to interferon, impressive responses in combination with zivudine have been reported in such patients.[8, 23-25]

IFN-α has antitumor effect in multiple myeloma, with a 15% response rate. A particularly beneficial effect is noted in IgA myeloma treated with natural IFN-α. Intermittent melphalan (prednisone treatment and IFN-α) is regarded by many clinicians as the standard primary therapy for patients with multiple myeloma since there is evidence of better results of chemotherapy when combined with IFN-α.[2, 26, 27] IFN-α is used in the treatment of renal carcinoma and ovarian carcinoma alone and in combination with chemotherapy.[27] While with IFN-α in breast cancer patients, 22 to 41% response rates were reported, with recombinant IFN-α, this was not confirmed. IFN-α has been less effective in the treatment of gastrointestinal cancer and of some

other solid tumors.[8, 16] In advanced malignant melanoma the response rate of 12-22% with IFN-α alone have been reported.[2]

With IFN-α as adjuvant therapy to surgery, the disease free survival of patients with osteogenic sarcoma has been 50%.[5, 6]

Experience of the Oncological Institute of Ljubljana

At the Oncological Institute in Ljubljana, IFN-α was introduced in clinical use in 1976 for treatment of patients with pleural carcinosis from breast cancer. After intrapleural applications the malignant cells disappeared, however, no systemic effect was noted and the advanced metastatic disease progressed. IFN-α in patients with pleural carcinosis from breast cancer was continuously studied. There was evidence that IFN-α, as addition to systemic treatment, is an effective means of paliative treatment of pleural carcinosis. There were some observations that IFN-α seemed to affect the survival of patients with inflammatory breast cancer and pleural carcinosis.[29]

IFN-α has been shown to be effective in non-small lung cancer patients with pleural carcinosis. Following intrapleural applications, the effusion was cleared from cancer cells and haemorrhagic admixture in a majority of patients, it did arrest fluid accumulation with minimal side effects and probably did prolong the survival in these patients.[30] In a non randomized clinical trial of patients with non-small-cell lung cancer treated with intrapleural application of IFN-α in combination with radiation therapy it seemed that the survival of these patients was prolongued.[31] At present a randomized clinical trial is underway to study the effect on the survival of patients with non-small-cell lung cancer and pleural carcinosis, treated with radiation alone or in combination with IFN-α.

Serum interferone levels have been studied in patients with breast cancer and non-small lung cancer treated with intrapleural application of IFN-α. A correlation of the clinical effect and the levels of serum IFN-α could not be established.[32]

IFN-α has been given locally in patients with glioblastoma and malignant astrocytoma. This treatment was combined with chemotherapy and radiation. The study showed that with this combination therapy the malignant tumor could be eradicated succesfully, as confirmed by histological examination. The treatment, however, had unacceptable levels of neurotoxicity.[33]

At the Institute of Oncology in Ljubljana a prospective randomized trial study was undertaken in 1988 in patients with malignant melanoma stage IIA and B to establish the role of interferon as an adjunct to surgery. The survival of the 160 patients treated with IFN-α was significantly higher than in the 161 patients of the control group.[34] In a randomized trial (70 pts) it was further shown that patients with advanced malignant melanoma treated with IFN-α additionally to DTIC have a significantly better survival than those treated with DTIC alone.[35]

Conclusions

There is no doubt that IFNs are a tool for treatment of malignant tumors. Their cytotoxic effect, however, is not strong enough and does not last, cures of systemic malignant disease are rather exceptional with IFN alone. It seems reasonable to expect that clinical trials with IFN in combination with chemotherapy and radiotherapy will improve the results in certain groups of patients. It is possible that with a better understanding of problems, such as antagonism to IFN by some substances, antibodies to IFN, the effect of IFN on various oncogenic systems, the clinical use of IFN will yield better results. At present, there is a vast field of investigative work still open, but, in the meantime, it seems necessary to proceed with clinical trials of different types of IFN, the natural IFN-α again beeing the most interesting one.

Our experience is with IFN-α produced at the Institute of Immunology in Zagreb. In terms of low toxicity, high tolerance and the clinical effect, it concurs with that of others. In our opinion, it constitutes a promising tool for further clinical trials.

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Diagnosis and treatment of radiation damage – the acute radiation syndrome

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Radiation mainly yields to a damage of highly reproductive cells, i.e. radiosensitive tissues like bone marrow, gastrointestinal mucosa, and hair follicles. With increasing doses radiation causes damage of more differentiated, i.e. relatively radioresistant organs like the central nervous system as well. The acute radiation syndrome presents with an uniform sequence of 3 phases: the prodromal stage with unspecific symptoms like vomiting and nausea, followed by a phase of subjective well-being, i.e. the latency phase. The third phase of the acute radiation syndrome has been divided into three major catagories: 1. bone marrow syndrome, 2. gastrointestinal syndrome, and 3. central nervous syndrome. Each syndrome is defined by dose, survival time, and symptoms. Survival of the patients is mainly limited by radiogenic damage to the bone marrow, and causal treatment like bone marrow transplantation may be successful after whole-body irradiation below 10 Gy. Whereas after applied doses above 10 Gy the therapeutic approach will predominantly be palliative preventing patients from pain and suffering.

Key words: radiation injuries-diagnosis-therapy

Introduction

The development of radiation biology began immediatly after the discovery of the X-rays by Konrad Wilhelm Röntgen in 1895. Apart from the usefulness of radiation in medicine and technology radiation-induced damages were observed soon after the first applications of X-rays. Becquerel and Curie suffered from an acute radiation dermatite, the so called radium burn. Curie died of aplastic anemia probably due to chronic radiation exposure. Since the tragedy of Hiroshima and Nagasaki and the accident that occured at the Chernobyl nuclear power station in april 1986[1] the awareness of the hazards of radiation has been increased. Due to these tragedies human data on the effects of a single-body radiation could have been obtained.

Even if radiation syndromes are very rare cases in clinical routine patient management, the knowledge of both their clinical symptoms and treatment should be of interest not only for those professionals dealing with X-rays. However, the clinical symptoms depend on the body region exposed, and the level of the radiation dose as well as on the duration of radiation exposure. Therefore, clinical symptoms of radiation syndromes show a great variation. The symptoms occuring promptly include simple skin reactions as well as the acute radiation syndrome. On the other hand, the development of neoplasms are well-known as late side effects caused by radiation. Since data on humans being exposed to whole-body irradiation are well-known the sequence and intensity of clinical symptoms may be used to estimate the radiation dose to which an individual was exposed accidentally.

In this paper we describe both basic mechanisms and effects of radiation in different tissues as well

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as clinical symptoms of radiation injury. The latter is examplified by a radiation accident which happened in Israel in 1990.

Basic mechanisms of radiation damage

The interaction of radiation with tissue occurs within seconds. In the first physical stage high energetic particles deposit their energy within 10^{-18} to 10^{-12} seconds predominantly in water molecules. In the following physico-chemical stage activated particles transfer their energy to biological molecules, thereby producing free radicals via ionization. These radicals interact in the so called chemical stage with surrounding biological molecules, e.g. DNA, RNA or the core membrane. The altered biological molecules lead to delayed biological effects of radiation within hours, days or even years. Thus, it is reasonable that biological effects of radiation mainly depend on the amount of energy (Joule per kilogramm = Gy) absorbed in tissues.

Since different types of radiation yield to same physico-chemical effects, i.e. the ionization with consecutive production of free radicals, their biological effects are mainly comparable. However, different types of radiation differ in their amount of free radicals generated per unit of energy and, thus, different types of radiation produce varying degrees of damage with the same dose. This different relative biological effectiveness is due to the fact that the linear energy transfer (LET) for each type of radiation is different: For the same total dose, the radiation of high LET (alpha particles: LET = 20) produces greater damage than that of low LET radiation (X-ray and gamma-ray: LET = 1).

Molecular damage

Molecular damage caused by radiation is based on different mechanisms. From an absorbed dose of 1 mGy single-strand breaks of DNA occur in 50 % of the irradiated cells. However, both single-strand and double-strand breaks of DNA are repairable, thus changes in the genome are effectively avoided.[2-5] From 0.1 to 1 Gy the biosynthesis of DNA, RNA and proteins (in sequence of their decreased sensitivity) is reduced. The production of antibodies is altered from an absorbed dose of 2 Gy.

The radiosensitivity of different cytoplasmic organelles differs. The nucleus and its membrane are more radiosensitive than other subcellar structures such as mitochondria, lysosomes, cell membrane und the golgi apparatus. In addition, the radiosensitivity of the cell is related to the cell cycle which is divided into four phases. During the mitosis (M) period and the post-DNA synthesis phase (G2) the cell is more radiosensitive than in the late pre-DNA synthesis period (G1). On the other hand, cells are relativly radioresistant during the non-growth period (G0) and the DNA synthetis phase (S).

The technique of obtaining synchronized cells has improved new tumor therapies: prior to irradiation tumor cells are synchronized by cell toxines in order to increase their radiosensitivity.

Effects of radiation on organs

In 1906 Bergonié and Tribondéau formulated some references concerning the radiosensitivity of cells: X-rays are more effective on cells that have a greater reproductive actvity. X-rays are more effective on cells of which the morphology and the function are the least fixed.

Thus, highly radiosensitive tissues are those with a high reproductive potency, e.g. bone marrow, lymphatic tissues, reproductive organs, mucosa of the gastrointestinal tract and hair follicles. Conversely, less radiosensitive are skin, eyes, liver, lung, and kidneys. A relative radioresistance has been observed in several tissues, e.g. central nervous system, heart, muscles, bones and fat tissue.

Bone marrow syndrome and lymphatic syndrome

Undifferentiated stem cells of the bone marrow are highly radiosensitive cells. Directly after radiation exposure granulocytosis as initial reaction of the bone marrow can be observed. This is followed by a leucopenia within hours due to a depressed cell production of stem cells located in the bone marrow.

Radiation-induced bone marrow damage is influenced by dose rate: the higher the dose rate the greater the damage. An absorbed dose of 2.5 Gy destroys 5 % of the stem cells, whereas after a radiation exposure of 6.5 Gy only 5 % of the stem cells maintain their ability to proliferate. Therefore, a little increase of the absorbed radiation dose causes a marked increase in the number of destroyed stem cells. This illustrates the extreme steepness of the underlying dose-effect-curve.

The sequence of cell reduction in the peripheral blood is uniform. This mainly reflects the difference of mean life-time of the different cell types in the peripheral blood. After a whole-body irradiation of 5-10 Gy the number of lymphocytes decreases within hours and days followed by a reduction of granulocytes and thrombocytes. A decline of erythrocytes is seen from the third week after exposure according to their longer mean life-time.

Gastrointestinal tract

The signs and symptoms associated with the gastrointestinal syndrome may be due to the failure of both intestinal mucosa and the bone marrow.[6] Effects of radiation on the gastrointestinal tract are widely varying. An exposure of 4 Gy decreases the motility of the small intestin. After 10 Gy a decreased production of hydrochloric acid can be observed followed by fluid and electrolyte imbalance. This imbalance is due to a failure of intestinal absorption which leads to diarrhea and severe dehydration. The gastrointestinal damage is also associated with infection. Therefore, postirradiation infection may be due to the failure of the intestinal mucosa as well as to the failure of the irradiated bone marrow. The radiation-induced changes of mucosa membranes in association with the decreased motility may lead to the clinical picture of a radiogenic ileus as a late side effect of irradiation.

Skin

Skin changes following radiation of the respective anatomical region differ between individuals. Furthermore, different structures of the skin show a different radiosensitivity. Hair follicles are highly radiosensible. An absorbed dose of as less as 1 Gy leads to an inhibition of growing hair follicles. 4 Gy produce a temporary and 20 Gy a permanent epilation. From a radiation dose of 10 Gy an initial erythema may appear according to capillary dilatation and release of histamine-like substances: the acute radiation dermatite. Months after an irradiation epidermis becomes atrophic associated with variations of pigmentation, fibrosis and ulcerations due to rarified vascularization. As late side effect of radiation skin neoplasms such as spinalioma may occur.[7]

Eyes

Different radiosensitivity occurs in different structures of the eyes as well. The most radiosensitive part of the eye is the lens, whereas retinal tissue and the optic nerve are relatively radioresistent. After low radiation doses conjunctivitis, blepharitis and an epilation may occur. From a radiation dose of 10 Gy corneal ulcerations may appear as well as radiogenic cataracts.

Nervous system

Nerval tissue consisting of well differentiated cells with an absence of reproductive activity is markedly radioresistant. The spinal cord is the most radiosensitive substructure in the central nervous system.[8] Radiogenic damage of the spinal cord occurs from 40 Gy with consecutive neurological signs. Postirradiation effects have been observed such as post radiation myelitis, and hyaline thickening of blood vessels with the development of paralysis.[9, 10] In contrast, glial cells like astrocytes, schwann cells or oligodendrocytes have still reproductive activity and, therefore, they are much more radiosensitive.

Bone

The mature adult skeleton is well differentiated and for this reason relatively radioresistant. On the other hand, bones of the adolescents may easily be damaged by radiation causing a retardation of growth. In case of unilateral application of irradiation an asymmetric growth with inherent orthopedic problems can be observed.

Respiratory system

Although lung and pleura are relatively radioresistant clinical signs of lung fibrosis and pneumonia may occur after high dose irradiation. Moreover, irradiated lungs have a higher risk of secondary diseases, e.g. emphysema following chronic bronchitis, atelectases or neoplastic disorders.

Acute radiation syndrome

General considerations

The acute radiation syndrome has an uniform sequence of symptoms. The prodromal stage is characterized by headache, nausea and vomiting within 1 to 2 days. These symptoms subside as rapidly as they develop. Thereafter the patient feels more comfortable which is called the latency phase. From the third day after radiation exposure the main symptoms of the acute radiation syndrome may occur such as the bone marrow syndrome, the gastrointes-

tinal syndrome or the central nervous system syndrome. The intensity, the time course, and the number of symptoms depend on the radiation dose applied. With increasing radiation doses more symptoms appear earlier, and symptoms are more pronounced.

Prodromal stage

The prodromal stage is defined by symptoms occuring within the first 48 hours after radiation exposure. The cardinal symptom of the prodromal stage is vomiting with nausea and lack of appetite. The time of occurence of symptoms can be used as a prognostic factor *quoad vitam* to estimate the radiation dose applied accidentally. If vomiting occurs within two hours after radiation the dose will be potentially lethal. Vomiting within 30 minutes after irradiation is considered being a sign of a certain lethal dose.

Moreover, there may be some more uncharacteristic symptoms occuring in the prodromal stage, i.e. fever, erythema of the conjunctiva as well as erythema of the oropharyngeal mucosa. The latter points on a dose higher than the LD_{50}. The central nervous system may present with confusion, convulsion and unconsciousness in the prodromal stage.

The therapy of the prodromal stage is limited to palliative treatment, e.g. effective antiemetics.

Latency phase

The latency phase is characterized by subjective well-being for about 1-2 days. This is due to the relatively radioresistant differentiated cells which are still able to function until their physiological degradation. Thus, symptoms of acute radiation syndrome occur when there is a lack of supplies caused by the radiation-induced damage of highly reproductive stem cells.

Radiation syndromes after latency phase

The signs and symptoms produced by whole-body exposure are referred to as the radiation syndrome. Radiation syndromes have been divided into three major catagories: 1. bone marrow syndrome, 2. gastrointestinal syndrome, and 3. central nervous syndrome. Each syndrome is defined by dose, survival time, and symptoms.

Bone marrow syndrome

Bone marrow syndrome is defined by bone marrow depletion with subsequent pancytopenia yielding to a consecutive decrease of lymphocytes, leukocytes, and platelets within hours to days in the peripheral blood. This is followed by a delayed decrease of red blood cells within days to weeks. The pancytopenia following irradiation is the primary reason for death in bone marrow syndrome.

For the patient´s survival the vitality of a few stem cells in the bone marrow is required. Model calculations revealed that as less as 0.8 % surviving stem cells in the bone marrow are sufficient to maintain the patient´s survival. However, the dose-effect-curve is extremly steep. Consequently, only little differences in the dose applied cause marked changes of the survival rate. Thirty days after whole-body exposure with 2,5 Gy 95 % of patients are still alive whereas a dose of 6,5 Gy kills 95 % of patients. Thus, a 3 fold increased whole-body radiation dose decreases the patient's survival rate by the factor 20.

The clinical symptoms are mainly caused by the pancytopenia. Due to low platelet counts hemorrhagia may occur. A marked neutropenia increases the susceptablility to infection, i.e. infection with opportunistic germs. Concomitant damage of the gastrointestinal tract leads to fluid and electrolyte imbalance.

The therapy of bone marrow syndrome is adapted to the clinical symptoms. This includes application of antibiotics, antimycotics, infusion of platelets, and the balanced substitution of fluid and electrolytes. Moreover, cytokines may be helpful to accelerate differentiation of stem cells. Bone marrow transplantation may be considered in patients with whole-body doses of less than 10 Gy as the only causal therapeutic approach.[11-13]

Gastrointestinal syndrome

The gastrointestinal syndrome is characterized by a damage of mucosa. Complete destruction of proliferating basal cells in the upper gastrointestinal tract, e.g. duodenum and jejunum, can be observed from radiation doses of 10 Gy.

The clinical symptoms are directly derived from the damage described above. Patients may show up with diarrhea, mucosal ulcerations, malabsorption syndrome, fluid and electrolyte imbalance as well as with septic shock caused by an overgrowth of intestinal germs in these immunodeficient patients.[14]

The therapeutic approach is similar to that of treatment of bone marrow syndrome. This includes application of antibiotics, antimycotics, infusion of

platelets, and the balanced substitution of fluid and electrolytes as well as parenteral nutrition of the patients. Since gastrointestinal syndrome may occur even below whole-body doses of 10 Gy bone marrow transplantation may be considered useful in these patients.

Central nervous syndrome

The main pathogenetic mechanism of central nervous syndrome is a damage of small vessels. The resulting vasculitis leads to central edema via an increased permeability of capillaries. The central nervous syndrome is characterized by periods of agitation and apparent marked apathy, followed by signs of disorientation, disturbed equilibrium, ataxia, diarrhea, vomiting, opisthotonus, convulsions, prostration, coma and death. Death probably results either from a direct neuronal damage or via increased intracranial pressure.[15-18]

The therapeutic approach is directed against pain and convulsion, and vomiting in order to relief patients from suffering. Thus, this predominantly palliative treatment consists of analgetics, sedative agents, and antiemetic drugs.

Radiation accident in Soreq (Israel) on 21st of June 1990

On June 21st 1990 due to technological failure and human error a serious nuclear accident occured at the nutrition radiation factory in Soreq in Israel. A 32-years-old employe was irradiated by a highly active Co-60 source for the duration of about 2 minutes receiving a whole-body dose of some 20 Gy. Within 5 minutes after exposure he started vomiting. Consequently, he was submitted to the Tel Aviv hospital 2.5 hours after the accident. On admission he presented abdominal pain, nausea, persistant vomiting, generalized erythema, blepharoedema, and an increased body temperature of 40.7 °C. 8 hours after exposure he was transferred to the bone marrow transplantation unit in Jerusalem.

Due to suspected immunodeficiency the patient was isolated and his intestine was sterilized by oral antibiotics. To prevent viral infection the patient was treated with Aciclovir. The application of cytokines was performed in order to accelerate differentiation of vital stem cells due to massiv pancytopenia. Bone marrow transplantation was performed 4 days following irradiation. However, the donor, his brother was not perfectly compatible in his MHC-antigens. At the end of the first week the patient continued vomiting and exhibited both liquid and hemorrhagic diarrhea, i.e. gastrointestinal syndrome. Coloscopy revealed marked colitis with edema, hyperemia and multiple ulcerations. This was accompanied by oropharyngeal mucositis and an epilation of head, face, and pubic hair. Due to gastrointestinal syndrome the patient received parenteral alimentation in order to substitute the imbalance of fluid and electrolytes.

In the second week multiorgan failure occured with progressive decrease of renal and hepatic function. The patient developped abacterial pneumonia caused by cytomegaly virus, which was treated by virostatics. The patient became more and more disorientated on day 35 post irradiation, and died on the following day due to respiratory failure.

Conclusion

Although acute radiation syndrome is a rare problem in current clinical practice one should be aware of the signs and symptoms in order to ensure both immediate diagnosis and adequate subsequent treatment in case of radiation accidents.

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Comparison of TDF and LQ models using the bioeffects algorithm of a treatment planning system

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In this study, two examples, first with two-field AP/PA plans and second with four-field plans are evaluated for Co-60 beams using the bioeffects program of the Radiation Oncology Computer System (ROCS) treatment planning system. The bioeffects algorithm enables the summation of two or more treatment plans. Biomodifier tables, which convert the values of dose per fraction delivered over a period of time to Time Dose Fractionation (TDF) are included with the software. The biomodifier table is a standard ROCS two-dimensional table. By using the linear-quadratic (LQ) model, the biological equivalent dose versus the physical absorbed dose was determined and input as a new biomodifier table. The distribution of TDF values and the biological equivalent dose using the LQ model shows that the LQ model may be a better choice for a bioeffect algorithm. Furthermore, the LQ model may be implemented in the ROCS system.

Key words: neoplasms-radiotherapy; computer-assisted; bioeffects algorithm, radiotherapy planning, radiation therapy, dose response relationship

Introduction

The Time Dose Fractionation (TDF) model[1] and the linear-quadratic (LQ) model[2] are theories that attempt to predict the biological effects which occur during a course of radiation therapy. The TDF model is based on the iso-effect dose as a function of either the overall time, or total number of fractions of treatment. TDF has been used for many years as a time-dose model in radiotherapy since it is simple to use. The LQ model is based on the linear-quadratic shape of the cell-survival curves. It is postulated that radiation can be divided into two components, the α component is more important at low doses, and the β component more important at high doses. The parameter α/β is the dose at which the fractional log cell kill for these two components is equal.[2]

In this study, two field AP/PA and four field plans are evaluated using the bioeffects program of the ROCS (Radiation Oncology Computer Systems, Carlsbad, California, U.S.A.) treatment planning system for Co-60 beams. The ROCS treatment planning system has a bioeffects algorithm[3] which supposedly enables the summation of two or more treatment plans. A treatment is defined as a series of contours with external beam data, or planes of brachytherapy data. Biomodifier tables, which convert the values of the dose per fraction delivered over a period of time to TDF, are included with the software. The table values were derived from work done by Orton.[4,5]

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The biomodifier table is a standard ROCS two-dimensional table. By using the LQ model, the biological equivalent dose versus the physical dose was determined and input as a new biomodifier table. The distribution is compared using the TDF and the LQ models.

Materials and methods

A contour with AP/PA separation of 25 cm and lateral separation of 38 cm was used for external beam planning. In the first example, a setup of 80 cm SSD with AP/PA 18 × 18 cm^2 Cobalt-60 beams was used to deliver 1.8 Gy/fraction to the mid-plane. In the second example, four fields equally weighted, with 18 × 18 cm^2 AP/PA and 10 × 18 cm^2 lateral fields, 80 cm SSD Cobalt-60 beams were used. A total of 45 Gy was delivered in 25 fractions. A typical external beam biomodifier table provided by ROCS will convert cGy/fraction to TDF for the number of fractions per week and the total number of fractions specified. In this case, five fractions per week were used.

The beam arrangement in this simple example was chosen to demonstrate the application of the different models, i.e., TDF and LQ using the ROCS system. The contour may be considered as a thoracic region where the spinal cord dictates the normal tissue tolerance.

Withers[6] and Scalliet[7] showed that calculation of isoeffect dose equivalencies when altering the fraction size can be done using the formula
where D is a reference total equivalent dose delivered at a given fraction size d and D' is the unknown total equivalent dose delivered at a new fraction size d'.

$$\frac{D'}{D} = \frac{d + \alpha/\beta}{d' + \alpha/\beta}$$

Using a α/β of 2 Gy for late reacting tissues,[7] and a fraction size of 1.8 Gy, the equivalent total dose may be computed, e.g., for the 1.9 Gy isodose line in the daily dose distribution, such that

Equivalent does using LQ model = (1.9 Gy × 25) × (1.9 + 2)/(1.8 + 2) = 48.8 Gy

The biological equivalent dose of 48.8 Gy corresponds to an absorbed dose of 47.5 Gy. Similar calculations were computed for daily doses from 0.2 to 2.2 Gy, and these values were input as a two-dimensional table in the ROCS bioeffect program.

Results

Figure 1 shows the total dose distribution from standard treatment planning using the ROCS system. A total dose of 45 Gy was delivered to the mid plane, while the maximum dose was 56 Gy, for a setup of 80 cm SSD with AP/PA Cobalt-60 beams.

Figure 2 shows the TDF isolines using the bioeffect algorithm of the ROCS system. The TDF value was about 70 at the mid plane with a maximum of 97.

Figure 3 shows the equivalent dose distribution calculated using the LQ model. Again, 45 Gy was delivered to the mid plane. The maximum biological equivalent dose was found to be 61 Gy.

Figure 4 shows the total dose distribution from standard treatment planning using the ROCS system. A total dose of 45 Gy was delivered to the mid plane, while the maximum dose was 46 Gy, for the four-field setup of 80 cm SSD.

Figure 5 shows the TDF isolines using the bioeffect algorithm of the ROCS system. The TDF value was about 70 at the mid plane with a maximum of 73.

Figure 6 shows the equivalent dose distribution calculated using the LQ model. Again, 45 Gy was delivered to the mid plane. The maximum biological equivalent dose was found to be 47 Gy.

Discussion

The bioeffects program of the ROCS system is limited to a single external plan, which may be used with a brachytherapy plan. The biomodifier tables provided by ROCS, however, are somewhat outdated. Orton[8] states that a TDF of 100 is roughly equivalent to normal connective tissue and skin tolerance. In the simple AP/PA setup example where the spinal cord may be the sensitive normal structure outside the target volume, the dose equivalent may approach the normal tissue tolerance. The TDF in the spinal cord region may only show a value of 70 to 80.

The LQ model may be implemented here to demonstrate its use in treatment planning. Comparing figures 1 and 3, the biological equivalent total dose is higher than the absorbed dose. This is demonstrated by the larger volume of the 50 Gy isodose, and the maximum biological dose equivalent of 61 Gy.

In the four-field example, the biological equivalent total dose (Figure 6) is also higher than the

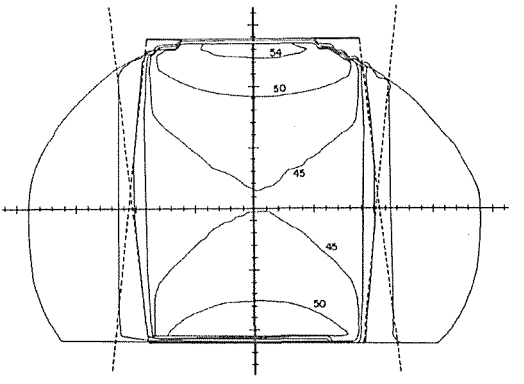

Figure 1. Total dose distribution from the regular treatment planning using the ROCS system. A total dose of 45 Gy was delivered to the mid-plane for the AP/PA setup. Numbers indicate the total dose (in Gy) to an isodose line.

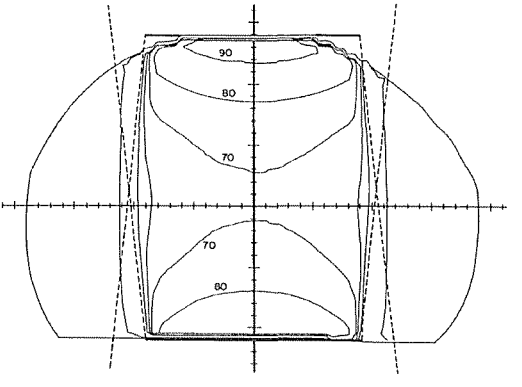

Figure 2. TDF isolines using the bioeffect algorithm of the ROCS system for the AP/PA setup.

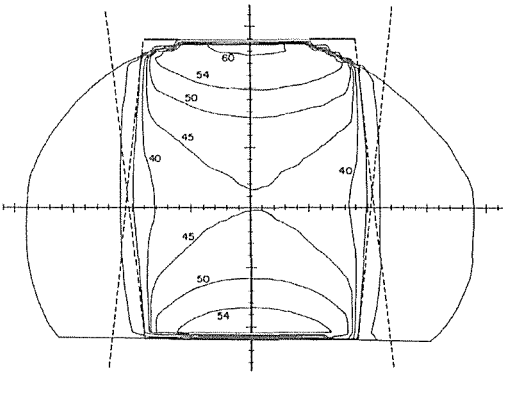

Figure 3. The biological equivalent dose distribution calculated using the LQ model for the AP/PA setup. Numbers indicate the total biological equivalent dose (in Gy) to an isodose line.

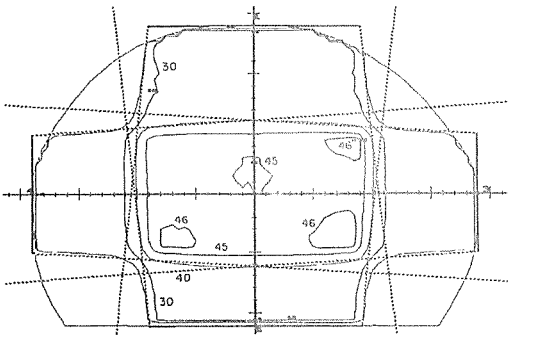

Figure 4. Total dose distribution from the regular treatment planning using the ROCS system. A total dose of 45 Gy was delivered to the mid-plane for the four-field setup. Numbers indicate the total dose (in Gy) to an isodose line.

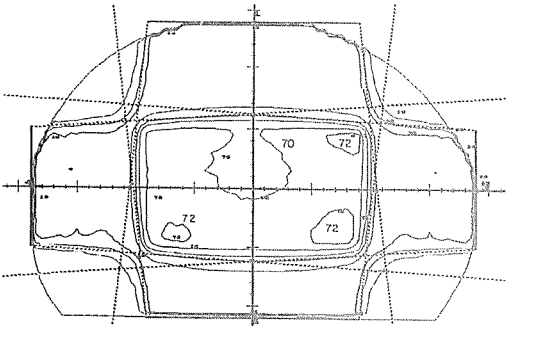

Figure 5. TDF isolines using the bioeffect algorithm of the ROCS system for the four-field setup.

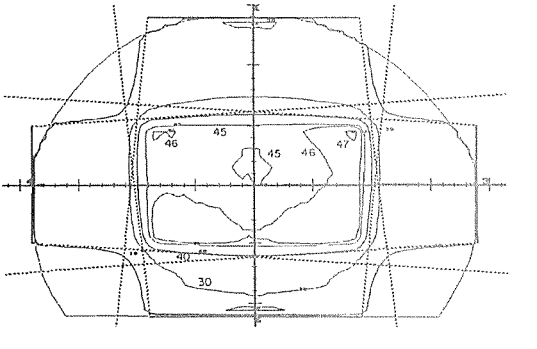

Figure 6. The biological equivalent dose distribution calculated using the LQ model for the four-field setup. Numbers indicate the total biological equivalent dose (in Gy) to an isodose line.

absorbed dose (Figure 4). This is demonstrated by a larger volume of the 46 Gy isodose, and a maximum biological dose equivalent of 47 Gy. Again, the TDF isolines in figure 5 do not give any useful information.

The biomodifier tables as provided by ROCS for the bioeffect algorithm have very limited use in treatment planning, since they utilize the TDF model. The LQ model is a better algorithm and it may be implemented easily in ROCS. Any model, however, will have to be used with caution since there are always limitations in its practical application.

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Book review

Atlas of applied internal liver anatomy

Eldar M. Gadžijev and Dean Ravnik

Springer Verlag Wien New York, 1996. Pages: 204; ISBN 3-211-82793-5

Every publication of a Slovene medical book abroad is an important event on its own, and more so if the book appears with such a distinguished publisher as Springer Verlag. This publication outlines the authors' work in the field of surgical anatomy of the liver, which dates back in the recent past, and is emerging as one of the foundation stones of what has been internationally recognized as Ljubljana school of liver surgery. The book sheds a new light on the relatively complex and insufficiently discussed topic of surgical anatomy of the liver, the field which is of paramount importance for every surgeon and particularly for all those involved in liver surgery. It is based on the practical experience that the authors have gained during their active involvement in the organization of the international school of hepatobiliary surgery held traditionally in Ljubljana.

The book is written clearly and systematically, starting with the Introduction by Stig Bengmark from Lund, one of the pioneers of European hepatic surgery. This is followed by sections dedicated to the portal vein, hepatic artery, biliary and hepatic vein systems. All the chapters are richly illustrated by photographic material based on the human liver casts produced according to the authors' original technology. Each photograph is accompanied by a schematic presentation of the section imaged, as well as by a detailed textual explanation. High-quality photographs present different liver structures using various colors: thus, the venous system is blue, biliary yellow and arterial red., which renders the presentation of this complex organ very vivid and clear.

The chapter on the portal venous system is subdivided into smaller logical units. It is well known that the portal venous system is the one which - together with the system of hepatic veins - provides the basis for functional surgical anatomy. By means of photographs and text, the chapter clearly presents both main portal branches, sector veins and the veins supplying different segments of the liver. In the chapter on the anatomy of the hepatic artery, the authors describe the course of the left and right hepatic arteries, and that of the common hepatic artery. There, the presentations of left and right accessory hepatic arteries stand out as particularly clear, which is of great importance for the surgeon in planning the procedure. The chapter ends with the presentation of anastomoses between the right and left hepatic arteries, and a case of arterial aneurysm. The chapter on the biliary system continues with a detailed description of the region up to the level of the segmental ducts, presenting their standard courses as well as all possible variations of those.

The last chapter in the book deals with the system of hepatic veins, which is of central importance in the functional, i.e. surgical anatomy of the liver, since it represents the basis for segmentation of the liver according to Couinaud. This chapter also shows basic features of the course of hepatic veins and also some of its variations. The book ends with an alphabetical index which renders search of a particular entity easier.

The book represents, on the one hand, an important step forward in understanding the surgical anatomy of the liver, and on the other, a relevant contribution of the Slovene medicine towards medical science in general. This valuable publication is expected to become one of the basic textbooks for surgeons engaged in hepatic surgery, and may also be of interest to other specialists concerned with liver disease. It should become part of every Slovenian medical library, and should set an example for other fields of Slovenian medicine. Clearly, this book places our medicine abreast with the state of the art in the most developed parts of the world.

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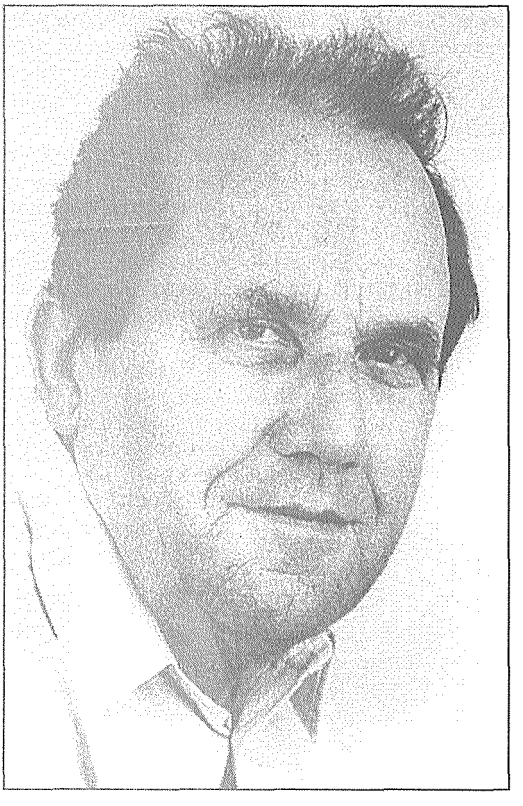
In memoriam

Prof. Ludvik Tabor

Recently, we sadly witnessed the end of the life circle of Prof. Ludvik Tabor, MD, a renown radiologist, long-standing university teacher and the Chairman of the Chair of Radiology.

He was born in 1924 in Ljubljana. There he also graduated from the Faculty of Medicine. Relatively early in his career he decided to specialize in radiology, which was not very popular at the time,



and completed his residency with the board exam in 1957. His academic interests became apparent soon after he had taken on a position at the Institute of Radiology of the University Hospitals in Ljubljana, when his first professional papers started to appear in national as well as international medical journals. In 1964 he was elected into the title of an Assistant Professor of Radiology at the Faculty of Medicine in Ljubljana. His thesis entitled "Genital Tuberculosis in Women and the Problem of Modern X-ray Diagnostics" has become a textbook widely used by residents in radiology. In 1970 he successfully defended his Doctoral thesis "Radiological Clinical Study of Congenital Anomalies of the Spine and Potential Disability" and thus became the first radiologist with doctoral degree in Slovenia. Osteoarticular radiology remained the main field of his interest throughout his professional career. From 1960 till his retirement, he functioned as a consultant in radiology at the University Department of Orthopedics, organized radiological service and set up a rich archive of radiograms. In 1974 he was elected Associate Professor and in 1978 Professor of Radiology at the Faculty of Medicine in Ljubljana. In the academic years 1977-78 and 1978/79, he was Deputy Dean of the Faculty of Medicine, and from 1981 all until his retirement in 1993 - i.e. for full thirteen years - Chairman of the Chair of Radiology. As a university teacher and lecturer he contributed to the education of several generations of medical and stomatology students, as well as of those attending the Junior College of Health Professionals, Department for Radiology Technicians, in Ljubljana. Here, his outstanding role as mentor to residents in radiology, particularly in the field of osteoarticular orthopedics, deserves to be pointed out.

He upgraded his knowledge in several foreign institutions, such as Cochin Hospital in Paris, Department of Orthopedics at St.Gallen Canton Hospital in Zürich, and the institutes of radiology in Bonn and Tübingen.

The main field of his interest was radiological diagnostics of osteoarticular disorders, particularly in the fields of orthopedics, hematology, injuries and radiology in gynecology and stomatology. His bibliography comprises 131 contributions that have been published in national and international journals, as well as 14 scientific research studies. He published three books independently, and two in

collaboration with other authors. He took active part as an organizer and speaker at numerous congresses and meetings of radiologists, orthopedists and traumatologists in the country as well as in different European centers and worldwide.

Prof.Dr. Ludvik Tabor played an active role in the establishment of the Institute of Radiology of the University Medical Center in Ljubljana, as well as through all the phases of its development, until this institution became the leading radiological center in the country. In 1976, in collaboration with Italian colleagues, he established an Alps-Adria community which resulted in regular annual meetings of radiologists from Italy, Austria and Slovenia. He was one of the founding members of the journal "Radiologia Iugoslavica", and the Editor-in-Chief of the same in years 1976-1981. In the period 1958-1969, he was the President of the Section of Radiology and Nuclear Medicine of the Slovenian Medical Association. Apart from that, he was a long standing Secretary General of the Society of Radiology and Nuclear Medicine of Yugoslavia.

He was a member of the International Society of Lymphology, European and International Society of Radiology, member of the Slovenian Medical Association (SZD), member of the Section of Radiology of SZD, member of the Association of Radiologists of Yugoslavia, member of the Society of Orthopedists and Traumatologists of Yugoslavia, and an honorary member of the Society of registered radiology technicians of Yugoslavia.

He received several awards: Golden Plaque of the Association of Medical Societies of Yugoslavia (1971), Award of the Faculty of Medicine in Ljubljana (1978), Silver Plaque of the Society of Orthopedists and Traumatologists of Yugoslavia (1978), Medal of Work with Golden Wreath (1980), Golden Plaque of the Society of Orthopedists and Traumatologists of Yugoslavia (1981), Plaque of the Association of Radiologists of Yugoslavia (1988), and Award of the University Department of Orthopedics in Ljubljana (1993).

This outline of Professor Tabor's active life would not have been complete, had it contained only the description of his rich professional career and ignored yet another very important field of his interest - painting, which was becoming more and more important part of his life as he grew older. His huge opus of water-paintings was partly exhibited at 23 independent and 30 group exhibitions. Perhaps, through painting he managed to free himself of all the restrictions which a successful medical career imposes on those in pursuit of it. As if in nature and colors of his water paintings he would hope to find a recuperation for the years spent amidst all shades of gray and black which befit radiologists profession. His attitude to nature and art is best reflected in the words that he wrote: "Art is a free recording of the vastness of spiritual awareness and sensation of what nature is offering to us so generously. Can there be anything more attractive than a record of life's credit to nature, a record that makes use of the kaleidoscope of light and shadows of something felt and seen through personal experience, a record of the eternally present rhythm of nature! Faced with the modern consumers society which hopes to find happiness in piling material goods and momentary enjoyments, incapable of sharing the inner joy of those who can think and act differently, there is nothing left but the possibility of retreat to what nature still has in store to offer. Some people find it difficult to understand that nowadays more and more people of different profession dedicate their free time to painting or some other arts. The answer is quite simple: In view of everything that modern civilization with its hectic daily routine not only offers but directly imposes on us, the art represents an asylum where we can again collect and put in order the bits of our shattered souls. To man, arts and nature offer a promise and chance that in the time such as ours he does not sink but survives and maintains his human dignity."

When in 1993 he decided to retire, he was still full of plans for future. But unfortunately, the merciless and long-lasting disease which he had learnt to live with and successfully fight for years, finally put an end to his planning and made him admit that he lost the battle.

It was with great sadness that we parted with Professor Tabor. We remember him with due respect. We, the Slovene radiologists, are truly obliged to him for everything that he did for out profession and Slovenian medicine in generally. He will stay in everyone's memory as a renown and highly respected expert, a teacher to many generations of radiologists and radiographers, and last but not least, as an artist and great admirer of nature and arts.

Prof. Vladimir Jevtič, MD,
Institute of Radiology
University Medical Center
Zaloška 7
1525 Ljubljana

European association of radiology junior radiologists exchange programme 1988

EUROPEAN ASSOCIATION OF RADIOLOGY

1. Aims

To create a direct link between Junior Radiologists from Western European countries and their colleagues from Eastern Europe. The former can share their longer experience with more advanced imaging procedures with their Eastern colleagues who have, generally, only recently acquired the same equipment. The final goal is to have a common hands-on experience in daily routine clinical practice. Moreover, the Visiting Junior Radiologists will be involved in some theoretical teaching, presenting a few lectures on the topic chosen for the visit.

2. Organisation

Each visit will consist of a one week visit by two Visiting Junior Radiologists.

3. Finances

3.1. Travelling and accommodation expenses will be paid by the EAR.

3.2. Visiting Junior Radiologists will take care of their travelling and claim their expenses to the EAR.

3.3. Host Institutions will take care of lodging, using low-budget accommodations, preferably within the university complex.

4. Applications

4.1. The EAR Executive Bureau selects the Institutions to be visited, matching them in accordance with the Junior Radiologists Forum, with the junior applicants.

4.2. The Host Institutions must send their proposals for the tutorial week to the Secretary General of the EAR (see address below), indicating:

- details of the equipment available in their Institution
- their topics of interest (consider alternatives)
- the preferred period of the year for the visit
- the availability of low-budget accommodations

4.3. The Visiting Junior Radiologists must send to the Chairman of the Junior Radiologists Forum (see address below) their application, with a short CV and written authorisation from their chairman to participate in the Exchange Programme. A copy shall be sent to the Secretary General of the EAR. The application must indicate:

- the main field of expertise
- the equipment worked with
- the period of the year most suitable for the visit, and the period when not available.

4.4. Deadline for applications: 1st November 1997

The EAR Exchange Programme is sponsored by General Electric Medical Systems Europe

Prof. M. Blery
EAR Secretary General
Dept. of Radiology
C.H.U. Bicetre
78, rue du Général Leclerc
F – 94270 LE KREMLIN-BICETRE
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Dr. Vasco M. Ramalho
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SPRMN
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Endoskopska retrogradna pankreatikografija pri ugotavljanju kroničnega pankreatitisa

Rubinić M

V članku je poudarjena pomembnost endoskopske retrogradne pankreatikografije (ERCP) pri ugotavljanju kroničnega pankreatitisa. Metoda je znatno bolj senzitivna kot druge radiološke, posebno neinvazivne diagnostične metode. S pomočjo ERCP, ki je kombinirana endoskopska radiološka metoda, razvrščamo kronični pankreatitis v tri skupine. Tako lahko tudi natančno načrtujemo nadaljnje zdravljenje, ki je endoskopsko ali klasično kirurško. V članku avtor analizira 370 bolnikov, ki jim je bil kronični pankreatitis ugotovljen z ERCP. 286 (77%) je bilo moških in 84 (23%) žensk. Večina bolnikov, to je 204 (55%), je bila starih od 40 do 50 let. Vsi bolniki so bili razvrščeni v že omenjene tri skupine. V skupini blagega kroničnega pankreatitisa je bilo 154 (42%) bolnikov, v skupini z zmernimi spremembami je bilo 123 (33%) bolnikov in v skupini znatnih sprememb 93 (25%) bolnikov. Pomembno je poudariti, da je od 286 moških bolnikov 211 (74%) uživalo alkohol in bilo kadilcev tobaka več kot pet let.

Radiol Oncol 1997; 31: 273-6.

Akutna abdominalna krvavitev zaradi pankreatitisa, diagnosticirana s kontrastno računalniško tomografijo

Puskás T, Rác S

Avtorja prikažeta primer 55-letnega bolnika, pri katerem se je razvila akutna abdominalna krvavitev zaradi pankreatitisa. Krvavitev je bila diagnosticirana z računalniško tomografijo (CT) ob aplikaciji intravenoznega kontrasta. Vendar s CT-jem krvavitev redko potrjujemo. Avtorja poudarjata pomembnost in prednost kontrasta pri takšni preiskavi. Razporeditev kontrasta je najizrazitejša v središču lezije.

Radiol Oncol 1997; 31: 277-8.

Radioprotektivno delovanje amifostina na žleze slinavke zajcev pri visokodoznem radiojodnem zdravljenju

Hübner R-H, Bohuslavizki KH, Brenner W, Klutmann S, Feyerabend B, Lüttges J, Tinnemeyer S, Mester J, Clausen M, Henze E

Poznan stranski učinek visokodoznega zdravljenja z radiojodom (HD-RIT) je okvara v delovanju žlez slinavk. Kasni stranski učinki zdravljenja so pomembni pri zdravljenju dobro diferenciranih ščitničnih karcinomov, ki imajo odlično prognozo. Zato so avtorji proučevali radioprotektivni učinek amifostina na zajčjem modelu. Pred in največ tri mesece po HD-RIT so naredili kvantitativno scintigrafijo žlez slinavk pri petih zajcih in aplicirali 1 GBq J-131.

Procent kopičenja Tc-99m-pertehnentata je bil upoštevan kot merilo parenhimske funkcije žlez slinavk. Tri živali so prejele 200 mg/kg amifostina pred HD-RIT in dve živali sta služili le za kontrolo. Žleze slinavke so bile preiskovane histopatološko. Pri dveh kontrolnih živalih se je 12 tednov po HD-RIT procent kopičenja pertehnentata značilno zmanjšal ($p<0,001$) - tako pri parotidnih žlezah (zmanjšanje za 63 %) kot pri

submandibularnih žlezah (zmanjšanje za 46 %). Histopatološko so ugotovili lipomatozo. Nasprotno pa se pri treh živalih, kjer so uporabili amifostin, procent kopičenja pertehnentata ni značilno zmanjšal (p=0,953) in se tako tudi parenhimska funkcija ni bistveno zmanjšala. Prav tako so ugotovili le nepomembno lipomatozo. Zaključili so, da lahko pri zajcih okvaro žlez slinavk po HD-RIT kvantitativno ocenjujemo s scintigrafijo in da amifostin značilno zmanjša okvaro žlez slinavk, ki nastane po HD-RIT. Menijo, da so rezultati dovolj ohrabrujoči, da bi amifostin preizkusili tudi na bolnikih z dobro diferenciranim ščitničnim karcinimom in bi na ta način izboljšali njihovo kakovost življenja.

Radiol Oncol 1997; 31: 279-85.

Diagnostični pomen planarne miokardne perfuzijske scintigrafije pri bolnikih s koronarno boleznijo

Klančič M, Miličinski M, Zorman D

Pri bolnikih s koronarno boleznijo uporabljamo neinvazivne in invazivne preiskave za potrditev bolezni ali spremljanje zdravljenja. Z neinvazivno miokardno perfuzijsko scintigrafijo dobimo podatke o prekrvitvi srčne mišice med obremenitvijo in v mirovanju. Koronarna angiografija pa je invazivna morfološka preiskava, ki jo je potrebno opraviti pred razširitvijo koronarnih arterij ali pred kirurško revaskularizacijo miokarda. Z retrogradno analizo planarnih scintigramov miokarda, opravljenih ob obremenitvi in v mirovanju po aplikaciji talija (Tl^{201}), smo želeli ugotoviti občutljivost in specifičnost miokardne perfuzijske scintigrafije in ugotoviti vzroke razhajanja izsledkov obeh preiskav. Primerjali smo izsledke 156 miokardnih perfuzijskih scintigramov in koronarogramov bolnikov s koronarno boleznijo. Kadar se izsledki delno ali povsem niso skladali, smo ponovno proučili obe originalni preiskavi.

Pri 62 % preiskovancev so se izsledki obeh preiskav skladali. Pri samo 5 bolnikih (3 %) so bili izsledki neskladni in vzroka nismo ugotovili. Večina preostalih 55 bolnikov z delno skladnimi izsledki obeh preiskav je imela bolj izražene motnje prekinitve kot je bila ocenjena stopnja zožitve na koronarni arteriji, kar je posledica razlike v naravi obeh preiskav. Anomalije na koronarnih arterijah smo ugotovili pri 3 % preiskovancev, zvijugane koronarne arterije s počasnim pretokom kontrastnega sredstva pri 9 preiskovancih (6 % vseh) in pri enem bolniku artrijsko hipertenzijo z izrazito hipertrofijo levega prekata. Senzitivnost miokardne perfuzijske scintigrafije je bila pri naših preiskovancih 100 % in specifičnost 50 %. Pozitivna napovedana vrednost za koronarno bolezen je bila 96 % in negativna 100 %. V zaključku ugotavljamo, da ima miokardna perfuzijska scintigrafija nedvomno mesto med preiskavami pri odkrivanju in spremljanju zdravljenja koronarne bolezni. Miokardna perfuzijska scintigrafija je postala še zanesljivejša z novimi tehnikami snemanja in radiofarmacevtiki, ki jih označujemo s tehnecijem in tako omogoča racionalnejše nadaljevanje diagnostičnih postopkov z bolj invazivnimi preiskavami.

Radiol Oncol 1997; 31: 286-90.

Pritisk medtkivne tekočine kot ovira pri terapiji čvrstih tumorjev

Pušenjak J, Miklavčič D

V zadnjih desetletjih je napredek na področju razvoja zdravil proti raku omogočil odkritje terapevtikov, ki so pokazali izjemno protitumorsko učinkovitost v in vitro pogojih. Na žalost ta zdravila niso bila uspešna v in vivo poskusih na čvrstih tumorjih, saj je bila njihova porazdelitev v tumorju nezadostna in neenakomerna. Čeprav imajo tumorji v primerjavi z normalnim tkivom višjo prepustnost in hidravlično prevodnost žil, je prehod molekul iz tumorskega ožilja zavrt zaradi visokega pritiska medtkivne tekočine (PMT) v tumorju. Ta fiziološka lastnost prav tako ovira transport molekul po tumorskem medceličnem prostoru. Vrednost PMT je

v središču tumorja enakomerno visoka, na robu tumorja pa pade proti vrednosti, ki jo ima PMT v normalnem tkivu. Ta gradient PMT povzroči odtekanje tekočine iz tumorja, ki zaradi konvekcije s seboj potegne molekule zdravila v tumorjevo okolico. Tam se molekule zdravila reabsorbirajo ter tako ne opravijo svoje naloge. Meritve kažejo, da PMT doseže v tumorju vrednosti od 2600 Pa do 6600 Pa, medtem ko je vrednost v normalnem tkivu nižja kot atmosferski pritisk v okolici (od –133 Pa do –798 Pa v s.c. in okoli –346 Pa v mišici). Za takojšnje in neposredno merjenje PMT trenutno uporabljamo dve metodi: WIN tehniko in mikroprebojno tehniko. Znižanje PMT v tumorju bi verjetno omogočilo optimalnejšo vsebnost in porazdelitev zdravila v tumorju in bi s tem izboljšalo protitumorsko delovanje zdravila. Zato so bili za znižanje PMT v tumorju preizkušeni različni postopki. V tem članku smo povzeli in analizirali rezultate dveh fizičnih (hipertermija, obsevanje) in kemičnega (vazoaktivne snovi) postopka, ki so jih preizkusili drugi avtorji.

Radiol Oncol 1997; 31: 291-7.

Urokinazni aktivator plazminogena, njegova inhibitorja in receptor – novi napovedni dejavniki pri solidnih rakih

Borštnar S, Čufer T, Rudolf Z

Urokinazni aktivator plazminogena (UPA), njegova inhibitorja (PAI1 in PAI2) ter njegov receptor (UPAR) igrajo pomembno vlogo pri razgradnji medceličnega tkiva in s tem pri prodoru tumorskih celic v okolico ter metastaziranju. Rezultati kliničnih raziskav kažejo na vpliv UPA, PAI1, PAI2 ter UPAR na potek bolezni in preživetje bolnikov s solidnimi tumorji, predvsem rakom dojk. Razvrščanje bolnikov glede na vsebnost UPA, PAI1, PAI2 in UPAR v tumorskem tkivu bi omogočilo ločevanje bolnikov v bolj in manj rizične skupine. Z agresivnejšim zdravljenjem bolnikov v bolj rizičnih skupinah pa bi dosegli izboljšanje prognoze, podaljšanje časa brez ponovitve bolezni in podaljšanje preživetja.

Radiol oncol 1997; 31: 298-304.

Zdravljenje malignih bolezni z interferonom-α

Jereb B

V kliniki uporabljamo več tipov naravnega interferona-a (IFN-a). Čeprav so interferoni bili prvi citokini, ki so se kot metoda zdravljenja uveljavili, še vedno vemo zelo malo o njihovem načinu delovanja na maligne bolezni. IFN-a lahko zavira celično rast. Šele pred kratkim pa so ugotovili, da IFN-a lahko deluje tudi direktno citotoksično na tumorske celice pri bolnikih z multiplim mielomom. Naravni levkocitni interferon še vedno najčešče uporabljamo v dozah, kakršne so bile objavljene v zgodnjih kliničnih preizkusih. Opisano je bilo, da so z visokimi koncentracijami IFN pri lokalni aplikaciji malignega melanoma, bazalioma, plevralne karcinoze, glioblastoma ugotovili popolno uničenje tumorja. Ne vemo pa, katere so optimalne doze interferona. Te so lahko različne za različne tumorje, pa tudi različne pri vsakem posameznem bolniku. Pravtako je trajanje zdravljenja še vedno odprto vprašanje. Interferoni so učinkovita sredstva zdravljenja, vendar njihov citotoksični učinek ni zadosten in ni dovolj trajen. Odprto je široko polje potrebnih raziskav, potrebno je nadaljevati klinične preizkuse z različnimi tipi interferonov, pri tem pa je gotovo IFN-a od vsen za klinika najbolj zanimiv.

Radiol oncol 1997; 31: 305-8.

Diagnoza in zdravljenje radiacijske poškodbe – akutni radiacijski sindrom

Klutmann S, Bohuslavizki KH, Brenner W, Müller A, Henze E

Sevanje poškoduje predvsem celice, ki se hitro delijo, to so radiosensitivna tkiva, kot so kostni mozeg, mukoza prebavnega trakta in lasni mešički. S povečevanjem doze se pojavijo poškodbe tudi na bolj radiorezistentnih tkivih, kot je tudi centralni živčni sistem. Akutni radiacijski sindrom lahko razdelimo na tri stopnje: prodromalno fazo z nespecifičnimi simptomi kot so slabost in bruhanje, tej sledi faza relativno dobrega počutja, to je latentna faza. V tretji fazi nastopi akutni radiacijski sindrom, ki ga zopet lahko razdelimo v tri skupine: sindrom kostnega mozga, gastrointestinalni sindrom in sindrom centralnega živčnega sistema. Vsak od sindromov je določen z dozo, preživetjem in simptomi. Preživetje bolnikov je odvisno od poškodb kostnega mozga, tako da je transplantacija kostnega mozga uspešna po obsevanjih celega telesa z dozami pod 10 Gy. Če je ekspozicija višja od 10 Gy, je možna le paliativna terapija za lajšanje bolečin.

Radiol Oncol 1997; 31: 309-14.

Primerjava TDF in LQ modela pri planiranju obsevanja ob uporabi bioefektnega algoritma

Ho AK, Sibata CH, Thomadsen BR

Avtorji so primerjali in ovrednotili dva obsevalna plana, prvi z dvema poljema (AP/PA) in drugi s štirimi polji, oba pa za gama žarke iz izvora Co-60. Pri tem so uporabljali program za planiranje ROCS (Radiation Oncology Computer System), ki upošteva tudi biološki učinek ali bioefekt. Bioefektni algoritem omogoča seštevanje dveh ali več obsevalnih planov. V program ROCS so vključene biomodifikacijske tabele, s pomočjo katerih je ob upoštevanju časa obsevanja mogoče spremeniti vrednosti obsevalne doze na frakcijo v časovno odvisno dozo na frakcijo (Time Dose Fractionation - TDF).

Te biomodifikacijske tabele so standardne dvodimenzionalne tabele programa ROCS. Z uporabo linearnokvadratnega modela (LQ) pa so avtorji določili biološko ekvivalentno dozo glede na fizikalno absorbirano dozo ter vstavili v program novo biomodifikacijsko tabelo. Primerjava med razporeditvijo TDF vrednosti in biološko ekvivalentno dozo, dobljeno z uporabo LQ modela, kaže, da bi bil LQ model lahko boljši za bioefektivni algoritem, poleg tega lahko LQ model vstavimo tudi v sistem ROCS.

Radiol Oncol 1997; 31: 315-8.

Notices

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

Oncology

October 13-20, 1997.

The ESO training course "Cancer Epidemiology and Cancer Registry" will be offered in Metsovo, Ioannina, Greece.

Contact ESO Balkans and Middle East Office, c/o Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Life science

October 16-19, 1997.

The international conference "Life Science '79" will be offered in Gozd Martuljek, Slovenia.

Contact Dr Gregor Serša, Institute of Oncology, Department of Tumor Biology, Zaloška 2, SI-1105 Ljubljana, Slovenia; or call +386 61 133 74 10; or fax +386 61 131 41 80; E-mail: gsersa α mail.onko-i.si

Lymphoma

October 18-22, 1997.

The ESO training course will take place in Athens, Greece.

Contact ESO Balkans and Middle East Office, c/o Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Radiation Oncology

October 20-24, 1997.

The "Annual Meeting of American Society for Therapeutic Radiology and Oncology ASTRO" will take place in Los Angeles, CA, USA.

Contact Vicky Carroll, ASTRO office, 1891 Preston White Drive, Reston, VA 22091, USA; or call +1 703 716 7588; or fax +1 703 476 8167.

Chest tumours

October 20-22, 1997.

The ESO advanced course "Chest Tumours" will be held in London, United Kingdom.

Contact European School of Oncology, Via Ripamonti, 66, 20141 Milan, Italy; or call +39 2 57 305 416; or fax +39 2 57 307 143.

Radiation Oncology

October 20-24, 1997.

The "Annual Meeting of American Society for Therapeutic Radiology and Oncology ASTRO" will take place in Los Angeles, CA, USA.

Contact American Society Therapeutic Radiology/Oncology, 1101 Market Street, 14th Floor, Philadelphia, Pa 19107-2990, USA; or call +1 215 574 3180; or fax +1 215 928 0153.

Oncology

October 22-24, 1997.

The ESO training course "New drugs in Oncology" will be offered in Ankara, Turkey.

Contact ESO Balkans and Middle East Office, c/o Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

Diagnostic radiology

October 23-25, 1997.

The training workshop of the "Recent European Initiatives on Quality Assurance and Radiation Protection in Diagnostic Radiology" will be organised in Luxembourg.

Contact Prof. Dr. F.E. Stieve, Bf5 - Institute of Radiation Hygiene, Ingolstaedter Landstrasse 1, D-85764 Oberschleissheim/Neuherberg, Germany; or call +49 89 31603 260; or fax +49 89 31603 111; or E-mail fstieve@bfs.de

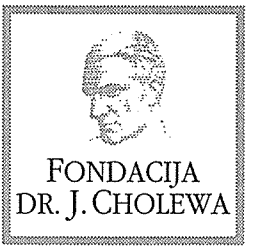
Skin pathology

October 23-29, 1997.

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

Contact ESO Balkans and Middle East Office, c/o Egnatia Epirus Foundation, 7A Tzavella St., 453 33 Ioannina, Greece; or call +30 651 72315/76992; or fax +30 651 36695.

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, SI-1105 Ljubljana, Slovenia.



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Activity of "Dr. J. Cholewa Foundation" for cancer research and education – report for the third quarter of 1997

"Dr. J. Cholewa Foundation" for cancer research and education continues with its activity as it was determined at the Assembly of the Foundation annual meeting and Executive council meetings in the end of 1996 and in the first half of 1997. The activity of the Foundation has been intensified during the course of 1997, as compared to the activity in the previous year. The Foundation continues to provide grants for cancer research and cancer education purposes to professionals involved in the field of oncology in Republic of Slovenia. The emphasis of Foundation's support has been and is being given on providing research and educational grants especially to the applicants from regional hospitals and health centers. In this regard, it is especially important that the collaboration between the Foundation and the European School of Oncology from Milan, Italy, is proceeding ahead successfuly. As already noted previously, all the applicants awarded educational grants for attending courses or other various meeting by the European School of Oncology are obliged to spread their newly acquired knowledge as widely as possible, while it is hoped and expected that applicants awarded research grants present the results of their research in respectable international scientific journals.

The Foundation continues to support regular publication of "Radiology and Oncology" international scientific journal, and of "ESO Challenge", the newsletter of the European School of Oncology. It is expected that the activity concerning the organisation of "Oncological weekend" meetings will intensify in the near future, thus presenting the Foundation with a new challenge. As new challenges arise, the Foundation is proud to have among its members respected experts and authors of important cancer textbooks and monographies published recently.

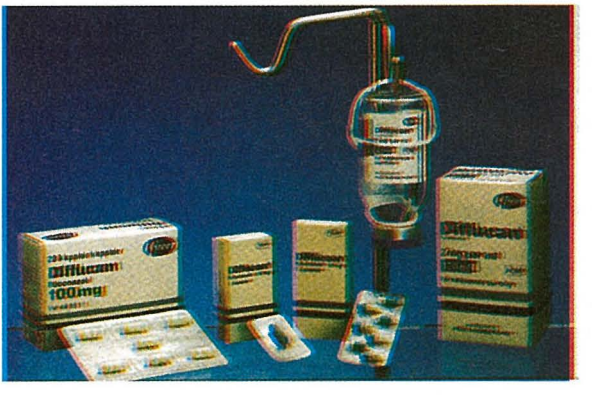
As the 1997 is coming to its close it is expected that annual meetings of the Executive council and the Assembly of the Foundation will take place in the near future.

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

DIFLUCAN*

(flukonazol)

Glivične okužbe kože	Vaginalna kandidijaza	Kriptokoki meningitis	Sistemska kandidijaza	Orofaringealna in sluznična kandidijaza
Odmerki: 50 mg/dan ali 150 mg/teden* *za tineo versicolor je priporočljiv odmerek 50 mg/dan	**Odmerek:** 150 mg	**Odmerki:** 400 mg (prvi dan) 200-400 mg/dan	**Odmerki:** 400 mg (prvi dan) 200-400 mg/dan	**Odmerki:** 50 mg/dan* * pri zelo hudih okužbah sluznice je morda potrebno 100 mg/dan
Trajanje: 2-4 tedne** **za tineo pedis je morda potrebno 6 tedensko zdravljenje	**Trajanje:** Enkratni odmerek	**Trajanje:** 6-8 tednov	**Trajanje:** Odvisno od kliničnega odziva	**Trajanje:** 1-2 tedna** **pri okužbah sluznice je morda potrebno 30 dnevno zdravljenje
		Profilaksa: 200 mg/dan	**Profilaksa:** 50 mg/dan	**Profilaksa:** 50 mg/dan



Hitro zdravljenje glivičnih okužb z dolgotrajnim učinkom

- pri glivičnih okužbah kože
- pri vaginalni kandidijazi
- pri oportunističnih glivičnih okužbah

Povzetek informacij za predpisovanje zdravila
Indikacije in odmerki: obrni. **Uporaba pri starejših:** kot zgoraj, razen pri ljudeh z ledvičnimi okvarami - glej popolne informacije za predpisovanje. Ne priporočamo uporabe pri otrocih mlajših od 16 let, razen kadar se zdi to lečečemu zdravniku nujno potrebno - glej popolne informacije za predpisovanje in priporočljive odmerke za otroke starejše od enega leta. Bolniki z ledvičnimi okvarami: morda so potrebni manjši odmerki - glej popolne informacije za predpisovanje. **Dajanje zdravila:** DIFLUCAN lahko dajemo oralno ali v obliki intravenske infuzije. Odmerki so pri oben načinih enaki. **Kontraindikacije:** Znana preobčutljivost na flukonazol ali sorodne triazole. **Opozorilo:** Pri bolnikih, pri katerih pride do pomembnega povečanja jetrnih encimov, moramo pred nadaljevanjem zdravljenja z DIFLUCANOM oceniti razmerje med tveganjem in koristnostjo. Poročajo tudi o anafilaktičnih reakcijah. **Varnostni ukrepi:** Ker so na voljo le omejeni podatki, odsvetujemo uporabo pri nosečnicah, razen kadar se zdi to lečečemu zdravniku nujno potrebno. **Dojenje:** ne priporočamo uporabe. **Interakcije z drugimi zdravili:** Potrebno je skrbno spremljanje bolnikov, ki istočasno jemljejo antikoagulanse, oralno sulfonilurejo ali fenitoin, ciklosporin in teofilin. Pri bolnikih, ki istočasno jemljejo rifampicin, so morda potrebni večji odmerki DIFLUCANA. **Stranski učinki:** Najpogostejši stranski učinki so vezani na gastrointestinalni trakt: slabost, abdominalno nelagodje, diareja in vetrovi. Poročajo tudi o kožnem izpuščaju. Pri bolnikih s hudo osnovno boleznijo so med zdravljenjem z DIFLUCANOM in primernimi učinkovinami opazili spremembe v testnih rezultatih ledvičnih in hematoloških funkcij ter bolezenske spremembe jeter, vendar pa sta klinična pomembnost in povezava z zdravljenjem še nepotrjeni.
Na željo posredujemo dodatne informacije. Pred predpisovanjem DIFLUCANA se je potrebno seznaniti s celotnimi informacijami za predpisovanje zdravila.

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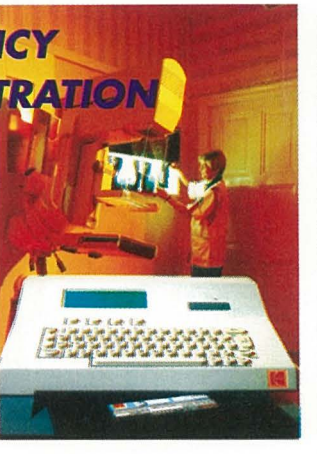

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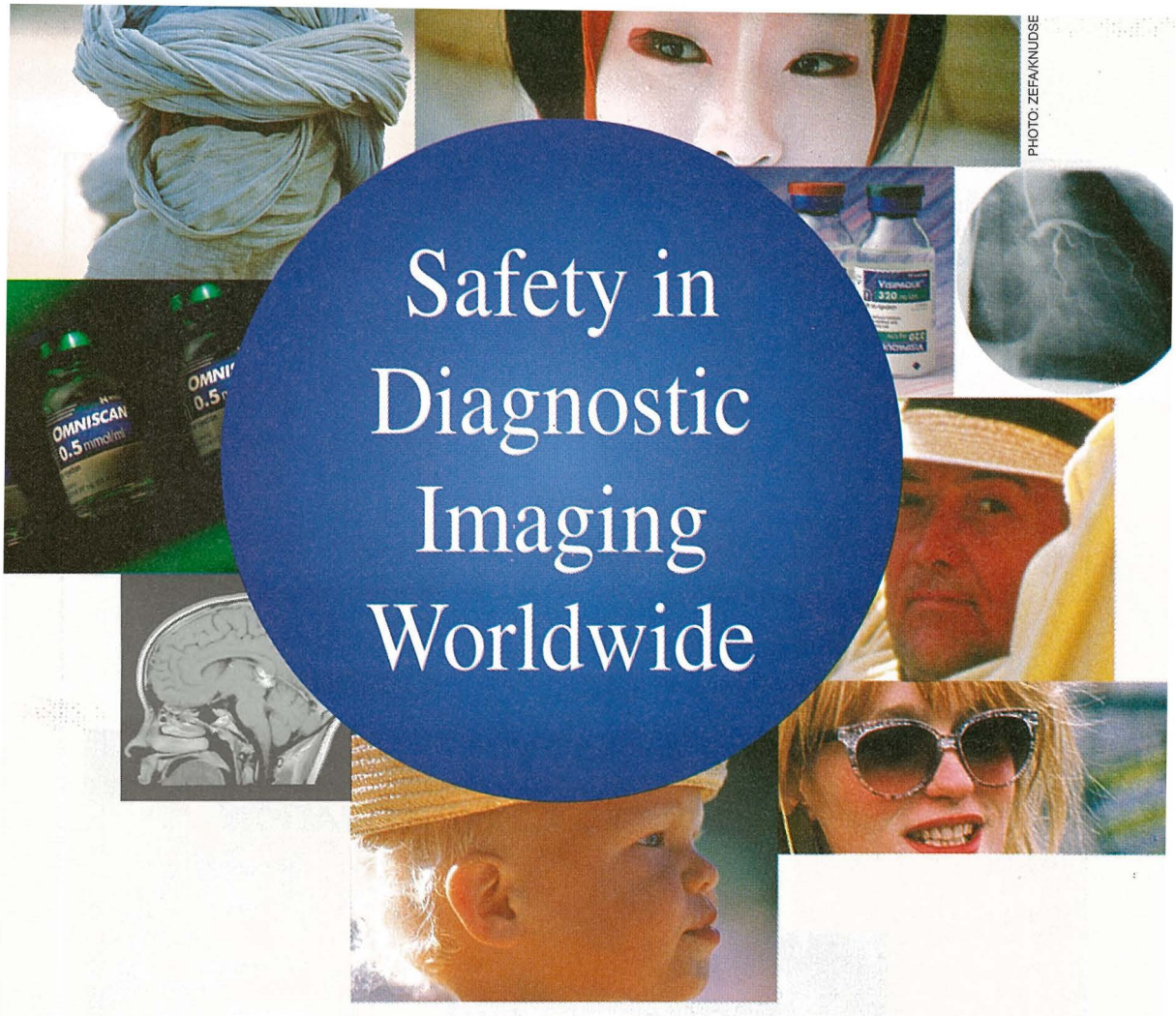

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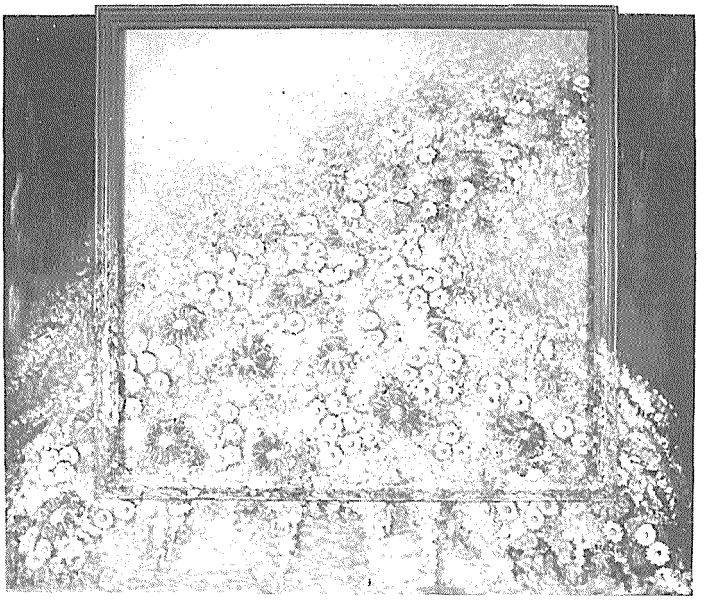

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Kontraindikacije: Otroci do 1 leta starosti, akutna zastrupitev z alkoholom, uspavali, analgetiki in drugimi zdravili, ki vplivajo na CŽS, zdravljenje z inhibitorji MAO. **Interakcije:** Pri sočasni uporabi zdravil, ki delujejo na osrednje živčevje, je možno sinergistično delovanje v obliki sedacije pa tudi močnejšega analgetičnega delovanja. **Opozorila:** Pri predoziranju lahko pride do depresije dihanja. Previdnost je potrebna pri bolnikih, ki so preobčutljivi za opiate, in pri starejših osebah. Pri okvari jeter in ledvic je potrebno odmerek zmanjšati. Bolniki med zdravljenjem ne smejo upravljati strojev in motornih vozil. Med nosečnostjo in dojenjem predpišemo tramadol le pri nujni indikaciji. Bolnike s krči centralnega izvora skrbno nadzorujemo. **Doziranje:** *Odrasli in otroci, starejši od 14 let:* 50 do 100 mg 3- do 4-krat na dan. *Otrokom od 1 leta do 14 let* dajemo v odmerku 1 do 2 mg na kilogram telesne mase 3- do 4-krat na dan. **Stranski učinki:** Znojenje, vrtoglavica, slabost, bruhanje, suha usta in utrujenost. Redko lahko pride do palpitacij, ortostatične hipotenzije ali kardiovaskularnega kolapsa. Izjemoma se lahko pojavijo konvulzije. **Oprema:** 5 ampul po 1 ml (50 mg/ml), 5 ampul po 2 ml (100 mg/2 ml), 20 kapsul po 50 mg, 10 ml raztopine (100 mg/ml), 5 svečk po 100 mg.

Podrobnejše informacije so navoljo pri proizvajalcu.

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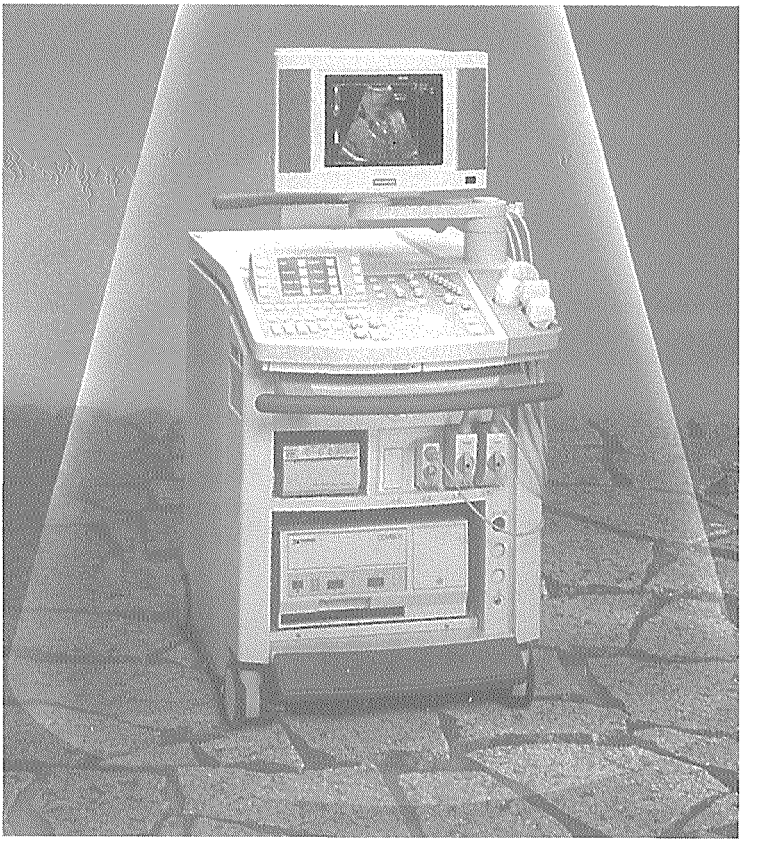

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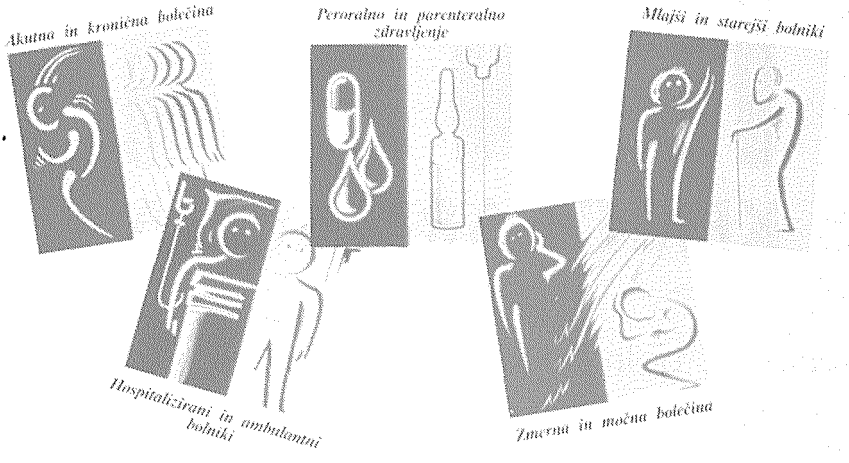

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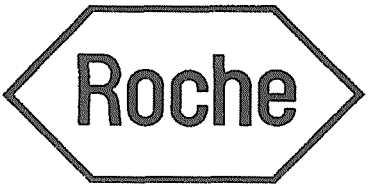

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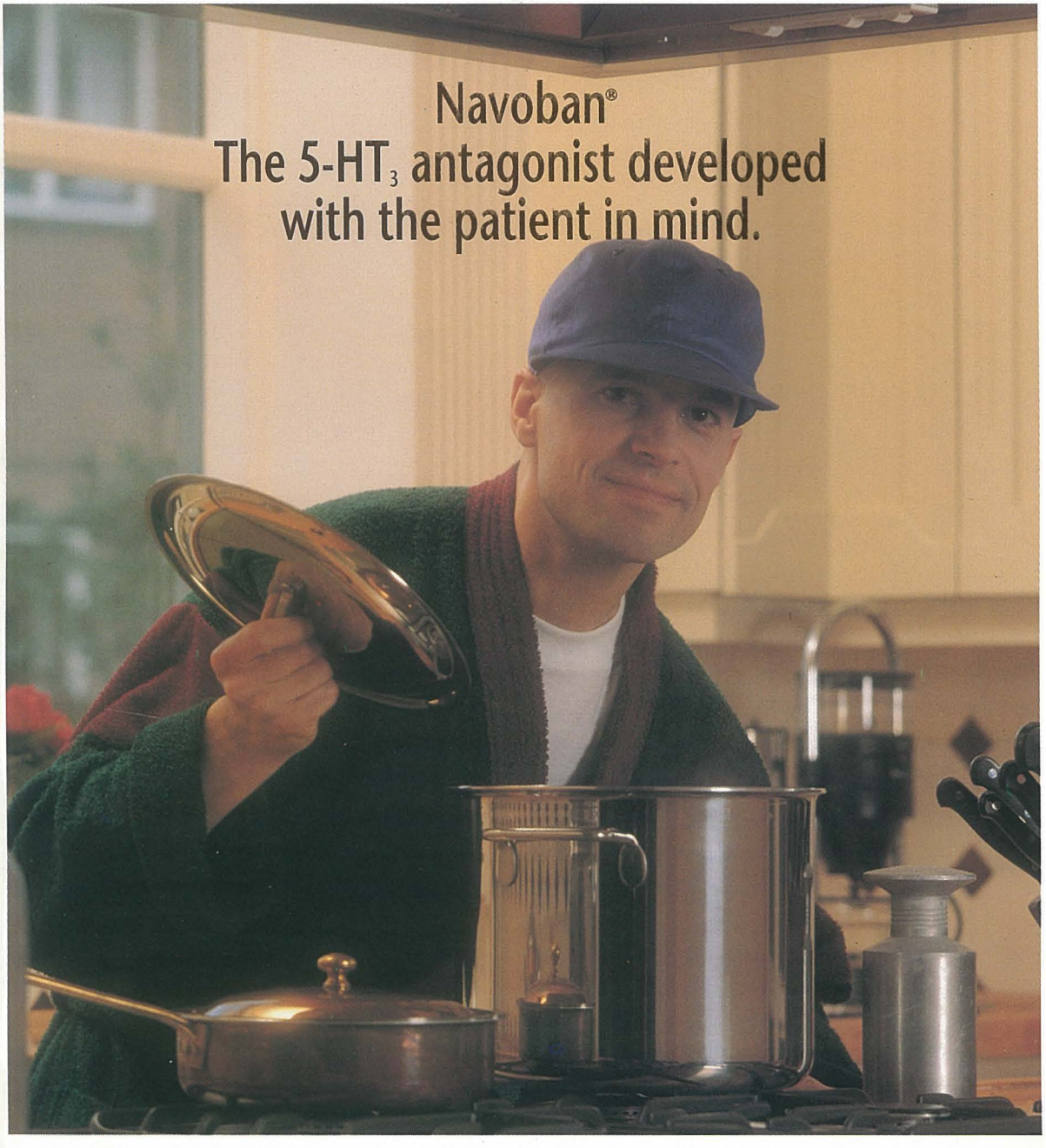

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