RADIOLOGY AND ONCOLOGY

1992
Vol. 26 No. 3
Ljubljana

ISSN 0485-893X

RADIOLOGY AND ONCOLOGY

Established in 1964 as ***Radiologia Iugoslavica*** *in Ljubljana, Slovenia.* ***Radiology and Oncology*** *is a journal devoted to publication of original contributions in diagnostic and interventional radiology, computerized tomography, ultrasound, magnetic resonance, nuclear medicine, radiotherapy, clinical and experimental oncology, radiophysics and radiation protection.*

Publishers
Slovenian Medical Society –
Section of Radiology,
Croatian Medical Association –
Croatian Society of Radiology

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Printed by
Tiskarna Tone Tomšič, Ljubljana, Slovenia

Published quarterly

Bank account number 50101 678 48454
Foreign currency account number
50101 620 010 27621 5130/6
LB – Ljubljanska banka d.d. – Ljubljana

Subscription fee for institutions 100 USD, individuals 50 USD.
Single issue for institutions 30 USD, individuals 20 USD.

According to the opinion of the Slovenian Ministry of Information, the journal RADIOLOGY AND ONCOLOGY is a publication of informative value, and as such subject to taxation by 5 % sales tax.

Indexed and abstracted by:

BIOMEDICINA SLOVENICA
CHEMICAL ABSTRACTS
EXCERPTA MEDICA/ELECTRONIC PUBLISHING DIVISION

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Radiol Oncol 1992; 26: 193-204.

Stomach emptying following vagotomy and pyloroplasty under condition of radiological examination

Milivoj Dujmović, Ivan Lovasić, Dragica Bobinac

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The paper comprises a complete radiological aspect of stomach emptying in 1358 patients who underwent vagotomy and pyloroplasty during a twenty-year period from the beginning of 1965 up to the end of 1984. Vagotomia selectiva anterior (VSA) combined with vagotomia totalis posterior (VTP) was most frequently carried out, whereas vagotomia supraselectiva anterior (VSSA) and vagotomia supraselectiva posterior (VSSP) were applied in 21 cases. Sec. Finney was performed as a rule and sec. Heineke-Mikulicz in 8% of subjects.

The first control examination was made in all the patients between the eighth and the tenth days after surgery in two stages with a time difference of five hours. This examination is indispensable because of early retention verification. The second stage significance lies in the fact that early retention should not be treated in patients showing pseudo signs of aggravated emptying immediately after the contrast has been used.

Early retention was verified in 40% of patients, accounting for 1.1% of gastroplegia. All these patients underwent the second examination up to the stomach emptying normalization at the end of the eighth week postoperatively.

The average time shortening of the initial emptying (6'') rather than the time of a complete emptying (23') was more markedly expressed at late control examinations.

Late retention was verified in 44 patients. Twelve examined cases from this group expressing aggravated emptying in standing position only were separated. Most of late retention patients were accompanied by ulcus relapse. One part of these reretentions was of transient character disappearing after a drug therapy.

Key words: pylorus – surgery; vagotomy; gastric emptying

Introduction

The history of vagotomy and pyloroplasty as the surgical method of ulcus disease treatment has been closely associated with the problem of gastric emptying after surgery. The first truncal vagotomies were performed in 1914 by Exner and Schwaryman, then Latarjet (1922) and Mc Crea (1925) combined with gastroenteroanastomosis. Vagotomy fell into oblivion from that time because of the expressed postoperative complications, the problem of gastric content evacuation in the first place. The se-

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UDC: 616.334-089.844:616.33-008.1-073.75

cond attempt of introducing this method by Dragstedt and Owens (1943) was also discredited by the problem of postoperative retention and gastric dilatation. Therefore, this method was not of interest again. Griffith (1958) and Frankson introduced a selective vagotomy. Related to the stomach, the selective vagotomy has also been a total one, thus leaving the drainage problem to be still actual. Holle (1968), Hedenstedt and Grassi brought in a proximal selective vagotomy in order to solve the question of parasympathetic denervation of the gastric acidosecretory area together with simultaneous maintenance of the motoric innervation of the pyloric part. Hence a normal physiological stomach emptying without drainage procedure has been achieved.[1-8]

Radilogical aspect of gastric emptying following vagotomy and pyloroplasty in the early and late postoperative stages has been of special interest for the radiologists and surgeons because of their efficiency assessment and prevention of the peptic ulcus relapse, considerably caused by the aggravated stomach emptying.

The purpose of this paper is the evaluation of speed and classification of various gastric emptyings in the early and late postoperative stages in patients who underwent vagotomy and pyloroplasty, following a longtime follow up. It should be taken into account that a comparison with the results of other authors is very difficult because of various types of vagotomy and pyloroplasty and all their possible mutual combinations.

Patients and methods

In the course of a twenty-year period, from the beginning of 1965 to the end of 1984, 1358 patients underwent vagotomy with pyloroplasty. Heineke-Mikulicz pyloroplasty was applied as a drainage method in the early stage only, and sec. Finney later. Table 1 displays applicable kinds of vagotomy and the types of drainage operations. Anterior selective and total posterior were the most frequently performed vagotomies in combination with Finney's pyloroplasty (72 %). The number of operated patients amounted to 1154 (85 %) males and 204 (15 %) females.

Indications for vagotomy and pyloroplasty are presented in Table 2. The group of patients with perforated duodenal ulcus, operated urgently without preparation, often presenting with already developed symptoms of perforation, should be regarded separately.

Gastric wall motility being reduced by vagotomy renders stomach emptying during the early postoperative course difficult, regardless the simultaneous drainage operation. Therefore the surgeon is faced with a problem how to keep the stomach empty in the early postoperative course. As a rule, gastric decompression was carried out in our operated patients by means of a nasogastric probe.

Early clinical signs of retention were very uncertain and the suspicion of such condition indicated a particular radiological treatment. Abdominal plain film could help us to reveal the early gastric retention during the first few postoperative days.

The first postoperative follow-up of the gastric emptying was routinely performed in all the patients between the eighth and the tenth days following surgery, on the first (early) postoperative examination after the nasogastric probe had been removed. Among the vast number of elements concerning gastric and duodenal X-rays, recording the presence of gastric content on an empty stomach, the time of the first contrast medium passage through the pylo-

Table 1. Applied types of vagotomy and drainage operation.

Vagotomy	Drainage operation	No.
VSA + VTP	Pyloroplastica sec. Finney	974
VTA + VTP	Pyloroplastica sec. Finney	249
VSA + VTP	Pyloroplastica sec. Heineke-Mikulicz	8
VTA + VTP	Pyloroplastica sec. Heineke-Mikulicz	96
VSSA + VSSP	Pyloroplastica sec. Heineke-Mikulicz	10
VSSA + VSSP	Pyloroplastica sec. Finney	21
Total		1358

VTA – vagotomia totalis anterior
VTP – vagotomia totalis posterior — truncal (total) vagotomy (TV)

VSA – vagotomia selectiva anterior
VSP – vagotomia selectiva posterior — selective vagotomy (SV)

VSSA – vagotomia supraselectiva anterior
VSSP – vagotomia supraselectiva posterior — proximal selective vagotomy (PSV)

Table 2. Four stages of stomach content emptying at various indications for vagotomy and pyloroplasty on the first postoperative examination.

	Chronic duod. ulcus	Chronic duod. ulcus with bulbostenosis	Perforated duod. ulcus	Bleeding ulcus	Other causes	Total	%
Complete emptying	141	137	165	108	40	591	43.5
Marked lagging of the contrast medium	63	46	80	34	6	229	16.9
Early retention	120	108	210	85	0	523	38.5
Gastroplegia	0	10	5	0	0	15	1.1
Total						1358	100.0

robulbar area and the time of the complete emptying were of special interest. Control of the complete gastric emptying was carried out between the fifth and the sixth hour after the contrast intake. This time interval has been used by a majority of authors.[9–14] The patient was allowed to ingest the food assigned to him during these postoperative days between the first and the second part of the examination.

The examination was carried out in standing position only, on an empty stomach and without special preparation, using 200 ccm of barium suspension. The second postoperative examination comprised all the elements of a routine roentgenological examination during the time span from the second up to the sixth month after surgery. The aforementioned details from the first examination have been specially emphasized. It was performed in the supine position. Not all the patients underwent this examination, but only those who came to the checkup for some disorders, those suspected of some complications (a retention), and those randomly invited for a verification of gastric emptying function.

According to our opinion, vagotomized stomach with pyloroplasty assumes its definite shape two months following surgery, and the accompanying postoperative changes (spasm and oedema) disappear from the pylorobulbar area. The early retention also disappears. Nevertheless, further changes, less in morphological but more in functional sense, are observed from the second to the sixth month. The speed and the way of gastric emptying can be considered as completely stabilized and definite six months postoperatively. Therefore, the second postoperative follow-up examination (late) takes place during the time interval between the second and the sixth month after surgery.[15]

Later follow-up examinations were made after that period. The time span from the surgical intervention ranged even 10 to 20 years in a great number of patients.

Results

The early gastric retention and gastroplegia during a few days following surgery up to the first control examination can be radiologically established by the abdominal plain film.

Taken vertically, it enables us to determine the level, height and extent of gastric juicy content and the fundal gas bubble size above it. Ectatic stomach full of secretion gives the shadow intensity of soft particles shifting downward the small intestine loops and the left half of the transversum laterally. The examination can be completed by diascopy with one draught of Gastrographin. When such a picture was found before the first control postoperative examination had been done we receded from its performance. Inserted nasogastric probe made the retention treatment easier.

Stomach emptying follow-up was carried out in all the operated patients at the first postoperative examination using the abdominal X-ray taken in standing position five to six hours after

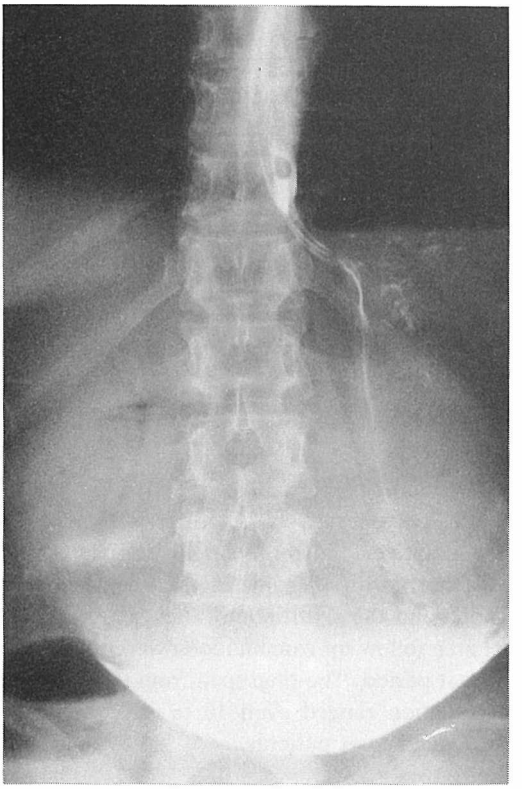


Figure 1. Gastroplegia. Atonic, greatly dilated stomach with signs of alimentary retention.

an intake of 200 ccm barium suspension. According to our own experience, and with regard to the operative indications, the operated patients were grouped into four speed levels till the complete emptying (Table 2). The complete stomach emptying implied, the absence of gastric contrast medium on the control X-ray (Figure 2b). Marked lagging refers to a smaller quantity of residual contrast medium along the lower antrum contour or mixed with gastric content (Figure 4b).

Expressed retention (the early retention) denoted a lagging of a greater part of taken barium suspension, usually accompanied by hypersecretion, hypotonia and gastric dilatation (Figure 3b, 5b). Atonic very dilated stomach, usually with signs of alimentary retention is marked as gastroplegia (Figure 1). Sometimes, there is a question of complete contrast retention without signs of passage through the pylorobulbar area twelve and twenty-four hours after the examination has commenced.

Complete gastric emptying is established in most of the operated cases (591 or 43.5%). Noted retention of gastric contrast medium mixed with secretion and meanwhile ingested food, or sedimented in the sinus area was not taken as a clinical problem after our initial experience. Therefore, this group of patients (229 or 16.9%) was added to the first one, as no clinical treatment was required. The early gastric content retention with hypotonia and hypersecretion was recorded in 523 operated patients (38.5%). Radiological symptoms of retention were even more markedly expressed in the last group of 15 operated subjects (1.1%).

A special care has been paid to these two groups of patients followed up by repeated examinations till the complete normalization of stomach emptying. Nasogastric probes were again inserted in all of them because of content evacuation. The follow-up examinations revealed a complete normalization of gastric emptying at the end of the fourth week following surgery. Only a small number of patients required a 6–8-week course to reach the same condition. Changed states of gastric emptying in 100 chosen patients with early retention and gastroplegia during the first two months following surgery are listed in Table 3. Complete absence of discomfort in a majority of patients with early retention is amazing. No difference in gastric emptying was observed between the two drainage methods applied.

Monitoring the speed of complete gastric emptying, various types of evacuation of its content were observed. A time relation between the initial and the complete stomach emptying was also followed up. Under commencing or the initial emptying, the time interval from the moment of contrast medium passage through the cardia and pylorobulbar area has been understood. Surprising results were obtained here, being very important for prevention of the prolongation of early retention. The fast initial emptying means the contrast medium passing through the pylorobulbar area in the

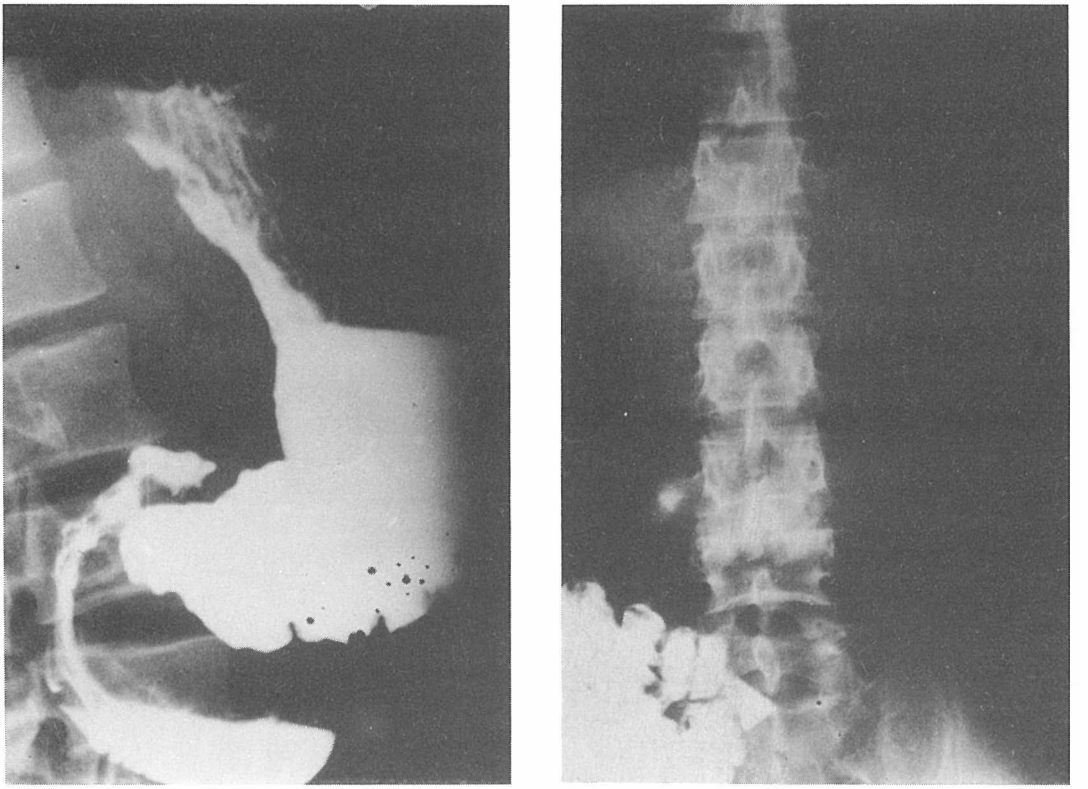


Figure 2a, b. Fast initial emptying (a), without retention (b).

first minute after it has passed through the cardia. The contrast passage after this time was considered as late initial gastric emptying. Complete gastric emptying was established by a routine abdominal X-ray performed in standing position five to six hours after the commencement of examination. Such observation of gastric content evacuation was applied in 624 operated patients treated in the course of last ten years, who underwent vagotomia totalis anterior (VTA) and vagotomia totalis posterior (VTP) or vagotomia selectiva anterior (VSA), and vagotomia selectiva posterior (VSP) combined with Finney's pyloroplasty (Table 4). It is evident from Table 4 that the greatest number of the examined were of the first (Figure 2a, 2b) and the fourth type (Figure 5a, 5b) (82.7%).

The number, and especially the way of emptying found in the second (Figure 3a, 3b) and the third type (Figure 4a, 4b) are amazing. The second type reveals normal initial gastric emptying accompanied by retention on the control X-ray in 62 examined patients (9.9%) six hours later. Conversely, in the less frequently found third type (46 or 7.4%) late initial stomach emptying is not accompanied by retention during the second stage of examination.

Table 5 displays the relation between normal initial emptying and an early retention present at various types of vagotomy together with the same kind of drainage operation (sec. Finney). The sample of 150 operated patients using VTA and VTP, VSA and VTP method consecutively, and all the operated subjects with a combination of vagotomia supraselectiva anterior (VSSA) and vagotomia supraselectiva posterior (VSSP) are listed. Obviously, as expected, early retention is mostly associated with total bilateral vagotomy. Monitoring of VSA

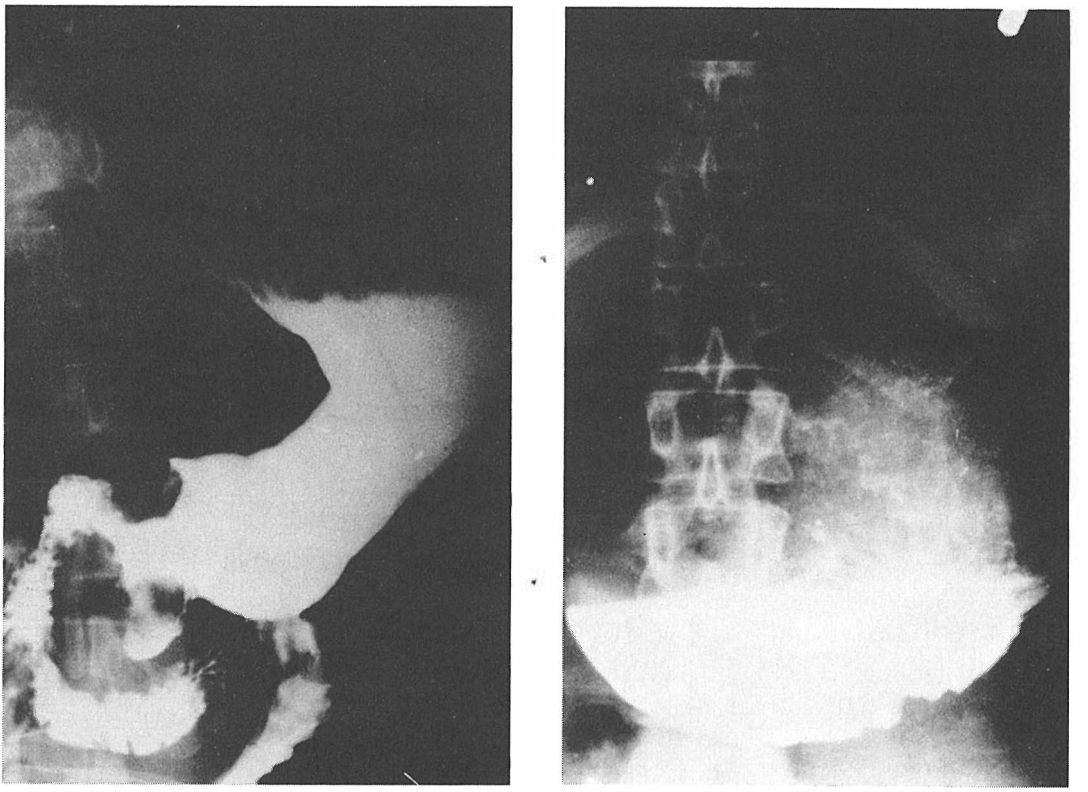


Figure 3a, b. Fast initial emptying (a), with retention (b).

and VTP stomach is much better. Retention is present in the bilateral supraselective vagotomy with drainage operation to a much lesser extent.

Definite picture of speed and the way of gastric emptying were investigated by late follow-up examinations in a group of 120 operated subjects. For the comparison sake, the speed of evacuation was followed up in the same number of inoperated patients with ulcus and 120 examined controls without it. The number of TV and SV patients was equal. Neither food nor liquids were taken by the examined patients during the course of examination till complete gastric emptying. To our opinion, the ingested solid-food meals mixed with contrast medium should be more appropriate for monitoring the speed of emptying. Notwithstanding, we decided on presentation of speed evacuation in

Table 3. Normalization of stomach emptying by the end of the second month following surgery in 100 patients with early retention and gastroplegia.

The first postoperative examination (8–10 days following surgery)	100
Follow-up examination (4 weeks following surgery)	16
Follow-up examination (6 weeks following surgery)	6
Follow-up examination (8 weeks following surgery)	0

Table 4. Types of stomach emptying on the first postoperative examination.

1 type	Fast initial emptying without retention	331	53.0%
2 type	Fast initial emptying with retention	62	9.9%
3 type	Late initial emptying without retention	46	7.4%
4 type	Late initial emptying with retention	185	29.7%
Total		624	100.0%

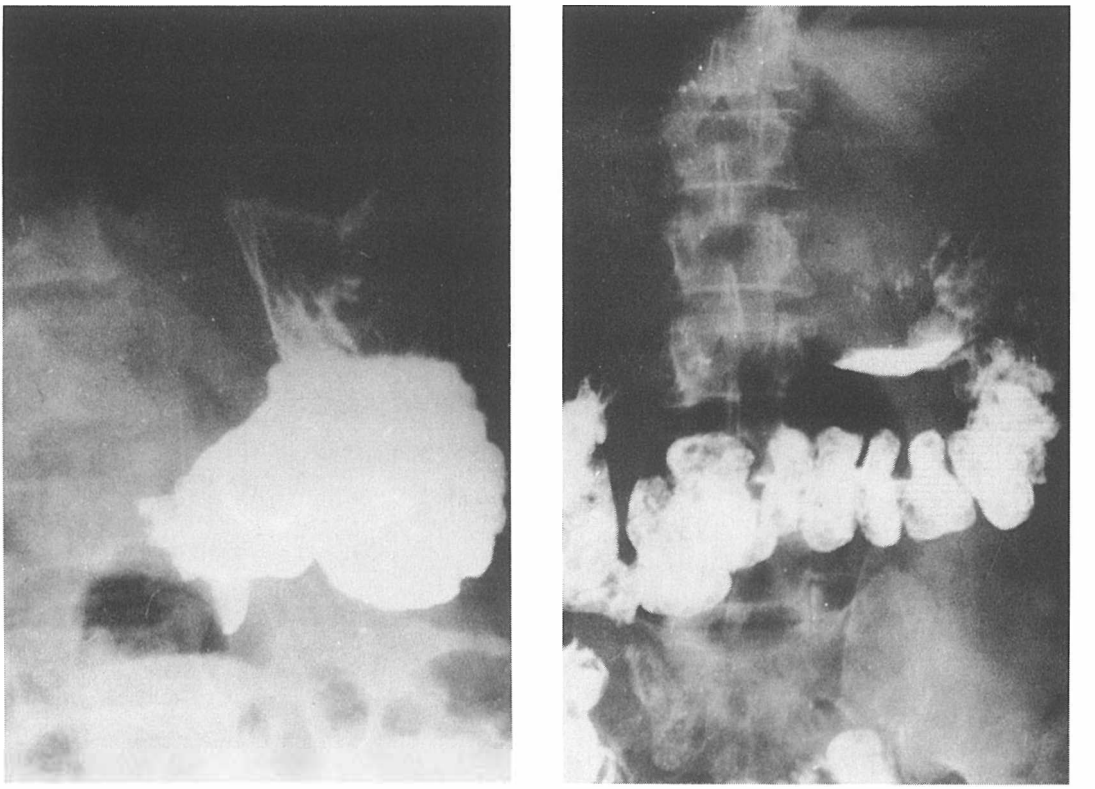


Figure 4a, b. Late and decelerated initial emptying (a), without retention (b).

vagotomized stomach with pyloroplasty under conditions of radiological examination in order to enable a possible direct comparison with findings of the examined subjects with healthy stomach and duodenum, or with findings of patients having duodenal ulcus.

Evacuation continuity through the extended and malformed pylorobulbar area and duodenal curvature, regardless the evacuation speed and radiological-anatomical gastric X-ray,[8, 15] can be different. Normal initial gastric emptying can be manifested in two ways. It can be continued and discontinued. Continuous initial emptying is expressed by contrast medium passage through a very dilated pylorobulbar area and duodenum (Figure 6a) and much more rarely

Table 5. Rate of normal stomach emptying and early retention in various types of vagotomy on the first postoperative examination.

	VTA and VTP	VSA and VTP	VSSA and VSSP
Normal emptying after 5–6 hours	78	96	18
Early retention	72	54	3
Figure ratio of normal emptying and early retention	1.08 : 1	1.08 : 1	6 : 1

Table 6. Average duration of initial and complete emptying in operated and inoperated examined subjects.

	Vagotomy and pyloroplasty	Inoperated patients with ulcus	Inoperated examined without ulcus
Duration of initial emptying	6"	2' 3"	33"
Duration of complete emptying	23'	1^h 30'	1^h 2'

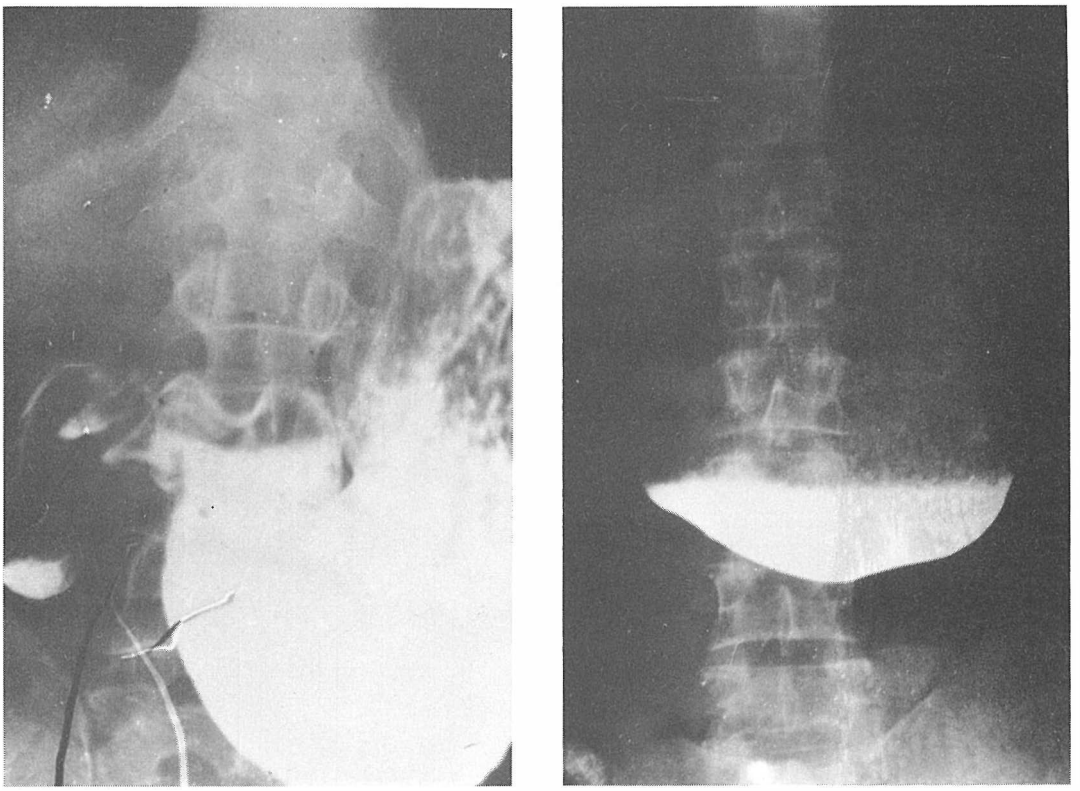


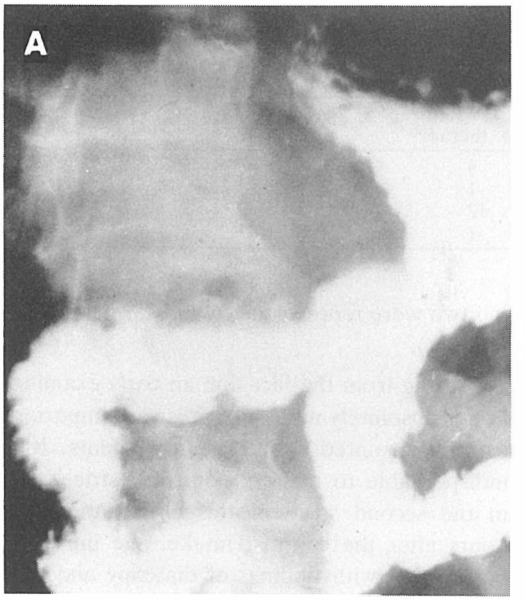
Figure 5a, b. Late and decelerated initial emptying (a), with retention (b).

by the picture of "watering-can" (Figure 6b). Occasional spastic contractions with evident oedema (Figure 6c) in pylorobulbar area have been established at discontinued initial evacuation.

The time of initial and complete emptying of vagotomized stomach with pyloroplasty is presented in Table 6. The mean duration of initial evacuation is to 6 seconds. In other words, the contrast medium practically rushes through the stomach. It is verbatim et literatim so with the hypertonic shape of vagotomized stomach[15] since the plastic pylorobulbar area represents the lowest point of the operated stomach. The contrast halts for a moment in the sinus being immediately moved through dilated pylorobulbar area into the duodenum at normotonic gastric form.[15] Comparing the values for the operated stomach to those of the control group, the time differences of the initial emptying are obviously greater related to the complete ones. The time of the initial evacuation is six times shorter in patients with operated stomach compared to the controls and twenty times shorter related to the initial gastric emptying in inoperated patients with duodenal ulcus. The time ratio of the complete evacuation of the operated stomach according to that one in the patients from the control group makes 1:3, being 1:4 related to the patients with duodenal ulcus. No differences were observed with respect to the type of vagotomy and pyloroplasty.

Here, it was not possible to distinguish four ways of evacuation in such an expressed form as during the first examination. The forms of fast initial and slower complete evacuation, and slower initial but faster complete emptying can be only foreboded.

A certain number of subjects developed again the feature of slowed down evacuation of vago-



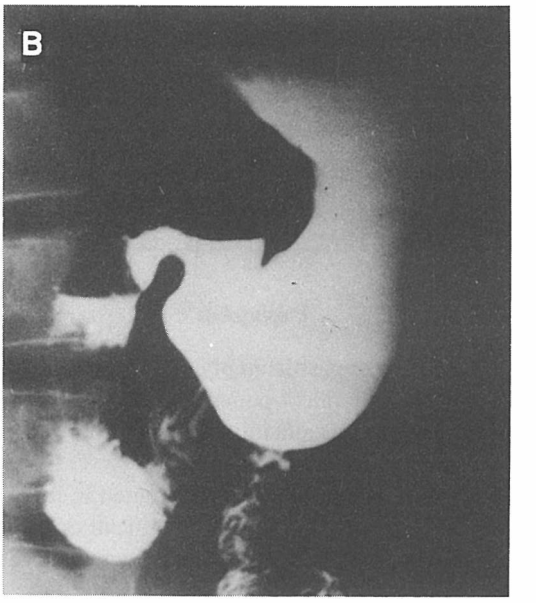
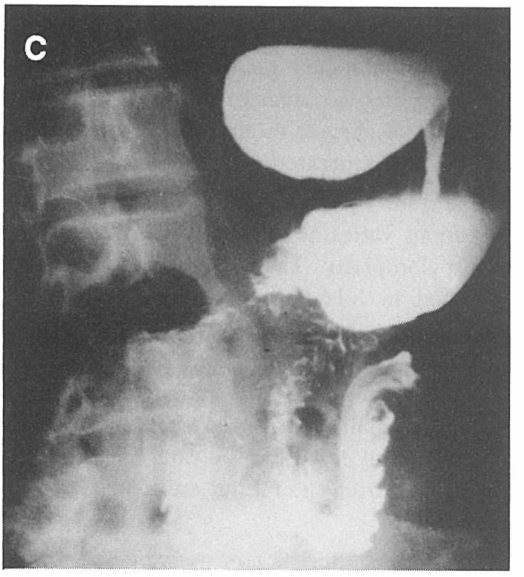


Figure 6a, b., c. Continued initial emptying through simply dilated pylorobulbar area (a), and by the picture of "watering-can" (b). Discontinued initial emptying (c).



tomized stomach with pyloroplasty at late examinations. It occurs as a primary or a secondary side effect associated with the relapse of ventricular or duodenal ulcus.[15] Delayed evacuations without discomforts were found in lesser number of cases.

Two groups can be distinguished in all these cases. In the first, bigger group (32 examined patients) a slowed down evacuation is present in standing and in the right hip lying position. In the second, smaller group (12 examined patients) the decelerated emptying is evident in the standing position only. The gastric content just poured over into the duodenum and the incipient jejunal folds, being completely evacuated in a few moments in the right hip lying position. These two groups of the examined patients ranged according to radiologically verified diagnosis before and after a drug therapy, are demonstrated in Table 7. The same number of retentions in the second smaller group before and after therapy is evident, while the number of retentions markedly decreased in the first, greater group after the drug therapy in those examined patients where the retention was followed by ulcus relapse.

Radiological gastric picture showing retention in the standing position only, displays its characteristic shape. Hypotonic, ectatic stomach as if hung in pylorobulbar area being narrowed against this area. Lower antral contour is elongated and markedly lower set than the plastic area.

Table 7. Decelerated gastric emptying at late examinations.

	Decelerated gastric emptying in standing and lying position		Decelerated gastric emptying in standing position only	
	Before the therapy	After the therapy	Before the therapy	After the therapy
Ventricular ulcus relapse	8	4	5	5
Duodenal ulcus relapse	3	1	1	1
Stenosis with clinical signs of relapse	12	12	0	0
Without symptoms of relapse	3	1	6	6

Discussion

A follow-up of gastric emptying was carried out in all the operated patients during the first postoperative examination between the eighth and the tenth day following surgery. Our findings were compared with those cited in literature. The comparison was very difficult or completely impossible because of various methods of vagotomy and pyloroplasty applied, all their possible mutual combinations and modifications in different teams of surgeons.

The evacuation has been considered complete or satisfactory, if there was no contrast medium in the stomach, that is, if it lagged behind in small quantity along with the antral wall, or was mixed with the content five to six hours from the commencement of the examination. The signs of early retention were found at 40 % of the patients only (Table 3), the lesser number of which corresponded to gastroplegia (1.1 %). In spite of the lesser frequency of early retention for the selective vagotomy (20 %) reported by Sapounov, gastroplegia took greater part among his findings (2.5 %).[16]

Normal evacuation occurred during a four-week interval in those patients with early retention (Table 3). It was prolonged to the eighth week postoperatively in a lesser number of cases only. Early retention was most frequently associated with operations carried out because of perforated ulcus (accompanying peritonitis, greater preoperative trauma, always performed bilateral truncal vagotomy) (Table 2).

According to the way of evacuation, i.e. an information otherwise not found in literature, we described four types (Table 4). The most frequent ones, as had been expected, were the first and the fourth types (82.7 %). The remaining two were represented to a lesser percentage (17.3 %).

Starting from the fact that an early examination is absolutely necessary, it is very important to be acquainted with these statements. It is indispensable to make a control gastric X-ray in the second stage of this examination 5–6 hours after the contrast intake. We must not be satisfied with findings of diascopy and with the first X-ray only and ignore one fourth of early retentions (the second type) or expose to retention treatment the patients seemingly expressing signs of aggravated evacuation at the beginning of examination (the third type). All the established facts gain more importance if we know that a great number of early retention cases express no clinical symptoms, and that one part of chronic retentions can develop on the basis of untreated early retentions.

The rate of normal evacuations and early retentions varies at various types of vagotomy with pyloroplasty. The most unfavourable rate is noted in bilateral TV (about 1:1), being somewhat more favourable in VSA and VTP (about 2:1) and the most favourable in bilateral PSV (6:1). TV and SV findings differ from those cited in literature,[7, 14, 16] according to some of which early retention is a rare phenomenon. SSV data from literature are equal to our findings.[7, 17]

Six months after surgery we were not able to distinguish four ways of evacuation in such a marked form as at the first postoperative examination. The types with fast initial and slowed down complete gastric emptying, and slowed down initial but normal complete evacuation could be only discerned. Since all these times have been measured in seconds and minutes,

their analysis in this sense was of no practical importance.

According to literature, there are three essential causes for speed difference of the stomach emptying in the examined subjects with healthy stomach, in those with duodenal ulcus and the patients who underwent vagotomy with pyloroplasty. The patients with healthy stomach develop complete function of receptive relaxation and gastric wall accommodation, corpus especially, to a volume extension at the gastric content ingestion. The patient with ulcus suffers from dysfunction of distal antral part and the pyloric canal because of fibromuscular hypertrophy, inflammatory infiltration and degenerative changes of the intramural nerve plexuses. After vagotomy and pyloroplasty the situation changes because of the absence of ulcer and changed conditions of innervation.[10, 14, 18–22] The third cause is clear, being cited by all authors concerned with these problems. It refers to morphological and functional changes in the area of duodenal ulcus. Greater or smaller lumen narrowing, which takes the first place, is followed by spasm, inflammatory oedema etc. All these factors drop off by surgery.[10, 14, 18–22]

Figures in our Table 6 comply with these explanations, thus contradicting the rare quotations speaking about shortening of the initial and prolongation of the complete stomach emptying after a long time following surgery.[23]

A shorter time of the complete evacuation in our operated patients is also evident, to be distinguished from that aforesaid concerning VSP.

Differences in the duration of complete evacuation are smaller (Table 6), since the contrast medium gathering progressively in the stomach by lapse of time following surgery has the possibility of a certain stage of gastric wall adaptation. Hence, the supposition about a greater time difference of the initial and the complete emptying after food ingestion of vagotomized stomach with pyloroplasty is acceptable, especially if the food is of harder consistency.

The cases of late retention have been found after a longtime follow-up of our large group of examined subjects, usually being a side effect of peptic ulcus relapse or pylorobulbar area stenosis. Stenosis itself, together with ulcus discomforts, is a reliable sign of relapse.[15] Discussions whether the relapse is preceded by late retention, or whether the retention is caused by relapse are irrelevant. A small group of registered cases with aggravated gastric emptying in standing position only is of special interest. According to our opinion, this phenomenon is caused by cicatrical changes appearing during a longer postoperative course in pyloroplastic area and prepyloric part of the lesser curvature, weaker gastric wall tonus with impaired peristaltics of the prepyloric area and the existence of pyloroplastic ridge which becomes prominent, together with the first two causes, as an obstacle of gastric content evacuation. All these causes disappear in lying position.

Relating to the aforementioned, the relapse is thought to be more frequently preceded by retention. All the examined patients with aggravated evacuation, and even those with the presence of it in standing position only, are candidates for relapse.

It is evident (Table 7) that one part of retentions accompanying ulcus relapse are of transient nature and disappear after a drug therapy; these can be regarded as side effects of ulcer (oedema, spasm). No changes after therapy are observed in retentions with already formed stenoses. Obviously, there are no therapeutic effects in the group with aggravated evacuation present in standing position only. These patients are also candidates for relapse.

Conclusion

The first (early) postoperative follow-up examination has to be obligatorily carried out between the eighth and the tenth day following surgery in two stages, with 5–6 hour time interval. This examination is indispensable for verification and prevention of early retention.

Monitoring patients through the second follow-up examination until the normalization of gastric content evacuation is indispensable in all the cases of early retention. This period expires by the end of the fourth and certainly not later than by the eight week after surgery.

All patients suspected of ulcus relapse have to undergo later radiological follow-up examinations in order to verify or eliminate simultaneous late retentions.

All vagotomized patients with pyloroplasty suspected of retention, regardless the absence of clinical signs of relapse, must also be subjected to later radilogical examinations.

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Radiol Oncol 1992; 26: 205-8.

Contribution of mammography to diagnosis of breast tumours in women under the age of 30

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Mammograms of 274 patients aged between 15 and 30 years were analysed retrospectively. The analysis of 176 (64.2 %) mammograms was unreliable because of radiographically dense breasts. In addition to mammography, ultrasound (n = 42), needle biopsy (n = 98), cytologic examination of secretion from the breast-nipple (n = 28) and open biopsy (n = 17) were used as diagnostic methods. Diagnosis of the only carcinoma in the group (carcinoma intraductale) was set on the basis of positive mammographic, cytologic and echographic findings.

Because of the low percentage of breasts suitable for radiographic analysis, echomammography is the method of choice for the visualization of breasts in women younger than 30 years.

Key words: breast neoplasms-diagnosis; mammography

Introduction

Breast cancer is the most frequent malignancy in women; it represents about 20 % of all cancers in the female population.

According to the statistics of the Cancer Registry of Slovenia,[1] the incidence of breast cancer is 66 per 100.000 of Slovenian women. Every year more than 650 women are afflicted – 96 % of them older than 35. Women from the age group between 15 and 29 years represent 23 % of the Slovenian female population, or less than 1 % of breast cancers. Breast cancer incidence grows at the rate of 5 % per year in the Republic of Slovenia and the tendency shifts from the older to the younger age group.[2]

At present, mammography is the most important method for early detection of breast cancer. As regards its effectiveness, no other method has come even close to it.

There are several facts speaking against the use of mammography in women younger than 35 years: morphologic characteristics of the breast, because of which mammograms are often inadequate for analysis, the potential risk represented by exposure to radiation, and the fact that carcinoma of the breast in younger women is so rare that screening in this group of the population is ecconomically unjustified.

In our retrospective study we wanted to evaluate the contribution of mammography to diagnostic treatment of tumours in patients younger than 30.

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UDC: 616.19-006-073.75

Material and methods

The medical documentation of women aged 30 years or less, investigated radiographically during the past 11 years at the Breast Diagnostic Center in Maribor, was reviewed. We wanted to know which data from medical history and clinical status were an indication for mammography. Mammograms, echomammograms, cytologic findings of aspiration biopsies, cytologic findings of breast secretion smears and findings of open biopsy were analysed. The patients were x-rayed by means of a Senographe 500T CGR device using the cassette technique with unilayer films.

The classification of breast parenchymal patterns as suggested by Wolfe[3] was used in the analysis of mammograms.

Subjectively we evaluated whether the mammogram was suitable for analysis or not, whether the tumour was visible on the mammogram and how the findings influenced the decision about further diagnostic treatment.

Results

Our analysis comprised 274 mammograms of patients aged between 15 and 30 years. The indications for mammography were as follows: clinically determined tumour and/or marked nodosity (n = 125), pain (n = 78), nipple secretion (n = 30), preventive examination prior to plastic surgery (n = 3) and others (family history of breast cancer, inverted nipple, cancerophobia etc. (n = 40).

Classification of mammograms according to Wolfe showed that the fewest mammograms are in groups N (n = 28/10.2 %) and P1 (n = 70/25.5 %) and a little more in P2 (n = 75/27.4 %). Most mammograms were evaluated as DY (n = 101/36.8 %).

Of the clinically determined tumours and prominent nodosity (n = 125), only 25 (20 %) were mammographically visible, 10 of them partially.

Ten of the 15 mammographically determined tumours were clinically unpalpable. They all had mammographic characteristics of cysts or benign solid tumours. Only one patient was referred for biopsy.

Echographically we examined the breasts of 42 patients. In 12 cases we found a benign solid tumour, in 11 a cystic lesion, in 3 ductectasia, in one dilated ducts in the first quadrant of the breast and in 16 normal parenchymal structure. All clinically manifest tumours (n = 16) were echographically visible.

In 98 palpable solid lesions (tumours and prominent nodosity) a needle biopsy was done. The cytological results were in 23 cases PAPA I, 35 times PAPA II, 4 times PAPA II-III, 36 punctures (36.7 %) were inadequate for analysis.

In 28 secreting nipples a smear was taken. The cytological results were as follows: 14 times PAPA I, 8 times PAPA II, once II-III, once PAPA V, 3 smears were inadequate for analysis.

In the analysed group of patients, 17 open breast biopsies were carried out. Seven of them were made only on the basis of clinical results, because the lump was not mammographically visible. Histological findings were: two cases of fibroadenoma, 4 of fibrocystic breast disease, one of normal gland parenchyma. Of the remaining biopsies there were 5 cases of palpable solid lesions, which were also mammographically visible. Histological findings were: fibroadenoma in two cases, papilloma intraductale in one, unspecific granulation tissue in one, whereas in one case the result was not obtained.

Only one patient was sent for biopsy merely on the basis of mammography findings – the tumour was not clinically manifest. The histological findings confirmed a lipoma.

In the entire group, only one case of cancer was diagnosed in a 29-year old patient who came for an examination because of milk secretion from several ducts of the left breast and marked nodosity in the first quadrant of the same breast. Mammography detected a type DY with diffused microcalcifications in the left breast. The echomammogram revealed dilated ducts in the first quadrant of the breast, pathological findings because they usually can not be visualized in this area.

Discussion

At present, mammography is the very best method for early detection of breast diseases.

With reference to mammographic screening, several questions are raised: when to begin screening so it would be justified from the standpoint of the applicability of mammography at a certain age, from the standpoint of risk from radiation and from the economic standpoint.

Successful mammography, requires good technical devices, sensitive films and a physician with the required knowledge and interest, because interpretation of even technically perfect mammograms is not easy. This applies particularly to mammography in younger women where the findings are often false positive or false negative because of dense parenchyma. Radiographic density of the breast is the result of the presence of normal parenchyma in younger women, prominent ducts, dysplastic epithelium and stromal tissue. Breast tissue involutes with the age. It is replaced by fatty tissue which is radiographically transparent and facilitates the detection of pathological changes. That is a specially favourable circumstance since the age specific incidence of breast cancer shows a steep increase after the age of 35.[4] Because of the extreme radiographic density of the breasts, mammograms are frequently false negative in young women.

Hall[5] suggested the evaluation of mammograms according to whether they are, and to what extent they are adequate for analysis. He defined four categories roughly corresponding to the classification by Wolfe:

1. an adipose breast, suitable for mammographic interpretation,

2. the adipose tissue is predominant, the breast is relatively adequate for mammographic interpretation,

3. a relatively dense breast, suboptimal for mammography,

4. a dense breast, inadequate for mammographic evaluation.

According to this classification, Schutte[6] assessed a population of 938 patients. In the age group under 35 years, only 20 % of the mammograms were adequate for analysis, 26 % were relatively adequate, 29 % were suboptimal and 25 % were inadequate. This changes essentially in the age group over 35 years: 41 % were adequate for mammographic analysis, only 9 % were inadequate. Such classification should be a guide to the physician for proper treatment of the patient. Negative mammographic findings of a breast, inadequate for mammography owing to its structure, have no diagnostic value and must not cause a delay of the biopsy if it is indicated on the basis of clinical examination.[6,7]

According to the recommendation of the American Cancer Society, a base-line mammography should be done at the age of 35 to 40 years, whereas control checkups should be done once a year or every second year up to the age of 50, and after that every year.[8]

The hypothetic noxiousness of screening is based on the fact that at a yearly dose of 1 mGy (which can easily be reached using good devices and sensitive films) at the age between 35 and 75 years, the incidence increases for 1 % over the natural incidence.[9]

Feig[4] established that the risk of radiogenic cancer from small doses is neither proved nor disproved. If such risk does exist, it is negligible, particulary if compared with the high incidence of the natural occurrence of breast cancers detected by screening. The risk, if it exists, is lower in women past the age of 30, who benefit the most from mammography. Namely, the sensitivity of the breast to radiation depends on age. There are different explanations for this.

Molgavkar[10] is of the opinion that breast cancer develops in two stages. All carcinogens, including radiation, take effect during the second stage – the transformation of intermediary cells into tumours. Sensitivity to radiation or to any other carcinogen supposedly depends on the number of cells in the intermediary pool and the speed of cell division. A larger number of births and age supposedly decrease the risk for cancer. Korenman[11] is of the opinion that sensitivity to radiation depends on the estrogen-progesteron rate in blood at the moment of

exposure to radiation. This proportion is highest during adolescence, in the period of anovulatory cycles, in inadequate luteal phases and isolated estrogen stimulation. The estrogen window closes with age, births or both. Radiogenic carcinomas occur at least 10 years later. The duration of the carcinoma effect is not known, but studies show that it continues at least for the following 15 years. Owing to the unproved noxiousness of screening in older women, the question of "screening yes or no" is not raised. Since its benefit in younger women has not been proved, the risk becomes significant.

Our study confirms the assertion that tumours in dense breasts, prevailing in younger women, are mammographically difficult to diagnose. Also as a diagnostic test for the diferentiation of mammographically visible changes, mammography is far from being specific – there are numerous false positive cancer diagnoses.[12] Much more information on the nature of changes in the dense breast is obtained by ultrasound, therefore ultrasonic examination is the method of choice for the evaluation of the radiographically dense breast.

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Radiol Oncol 1992; 26: 209-11.

Congenital unilateral absence of the right pulmonary artery – diagnosis with digital subtraction angiography. A case report

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Congenital unilateral absence of the pulmonary artery is a rare developmental anomaly of the pulmonary artery. More often it comes associated with other heart anomalies. If the absence of the pulmonary artery occurs isolated, patients can be without symptoms for a long time. We present a case of a 20-year old man with dyspnea on physical effort. Native chest radiogram evidenced an anomaly, showing a pathognomonic characteristic pattern which imaged a reduction on the affected side without hilus and pulmonary picture. The left lung is hyperinflated, though with normal hilus and picture. Following clinical and laboratory investigations, bronchoscopy and bronchography, we performed i. v. digital subtraction angiography in order to confirm the diagnosis of the pulmonary artery absence.

Key words: pulmonary artery-abnormalities; aplasia; angiography, digital subtraction

Introduction

Congenital isolated unilateral absence of the pulmonary artery is a rare anomaly. It is more frequently associated with heart defects such as tetralogy of Fallot, patent ductus arteriosus, atrial septal defect, ventricular septal defect and others.

Isolated unilateral absence of the pulmonary artery may stay nonsymptomatic for a long period of time, and its discovery is mostly incidental – often it is found on a routine chest radiography. The patients may live longer without any severe respiratory difficulties.

Absence of the pulmonary artery, when associated with other heart anomalies, can be discovered soon after birth or in early childhood; these patients, however, have unfavourable prognosis.

Conventional chest radiogram shows reduced hemithorax on the affected side, rib interspaces are smaller, hemidiaphragm is more elevated, and the heart and mediastinum are displaced toward the affected side (Figure 1). The healthy side exhibits hyperinflated lung and a herniation across the midline; the hilus and vascular picture are normal, whereas neither of these can be seen on the other side.

Case report

We examined a 20-year old man who had not had any difficulties until recently when he started to experience dyspnea during fast walking or running.

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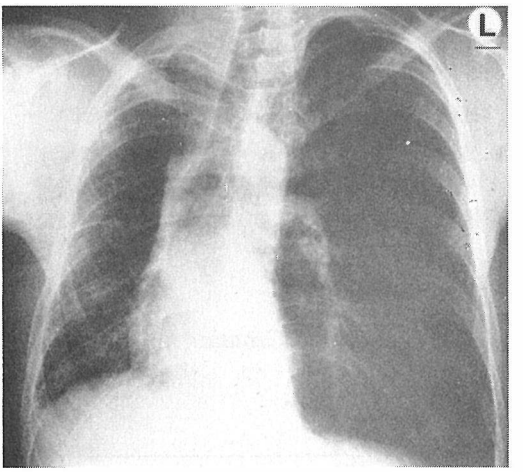

Figure 1. PA chest radiogram.

Physical examination revealed a tall, asthenic young man with asymmetrical thoracic cage; the right side was reduced, associated with dextroconvex scoliosis of the thoracic vertebrae.

The left side was normal whereas breathing on the right was intensified.

Cor: heartbeat moved to the right, RR 21/10

ECG: normal sinus rhythm 85 BPM. Incomplete right bundle branch block. Other cardiac findings were normal.

Laboratory findings were within the limits of normal values. Ventilation during rest and on exertion was satisfactory.

The concentration of respiratory gases in the arterial blood was normal (ABC).

Chest X-ray: (Figure 1): asymmetrical thoracic cage with reduced right side. Rib interspaces on the right were also smaller, the diaphragm was placed high and the heart and mediastinum were dislocated to the right. The trachea was also moved to the right. No hilar shadow or vascular picture could be seen on the right. The left side showed hyperinflated lung and midline herniation. The diaphragm was very low, the left hilus was normal and the vascular picture of the left lung lobe was regular.

The examination procedure was completed by bronchoscopy and bronchography which imaged normal trachea and bronchi. Afterwards we performed angiography by means of digital subtraction using a Philips DVI-CV unit. The patient was recorded in lying position with PA, RAO direction at 10°, and LAO at 40°. Contrast medium was introduced through the cubital vein.

Non-ionic contrast medium Iohexol (Omnipaque 350-Nycomed) was used, the application rate being 10 ccm per second, amounting to 30 ccm per series. The recording began two seconds after the first application of the contrast medium and lasted for 10 seconds. The i.v. DSA investigation imaged vena cava superior, right atriums and ventricle, the pulmonary artery and normal intrapulmonary branches of the left lung lobe (Figure 2).

In the venous phase, normal pulmonary veins, the left atriums and ventricle, aorta and the supraaortic artery were imaged (Figure 3).

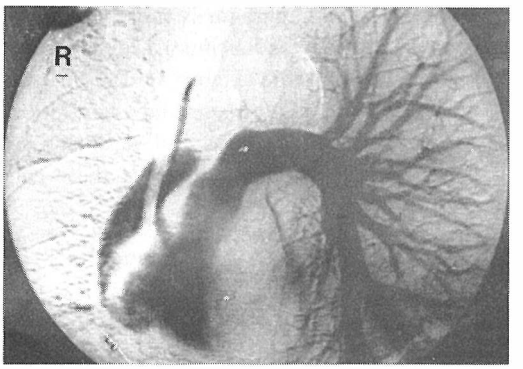

Figure 2. I.v. DSA of the pulmonary artery. The right pulmonary artery is missing.

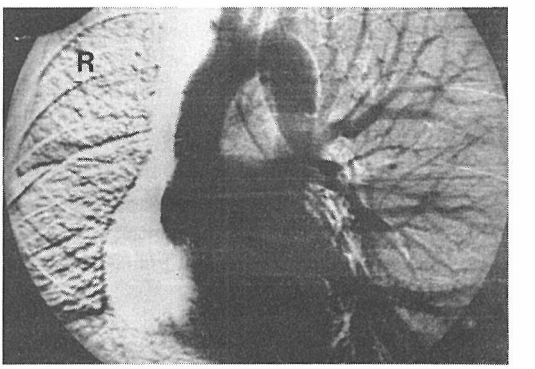

Figure 3. Venous phase. Pulmonary veins on the right are not imaged.

Discussion

Isolated absence of the pulmonary artery is a very rare anomaly which in our case caused dyspnea on exertion. All the laboratory findings were within normal limits though the chest radiogram was pathognomonic.

The correct diagnosis was established by i.v. digital subtraction angiography. This method can be completed also by CT and perfusion scintigraphy of the lung.

In this disease both radiogram and clinical picture can closely resemble those seen in Swyer-James syndrome, unilateral obstructive emphysema, pulmonary embolism or thrombosis, or in pulmonary artery stenosis.

In the diagnosis of the absence of the pulmonary artery, i.v. DSA represents the method of choice for the evaluation of the pulmonary artery and vein circulation, because it provides sufficient information on their function as well as anatomy.

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Radiol Oncol 1992; 26: 212-7.

The importance of computed and conventional tomography in pulmonary diseases

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Eighteen years have passed since the use of the first computed tomography (CT) unit and over 10 years from its use at our Institute. During that period the important technologic improvement of the units occurred as well as an increase in the indications for it suse. During 1991, the authors analysed a group of 34 patients; all had the conventional tomographies (TMG) and CT. Based on the parameters presented in the work, the diagnostic contribution of both methods was analysed, respectivelly. In almost all our cases, CT provided an additional and important information, comparing to the conventional TMG, so, the question of its usefulness has been raised. The aim of the paper was to show the contribution of CT in comparison with the conventional TMG in order to prevent diagnostic misinterpretations and reduce treatment expenses.

Key words: lung diseases-radiography; tomography; tomography, x-ray computed

Introduction

During the last years, conventional tomography (TMG) was exposed to the competition of two new methods of visualization, computed tomography (CT) and magnetic resonance (MR). The principle of the conventional tomography is erasure; some levels in the body are selected for presentation, while the structures at the surrounding levels become practically invisible, with the intentional provocation of the unclearness. The plane of the cross-section is selected individually, depending on pathology.[1, 2, 3] The development of digital techniques in radiology, set them as the imperative. They are based on the principles of manipulation by digital (numerical) data.[3, 4] Information about the absorption of irradiation during its transfer through the object, is presented in the form of analogous information; i. e., an analogous video signal is transformed into digital information, expressed in so-called digital binary numerical system. The transformation of information takes place in analogous-digital (A/d) convertor. The digital information presented numerically, may be computerized, and according to the need, using the D/a conversion, it can be transfered into an analogous information again, usually in video TV signal.[4] Besides the conventional TMG apparature there are modern digital techniques – CT and MR available for the evaluation of thoracic organs at our Institute. CT provides the axial sections of human body in the form

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of anatomic images, expressed by different absorptions of x-rays through the tissue. The differentiation of four radiologic densities (air, liquid, solid tissue, bone) is more sensitive in CT.[5] We have modest experience with MR, and a unit of small power – 0.04 T (Tesla). Having all those modern techniques of visualization at the disposal, from the first moment it became clear to us that it is important for the physician to define the algorithm of examinations, which enables the most appropriate diagnostic information, having in mind the comfort of the patient and economic limitations. The development of new radiologic techniques would cause some of them to be abandoned and others reduced. Therefore, the aim of our paper was to confirm our experience about the absolute advantage of CT by the objective parameters, in order to facilitate diagnostic procedure, avoiding TMG whenever possible. Our investigation is preliminary, and it has to be broadened by new cases, especially in the hilar region.

Material and method

During 1991, 34 patients were investigated. They underwent conventional TMG in the first phase, followed by CT. The total of 34 patients underwent both methods. Their mean age was 53 years (12 to 77 years). There were 18 males and 16 females. Besides the disease history, all patients had the conventional radiography for the orientation and planning of examinations.

Tomographies were performed on Siemens tomograph, with the possibility of slice determination from 1 to 10 mm. The most frequent slice thickness was 5 mm, frontal plane, rarely saggital and back oblique, at the angle of 55°. During the examination, the patients were positioned as is according to the plane of section.

CT examinations were performed on Somatom SF and DR "Siemens" units, with slice thickness 4 and 8 mm, at the dorsal decubitus plane and using contrast material. According to the referral diagnoses, the patients were divided into four groups: patients with infiltrative and expansive processes of the lung parenchyma, mediastinal tumors, hilar adenopathies and solitary lung metastases (Table 1). Two radiologists analysed the tomograms independently as well as the corresponding CT scans of the same patient. The following parameters were analysed: the expenses of examination, technical quality of the tomograms and scans, the contribution of the particular technique, densitometrically, in the complex radiologic image, topographically, morphologically, in small and large thoracic lesions (2 and over 5 cm), sensitive diffuse parenchymal lesions, in the analysis of the tumor nature or vascular pseudotumor, in mediastinum, hilar, pleural region, as well as the contribution relating to the associated lesions (Staging), evaluation of operability and aspiration biopsy. The advantage of the particular method was marked by "–" or "+". The mark "+" presented a greater contribution.

Results

Table 1 shows 34 patients with different pathologies. All patients underwent conventional, most frequently frontal TMG and CT scans, and were analysed on the basis of the objective parameters (Table 2). CT was superior in the image quality, which was 69 % in TMG, and 100 % in CT. The contribution of conventional TMG in hilar region, especially in the central hilar obstruction processes was 37.1 % and 100 % in CT. The advantages of CT relating to the TMG in hilar region, in hilar adenopathies have still been evaluated, and the results will be presented later. Relating to other parameters, such as densitometry, analysis of sensitive diffuse parenchymatous lesions, small and large thoracic solid lesions, analysis in the mediastinum and relating to the satellite lesions (axial sections eliminate the superposition), the evaluation of operability, transthoracic aspiration biopsy, CT is advantageous. The only advantage of tomography is in the low cost of the method. All other advantages presented on Table 2, refer radiologist to the use of CT,

Table 1. Distribution of 34 patients according to referral diagnoses.

Infiltrative and expansive processes of lung parenchyma	Hilar adenopathy	Lung metastases	Mediastinal tumors
1. Tu hili sin.	Lymphadenopathia hili dex.	Meta. pulmo sin. (Ca mucinosum tiliae)	Tu gl. thyroideae
2. Infiltratio (Tu.) hili dex.	Sarcoidosis hilo-pulm.	Ca mammae dex.	Tu mediastini
3. Pancoast apicis sin.	Lymphadenitis hili I. dex.	Meta pulm. I. dex.	Teratoca. mediastini
4. Infiltratio lobi sup. p. I. dex.	Sarcoidosis	Neo mammae dex. (Meta pulm.)	Tu mediastini
5. Infiltratio pulm. I. sin.	Adenopathia hili bill.	Meta pulmo. (Seminoma testis)	Tu mediastini
6. Infiltratio pulm. I. sin.	Sarcoidosis	Meta pulmo I. dex.	Tu mediastini (Laryngitis chr.)
7. Infiltratio lobi sup. p. I. dex.	Sy. Lupus erithematodes	Infiltratio rotunda pulm. I. sin.	Tu mediasthini (paratrachealis I. dex.)
8. Infiltratio lobi sup. p. I. dex.	Erythema nodosum		
9. Infiltratio pulm. I. sin.	Lymphadenopathia hili et mediastini		
10. Inflit. pulm. I. dex.			
11. Infiltr. lobi sup. p. I. sin. spec.			
Total 11	9	7	7

which would reduce the time of investigation and the expenses of treatment in the final balance.

Discussion

The recent technological improvement in radiology is indisputable. In this study, we correlated the contribution of conventional TMG and CT, in different chest diseases (Table 1 and 2). Analysing our results and correlating them with the literature data, a great consistency of the results is evident. Central, lobar and segmental bronchi, which are frequently the site of a malignant expansive process, as well as the mediastinum, are better presented by CT[3,6] (Figure 1, 1a). CT is the "window" to the

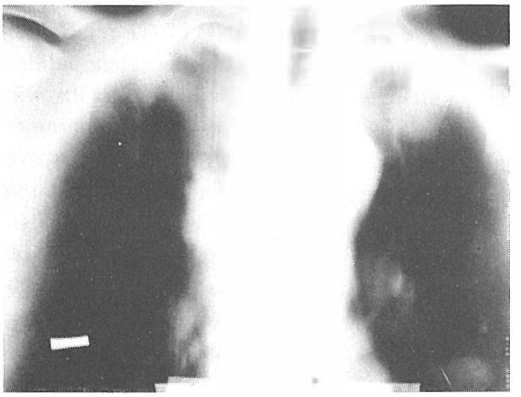

Figure 1. Frontal tomogram: irregular intensive shadowing in the upper pole of the right hilus.

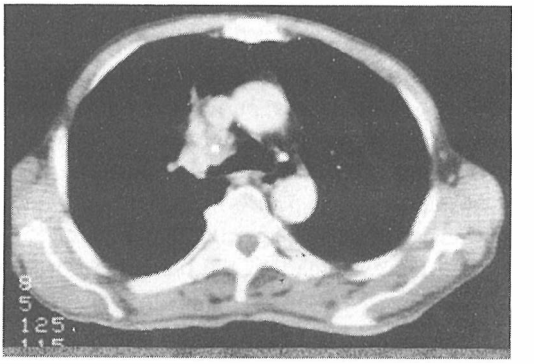

Figure 1a. Transversal CT slice at the level of tracheal bifurcation: clear presentation of the relations of tumorous mass and lumen of the right main bronchus and vena cava superior (Op. P. H. D.: Ca bronchi epiderm).

Table 2. Comparison of the possibilities of diagnostic techniques.

Possibilities	Conventional TMG	CT	MR
1. Principle of the activity	x-ray irradiation by the erasure	x-ray irradiation, slices	Magnetic field power + radio-waves + slices
2. Slice thickness	1 – 10 mm	2 to 8 mm	5; 7; 10 mm
3. Section plane	individually	Axial	individually
4. Complete thorax	–	+	+
5. Exposition time	0.5 – 6 sec.	2 – 5 sec.	10 sec. min sequences with more slices
6. Manipulations	Radiographer	Digital data	Digital data
7. Ionizating irradiation	++	+	–
8. Expenses	+/++	++	+++
9. Technical quality of the image	69 % +	100 % +	
10. The capacity of differentiation of two zones in density (densitometry) (air-solid; fat-liquid; calcium)	–	+	Natural contrast
11. Unexplained x-ray image	–	+	
12. Topographic presentation	–	+	
13. Morphologic presentation	–	+	
14. Small thoracic lesions (nodus, infiltration, enlightment)	–	+	
15. Large thoracic lesions	–	+	
16. Subtle diffuse parenchymatous lesions (interstitial syndrome)	–	+	Lack of protons
17. The nature of tumor or vascular pseudotumor (contrast material-bolus)	–	+	
18. Mediastinum	–	+	
19. Hilar region	37,1 %	100 %	
20. Pleura and interlobar septum	–	+	
21. Associated lesions	–	+	
22. The evaluation of operability	–	+	
23. Transthoracic aspiration biopsy	–	+	

human body, so that some regions, such as the thymus lodge, have become completelly accessible. We have analysed the presence of the enlarged lymphnodes and relations of bronchial and vasculary structures with expansive infiltrative process in the hilar region, which still present a problem for the analysis. The conventional TMG has contributed significantly in 37.1 % of cases, CT in 100 % of cases. Vock reports the contribution of frontal TMG in 59 %, TMG at the angle of 55° in 61 %, and CT in 82 %. The variations in the results can partially be explained by the fact that we mostly performed frontal TMG with few exceptions, by small series, including the central expansive processes where CT is superior, by the low technical quality of tomograms which satisfied our criteria in only 69 % of cases, while the technical quality of CT scans was satisfactory in 100 %. We shall present an accurate information an this comparation in hilar region after a more detailed investigation on homogeneous series, (hilar pathology) which is under way. By the help of a contrast bolus, CT contributed

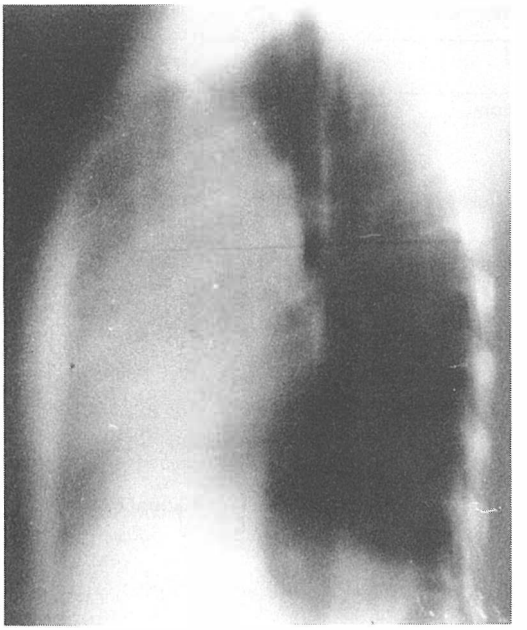

Figure 2. Profile tomogram, soft-tissue shadowing of the frontal mediastinum.

significantly to the differentiation of tumors or vascular pseudotumor, with an evident improvement in densitometric, morphologic, and topographic presentation of the associated lesions which is very important in the evaluation of operability. Relating to the lung parenchyma, the indications for scanning are constantly widened. Small thoracic lesions and subtile diffuse parenchymatous lesions in the frame of the interstitial syndrome, are better analysed by CT, especially the subpleural regions and interlobar septa. The scanner differentiates two zones of different densities ten times better than TMG. It identifies small infiltrations and enlightment[7] CT detects pulmonary nodes sized 0.4–4 mm (TMG detects nodes sized 5 to 10mm) with 10%–30% more contribution.[3, 6, 7] CT is usede for the detection of pulmonary metastases.[3] CT examination detects more metastatic lesions than x-ray of the lungs in 66%.[8] In 80–90% of the cases, metastases in lung parenchyma are localized subpleuraly.[3] Small diffuse calcifications may be presented and analysed densitometrically only by CT.[3] The superiority of CT is proved in the interstitial syndrome.[6] CT sensibility and specifity is about 90% in diffuse lung parenchymal involvement.[3] For the time being, lung parenchyma is in the domain of CT.[6] CT is indicated in the cases of

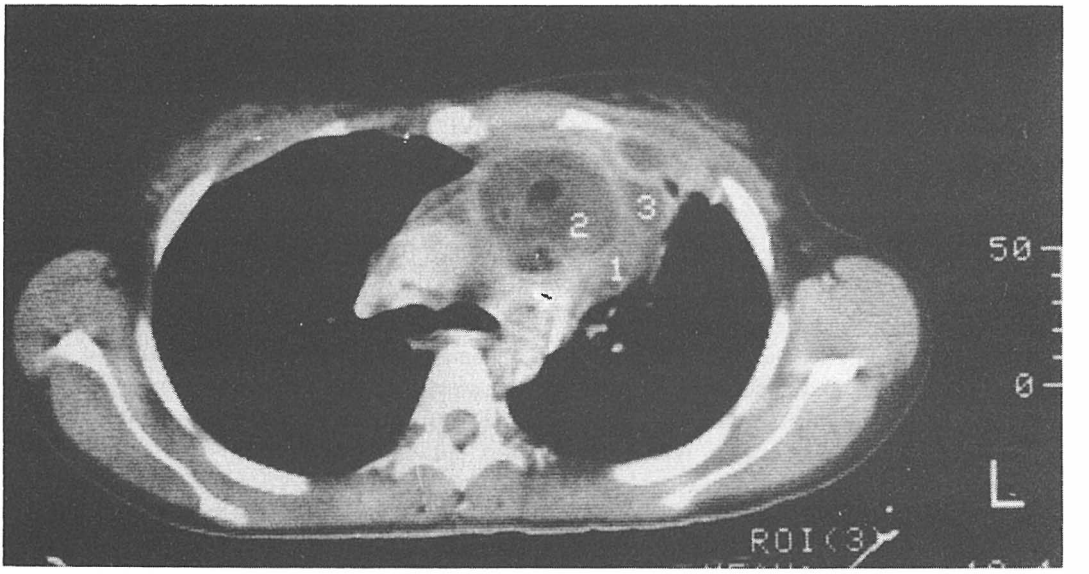

Figure 2a. Transversal CT slice at the level of tracheal bifurcation: clear presentation of the relation between the voluminous cystic tumorous mass of the front mediastinum and thoracic wall and vascular structures (Op. P. H. D.: teratoma cysticum).

neccessary topographic and morphologic accuracy, and in the suspected expansive or infiltrative processes in the mediastinum.[7] (Figure 2 and 2a).

But, this does not refer to every examination and apparature. Remy reports that inadequately obtained scans can be more dangerous than naive unclearness of TMG. In a number of indications CT replaces conventional TMG, which is frequently difficult for interpretation for an unexperienced as well as an experienced radiologist.[3] The examples of accurate indications for TMG are extremelly rare.[7] Therefore the use of lung TMG in the time of CT is questionable. Giron's categorical answer is negative.[5] TMG has to be performed when there is no scanner (out of order, overloaded, geographically distant) and in patients, whose state can be aproximally satisfactorily explained by tomography. If some indications remain to the lung TMG, it is more for the lack of scanner. Complex shadowing detected by conventional radiography has been immediatelly investigated by CT.[9] Conventional lung TMG becomes unnecessary when there is a CT available.

Conclusion

The development of digital technique has resulted in is an important improvement in relation to the conventional techniques. Our preliminary investigation, although performed on a small series, definitely shows the superiority of CT over the conventional TMG which would most probably be omitted, where CT is available. Lung parenchyma is now in digital technique since MR has been developed. But, because of the lack of protons in lung parenchyma it is not able to provide an adequate analysis. The fast development of technology brings about new surprises. Some radiologic techniques will be abandoned, while others will replace them.

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Radiol Oncol 1992; 62: 218-22.

Ultrasound gradation of malignant lymphoma extent

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For five years in the Internal Medicine Department of the Clinical Hospital Centre in Rijeka, the abdomen ultrasound examination has been in use for the purpose of grading the extent of malignant lymphomas. In this presentation our method of work, the preparation of patient, the structure of examination, and the evaluation of the obtained findings are described. A correctly carried out ultrasound examination of the abdomen yields data on any possible pathologic condition of the retroperitoneal lymph nodes, liver, spleen and kidneys affected by malignant lymphatic processes, which is a valuable piece of information for the clinical haematologist in determining the degree of the spread of the disease, and in prescribing the optimal therapy. It also enables the follow up of treatment results, and the entire course of the disease. The method is rated as effective when carried out with an adequate preparation of the patient, a well trained and experienced medical personnel, and a high resolution equipment.

Key words: lymphoma-ultrasonography; neoplasm staging

Introduction

"Malignant lymphomas" is a collective term for a group of diseases characterized by solid tumours formed by an abnormal growth of lymphatic and histiocytic tissue. The growth of lymphocytes or histiocytes, or of both, takes place in the lymph nodes, spleen and lymphatic tissue of digestive organs. The tissue of malignant lymphomas can be found, especially in the terminal stages, also in other organs, either in the form of focuses, of diffuse infiltration.

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UDC: 616.428-006.442-073:534-8

The group comprises Hodgkin's disease and Non Hodgkin lymphomas. Between them there is a great difference regarding the early localization of the disease. In Hodgkin's disease the first localization of the disease occurs in the lymph nodes in more than 90 % of cases, more often than not in the neck, whence the disease gradually spreads. In the case of Non Hodgkin lymphoma 40 %–60 % of the first localizations of the disease may occur outside the lymphatic system, whence it spreads into the lymph nodes and other organs.

A basic factor causing the occurrence of these diseases is the disturbance of lymphocytic transformation, so that the malignant lymphomas can be classified among the diseases of the immune system.[1]

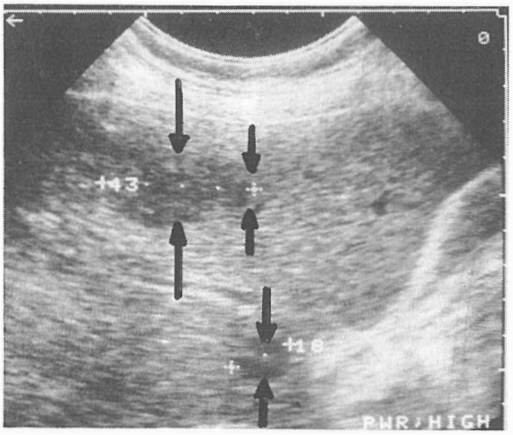

Figure 1. Hypoechogenic Hodgkin's infiltration of the enlarged liver.

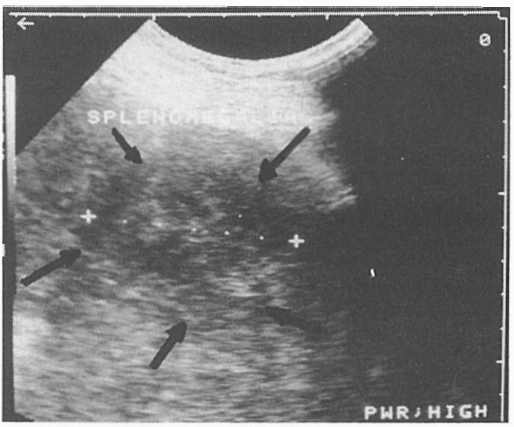

Figure 3. A big Non-Hodgkin's lymphoma of the spleen.

Hodgkin's disease includes four subtypes according to its histological appearance. The presence of Reed-Sternberg cells makes it clearly distinguishable from Non-Hodgkin's lymphoma. According to the Ann Arbor classification the prevalence of the disease is determined in four stages (Stage I, II, III, IV).[1]

Physical examination will reveal enlarged lymph nodes, infrequently in the spleen, but splenomegaly is later on discovered in 25 % to 75 % of the patients. Sometimes the spleen is the only localization of the disease. In the beginning the liver is rarely, but later on more often enlarged. As the disease develops, it may invade practically any organ.[1,2]

Non Hodgkin's lymphomas are histologically classified according to their structure, but also according to their immunological characteristics. The Lukes-Collins and Lennert (Kiel) classifications divide them according to the origin of tumor cells into T-lymphocytic, B-lymphocytic, neither T nor B, and histiocytic types. In addition to that the Lennert's classification also distinguishes between lymphomas of low-grade and high-grade malignancy.

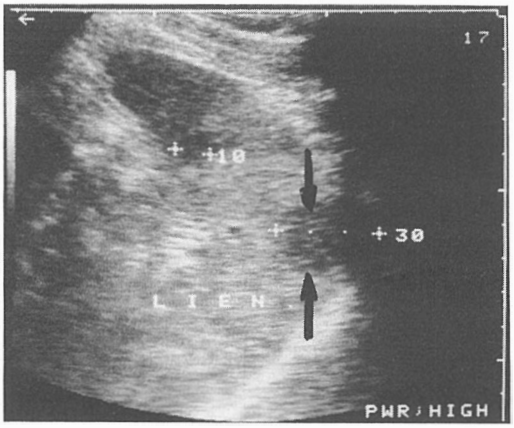

Figure 2. Hypocchogenic solitary Hodgkin's infiltration of the enlarged spleen.

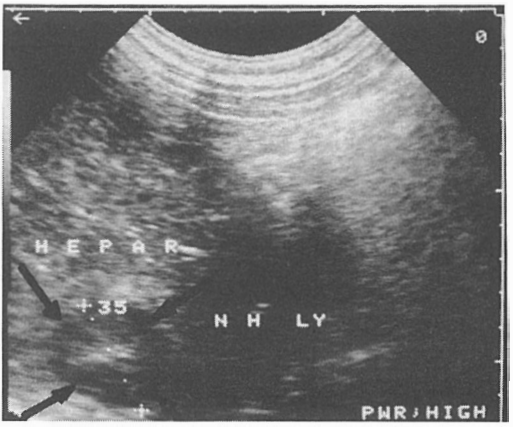

Figure 4. Non-Hodgkin's infiltration of the right lobe of the liver.

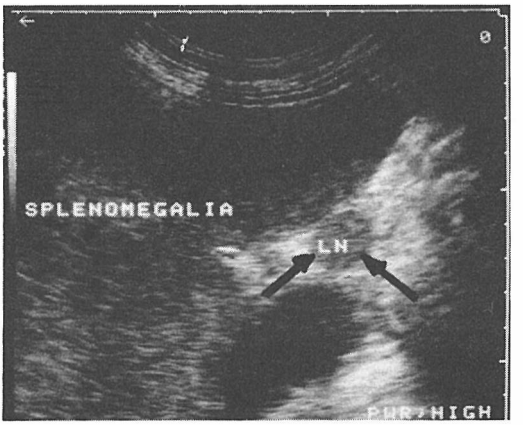

Figure 5. An enlarged hilar solitary lymph node of the spleen (Mb. Hodgkin).

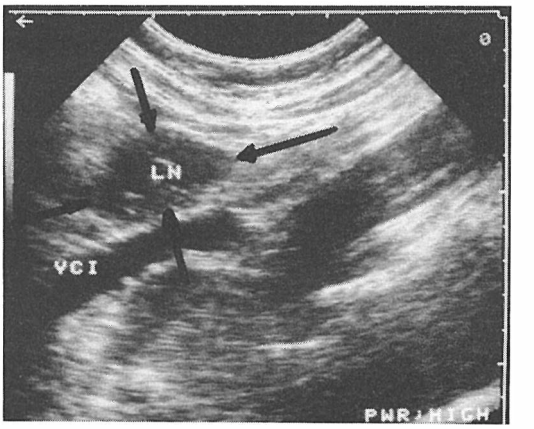

Figure 7. An enlarged paracaval lymph node (Mb. Hodgkin).

When determining the extent of disease, in Non-Hodgkin's Lymphomas, the same criteria as for Hodgkin's disease are applied (Stage I, II, III, IV).[1,2]

Material and methods

Malignant lymphomas are diagnosed cytologically and histologically. The material for the analysis is obtained by ultrasound-guided needle biopsy of the abdominal lymph nodes surgical extirpation of lymph nodes, blind needle biopsy of the enlarged spleen, ultrasound guided needle biopsy of focal lesions of the spleen, needle biopsy of bone marrow, and interoperatively by taking specimens from the alimentary tract. Apart from an early diagnosis, a precise determination of the extent of disease is indispensable for choice of proper therapy. To ascertain the presence of disease in the chest the method of choice is computerized tomography. Whereas for determining the presence of disease in the abdomen we preferably use ultrasound.

In our institution, lymphography of the abdomen is not applied, whereas the use of computerized tomography is restricted owing to high-

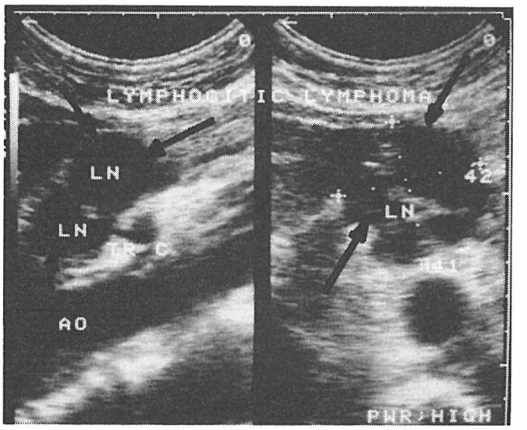

Figure 6. Enlarged paraaortic lymph nodes in Non-Hodgkin's lymphocytic lymphoma.

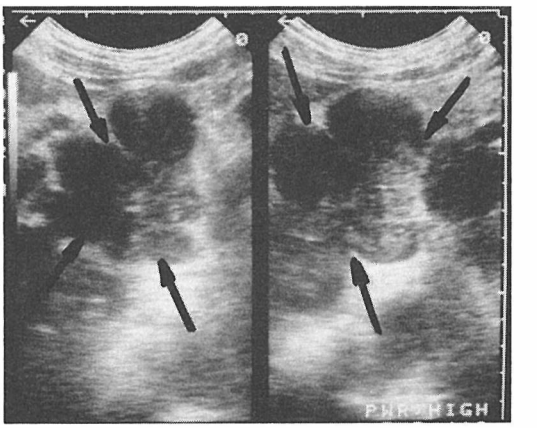

Figure 8. A retroperitoneal lymph nodal package (Non-Hodgkin).

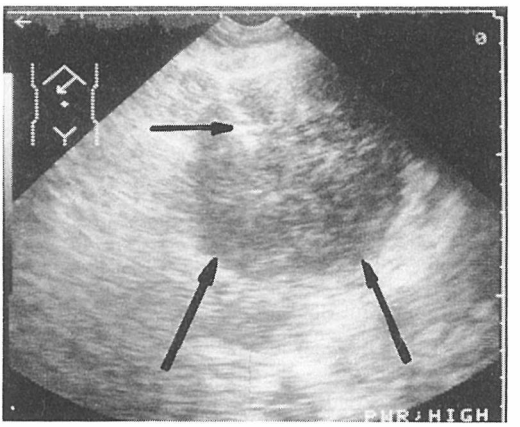

Figure 9. Cytobiopsy of the enlarged retroperitoneal lymph node-the top of the needle in the lymph node.

costs, and because the exposure to ionizing rays renders it unsuitable for repeated application or checkup.

Ultrasound of the abdomen is used during primary workup, suplemented by ultrasound guided needly biopsy, and repeated as a follow-up examination.

Our clinic carries out 7000 examinations by ultrasound a year; 180 of these are ordered by the Haematology Department or from the Haematology Outpatient Clinic. In the last five years 123 patients with malignant lymphomas have been examined by ultrasound. With these patients a detailed and high-quality ultrasound exploration of the whole abdomen is necessary, so the following rules are adhered to:

1. the alimentary tract should be cleaned and the patient should be on an empty stomach,

2. an analysis of the liver, spleen and retroperitoneum is to be carried out by means of subcostal and intercostal sections, both transversal and longitudinal,

3. screening of the complete abdominal aorta, inferior vena cava and other abdominal blood vessels,

4. with some patients, for the purpose of a detailed analysis of the superior retroperitoneum, the examination is carried out on a stomach filled with liquid.[3]

With patients suffering from malignant lymphoma a complete ultrasound analysis consists of the following data:

1. statement whether the liver is enlarged and whether it shows evidence of focal lesions,

2. statement whether the spleen is enlarged and whether is shows evidence of local lesions,[4]

3. statement whether the focal lesions of the spleen and liver, if any, can be reached by ultrasound-guided target biopsy,[5,6]

4. statement whether the retroperitoneal lymph nodes are enlarged and whether they can be reached by ultrasound-guided target biopsy,[5,6]

5. statement whether the topoanatomical connections of the abdominal blood vessels are normal or not,

6. statement whether the sonographic findings of the kidneys are normal, or there are any irregularities.

The screenings were carried out on a HITACHI EUB 410 apparatus, and sector and convex probes of 3,5 and 5,0 MHz.

Results und discussion

Out of the total of 123 patients suffering from malignant lymphoma subjected to ultrasound screening of the abdomen (most of them for more than once), 86 (70 %) manifested the presence of the disease in the abdomen. Enlarged retroperitoneal lymph nodes were found in 62 of the patients (50 %), Enlarged liver or spleen of homogeneous structure were found in 37 of them (30 %), whereas focal lesions in the liver or spleen were found in 12 patients (10 %).

Analysing the pathological changes in the abdomen found by ultrasound, certain regularities have been noticed, namely:

1. the retroperitoneal lymph nodes, solitary or in packages are, as a rule, of a homogeneous hypoechogeneous structure,[7]

2. the focal lesions of the spleen or liver are, as a rule, of hypoechogeneous structure, although we may find also mixed echogeneity, or even areas of hyperechogenity in them,[4,8]

3. hepatomegaly and splenomegaly without focal lesions, are mostly presented as normoechogeneous, infrequently as hypoechogeneous,[9]

4. we have not found an ultrasound criterion according to which an enlarged spleen or liver could be defined as a diffuse lymphatic infiltration.[9]

Conclusion

Today the value of sonographic screening of the abdomen in patients suffering from malignant lymphoma is indisputable.

The examination is important in the primary workup of the patient, but it is of paramount importance when determining the extent of disease which directly influences the choice of optimal therapy.

With 70% of the patients the abdominal organs are affected by the disease. Ultrasound is very important in the follow-up of treatment results and the total course of disease, since, for the difference from other kinds of examination, it can be repeated as it is simple, harmless and inexpensive.

When carrying out the examination, the mentioned rules have to be adhered to in order to obtain findings that could be of value to the heamatologist and therapist.

If the screening is carried out on a highly efficient apparatus and by experienced ultrasound specialists, the examination will prove to be a valuable method, indispensable in modern haematology.

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Serum TNF-α levels in melanoma-bearing and healthy mice

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To determine differences in tumor necrosis factor-α (TNF-α) persistency after TNF-α therapy, serum levels were monitored in tumor bearing and healthy mice. Melanoma B-16-bearing mice were treated peritumorally and healthy mice subcutaneously with recombinant human TNF-α, lacking 1-3 amino acids from N-terminal part (TNF-αNv3). In healthy mice the peak TNF-α serum levels were detected one hour after application, while in tumor-bearing mice two hours after application. Also TNF-α elimination from serum of tumor-bearing mice was slower compared to healthy mice. The data suggest that TNF-αNv3 pharmacokinetic mechanisms in tumor-bearing and healthy mice are different.

Key words: tumor necrosis factor; pharmacokinetics; melanoma, experimental; mice

Introduction

Tumor necrosis factor-α (TNF-α) is a monocyte/macrophage derived protein, originally identified by its ability to induce haemorrhagic necrosis of some tumors *in vivo*[1] and cytotoxicity against certain tumor cells *in vitro*.[2] The results of clinical trials with recombinant human TNF-α indicate that the side effects of TNF-α treatment can be severe.[3,4] For rational dose regimen, which could diminish the side effects, it is important to know how TNF-α is absorbed from the site of application, distributed through the body, and its activity preserved.

Despite the fact that TNF-α activity is at least partially species specific, animal models were often used to study pharmacokinetics of human TNF-α. However in all previous pharmacokinetic studies in mice,[5] rats,[6,7] rabbits and monkeys,[8] human recombinant TNF-α was applied to healthy animals.

Therefore the aim of our study was to compare absorption and distribution of human TNF-α in tumor-bearing and healthy mice. Besides antitumor effect, serum TNF-α levels were measured after local TNF-α application. Human recombinant TNF-α, lacking 1-3 amino acids from N-terminal part (TNF-αNv3), was applied peritumorally in melanoma B-16 bearing mice and subcutaneously in healthy mice.

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Materials and methods

Animals

Inbred C57Bl/6 mice were purchased from Rudjer Bošković Institute, Zagreb, Croatia. Animals were maintained in constant room temperature (24^0C) at a natural day/night cycle in a conventional mouse colony. Mice in good condition, without signs of fungal or other infections, 8-10 weeks old, were used in the experiments.

Tumors

Melanoma B-16 was maintained in C57Bl/6 mice by serial transplantation. Tumor cells from the fourth isotransplantat generation were prepared for the described experiments by gentle mechanical disagregation. Solid subcutaneous tumors, dorsolaterally in animals, were initiated by injection of 5×10^5 viable melanoma cells. The viability of the cells was determined by trypan blue dye exclusion test.[9]

Tumor necrosis factor

Recombinant human tumor necrosis factor-α analog, lacking 1-3 amino acids from N-terminal end (TNF-αNv3), was used (ZIMET, Jena, Germany). Specific activity was 2.2×10^7 U/mg, tested on L929 cells in the presence of actinomycin-D. Other properties of TNF-αNv3 were described before.[10] TNF-αNv3 was diluted in PBS (pH 7.4) before use.

Treatment

TNF-αNv3 was administered subcutaneously in tumor free and peritumorally in tumor-bearing mice.[9] The treatment was started when the tumors reached 30-40 mm^3 in volume. TNF-αNv3 application dose was 2 x 10^5 U per animal, which gave 9 x $10^3 \pm 1039$ U/g of animal.

Tumor measurement

Tumor growth was followed by measuring three mutually orthogonal tumor diameters with a Vernier calliper. Tumor volumes were calculated by formula $\pi/6 \cdot a \cdot b \cdot c$ (a, b, c are tumor diameters). From the measurements, arithmetic means (AM) and standard errors of the means (SE) were calculated for each experimental group with minimum of 10 mice. Growth delay of the tumors was calculated from individual tumor growth, by determining the time required for tumor to reach 150 mm^3 of volume, and subtracting the relevant time in the control group.[9,11]

Blood sample collection and handling

One day before TNF-αNv3 application blood was collected from all animals in the experiment for monitoring the serum TNF-α level. After the application of TNF-αNv3 blood samples were taken from four animals at the times indicated in the figures. Blood was collected from the orbital sinus of the animals, immediately centrifuged (3000 rpm/min) for 10 min at 4° C and sterilised by filtration (0.22 μm cellulose acetate filter, Costar). Samples were stored at -70° C for TNF-α assay.

Cells and culture conditions

L929 murine transformed fibroblasts were obtained from Istituto Zooprofilattico Sperimentale, Brescia, Italy. Cells were cultured in Eagle's minimal essential medium (EMEM) with 10% fetal calf serum (FCS). Incubation was carried out at 37° C in a humidified 5% CO_2 incubator.

Determination of TNF-α serum concentrations

a) L929 bioassay. Cytotoxicity of TNF-α was determined on L929 cells[12] in the presence of actinomycin D. The viable cells density was determined 20 h after TNF-αNv3 treatment.

Culture medium was removed and the cells, fixed with glutaraldehyde, were stained with crystal violet (0.5 % in 20 % methanol). Bound dye was eluted with 0.1 ml of 1% sodium dodecyl sulfate. The optical density was measured at 540 nm using microplate photometer CLS962 (Cambridge Life Sciences plc). Cytotoxic activity expressed as TNF-α U/ml was defined as the reciprocal of the dilution which gives 50% cell killing. The detection limit of the assay was 40 U/ml of serum. Cytotoxic activity for one sample was calculated as AM of six independent measurements. AM of three TNF-αNv3 activities in sera prepared from three mice in test group, are presented in figures.

b) TNF-α ELISA. Immunologically active TNF-α was determined by a "sandwich" enzyme immunosorbent assay (ELISA) specific for human TNF-α (Du Pont). The detection limit was 100 pg/ml of serum. TNF-αNv3 value for one sample was calculated as AM of two independent measurements. AM of three TNF-αNv3 values in sera prepared from three mice in test group, are presented in the results.

Statistical evaluation

The results were evaluated by Student's unpaired probability test and correlation coefficient. All statistical procedures were computed using CSS Programme Stat Soft. Levels of less than 0.05 were taken as indicating significant differences.

Results

Antitumor effect of TNF-αNv3

Melanoma B-16-bearing mice were treated peritumorally with 2 x 10^5 U TNF-αNv3, when tumors reached average tumor volume 34.4 ± 3.9 mm^3. Tumor growth delay after TNF-αNv3 treatment (3.8 ± 0.4 days) was significant ($P < 0.05$), compared to tumor growth in control animals, which were treated with physiological saline (Figure 1). No side effects were observed after peritumoral treatment with TNF-αNv3.

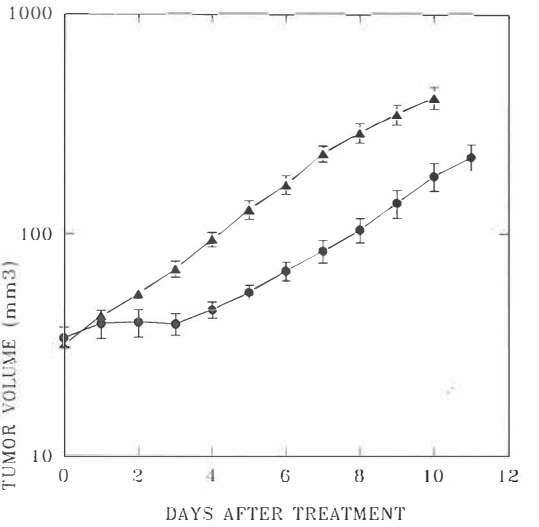

Figure 1. Antitumor effect of TNF-αNv3 on subcutaneous melanoma B-16 after peritumoral (●) treatment with TNF-αNv3 (2 x 10^5 U/mouse); controls (▲).

Endogenous TNF-α levels in mice before application of TNF-αNv3

Endogenous serum TNF-α levels were measured with L929-cell assay method, in sera collected one day before the TNF-αNv3 application from tumor-bearing and healthy animals. In all serum samples tested (15 from healthy and 24 from tumor bearing animals), endogenous TNF-α levels were below the reliable detection limit (40 U/ml) of the method.

The same serum samples were tested also on ELISA to test the method for possible interference of other immunological substances. Results were negative for all serum samples. This confirms that no component in the murine serum, prepared as described, interferes with our ELISA assay system.

Serum levels of TNF-αNv3 after peritumoral application

Serum TNF-α concentrations in B-16-melanoma bearing mice were compared to concentrations of TNF-α in healthy mice without tumors. Tumor-bearing mice were treated peritu-

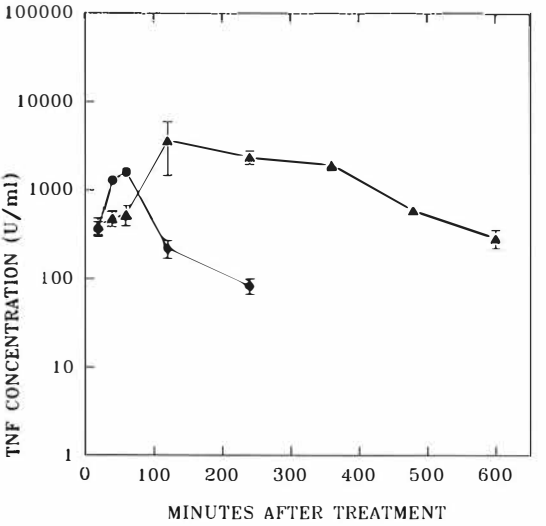

Figure 2. Mean ± SE serum levels time curves of cytotoxically active TNF-αNv3 after peritumoral application (2 x 10^5 U/mouse) in B-16-bearing (▲) and healthy mice (●).

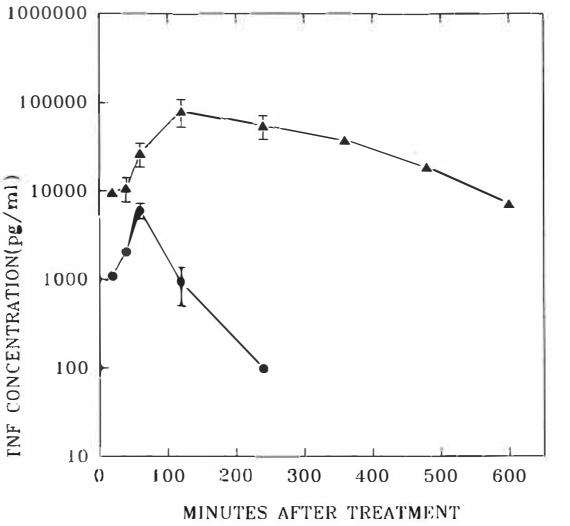

Figure 3. Mean ± SE serum levels time curves of TNF-αNv3 antigen after peritumoral application (2×10^5 U/mouse) in B-16-bearing (▲) and healthy mice (●).

morally, while healthy mice subcutaneously with 2 x 10^5 U TNF-αNv3. In the same serum samples, TNF-α cytotoxic activity (Figure 2) and immunologically active TNF-α molecules (Figure 3) were determined. Delayed TNF-α serum peak levels were observed in tumor-bearing mice (120 min.) compared to healthy mice (60 min.). Also, TNF-α serum concentrations were higher in tumor-bearing mice. The highest TNF-α serum level in tumor-bearing mice was 3.6 x 10^3 U/ml (L929 assay) or 8 x 10^4 pg/ml (ELISA), and 1.6 x 10^3 U/ml or 6 x 10^3 pg/ml in healthy mice ($P < 0.05$ in both assays). High TNF-α serum levels persisted in tumor-bearing animals, compared to quick clearance from healthy mice. Ten hours after TNF-αNv3 application its level in tumor bearing animals was 2.8 x 10^2 U/ml or 7 x 10^3 pg/ml, while in healthy mice already after four hours dropped to 83 U/ml or 1 x 10^2 pg/ml.

Discussion

The *in vivo* antitumor effects of murine TNF-α[13] and human TNF-α[14] have been reported on different murine tumors transplanted in syngenic mice. In our previous study antitumor effects of TNF-α analog TNF-αNv3 after peritumoral application was established on SA1 sarcoma and B-16 melanoma tumors.[9,11] In this study the potent antitiumor effect of TNF-αNv3 is reconfirmed on B-16 melanoma tumors.

The results of TNF-α serum level measurement show that TNF-αNv3 pharmacokinetic mechanisms in tumor-bearing and healthy mice are different. TNF-α concentration-time profiles, presented in Figures 2 and 3 indicate, that TNF-α in serum of B-16-bearing mice persists longer than in serum of healthy mice.

TNF-αNv3 was measured in sera cytotoxically and immunologically in tumor-bearing and healthy mice after peritumoral or subcutaneous application, respectively. Relationship between results obtained by the two assays shows almost perfect positive correlation ($R = 0.88$ for healthy and $R = 0.98$ for tumor-bearing mice). Besides, it was established that no component from sera interfered with ELISA assay used. Although TNF-α levels were often found to be increased in sera of cancer patients[15] we didn't detect endogenous TNF-α before TNF-αNv3

application neither in sera from healthy nor in sera from tumor-bearing mice. Therefore we believe that all TNF-α activity detected in serum originates from TNF-αNv3 applied.

The influence of B-16 tumor on the persistence of TNF-α activity in serum is documented for the first time. If other tumors also affect the persistence of TNF-α serum concentration in a similar way, the pharmacokinetic parameters from healthy animals can not be extrapolated to tumor-bearing animals; consequently for the prediction of human therapy only pharmacokinetic data obtained by tumor-bearing animal models can be used.

In conclusion, this study demonstrates that peritumoral treatment with TNF-α analog, lacking first three amino acids from N- terminal part, has antitumor effect on B-16 tumors. Comparison of TNF-α serum concentration-time profiles in tumor-bearing and healthy mice, indicate that the absorption, distribution and/or metabolism of TNF-Nv3 in B-16 tumor-bearing mice are significantly different from those in healthy mice. The mechanism for mentioned differences between tumor-bearing and healthy mice remains to be clarified in further studies.

Acknowledgement

The financial support by grant A185 of the Ministry for Science and Technology of Slovenia is gratefully acknowledged.

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Radiol Oncol 1992; 26: 228-32.

The influence of a moderately increased dose of vitamin E on 20-methylcholanthrene induced tumorigenesis in mice

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The influence of a moderately increased dose of vitamin E on tumorigenesis of 20-methylcholanthrene-induced tumours in mice was investigated. A tendency to enhancement was observed. In the experimental groups of mice the average latent period of tumours was markedly shorter than in the control groups, although the difference was not statistically significant.

Key words: neoplasms, experimental; methylcholanthrene; vitamin E; mice

Introduction

The effect of vitamin E on tumorigenesis was experimentally studied by varous authors. The results obtained were, however, highly inconsistent. Some reported an inhibitory effect of high doses of vitamin E, others observed no effect, or even an enhancing effect. The results of epidemiological studies also were controversial, which calls for further investigation of the effects of various doses of vitamin E on tumorigenesis.

The present study was undertaken to determine if excess vitamin E has an inhibitory or a stimulatory effect on 20-methylcholanthrene induced tumorigenesis in mice. Since other authors usually used very high doses of vitamin E, we decided to investigate the effect of only moderately increased doses of vitamin E.

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UDC: 616-006.6-092.9:615.356

Materials and methods

Experiment 1

Forty young female mice weighing on average 22 g were injected subcutaneously in the right hind-leg 1 mg 20-methylcholanthrene (Sigma) in 0.1 ml olive oil and then divided into the control group (Group 1) and the experimental group (Group 2). The mice were housed 5 per cage. The control group was fed a pelleted experimental diet consisting of natural ingredients, without addition of vitamins, according to the formula shown in Table 1. Vitamins were given in drinking water. The solution of vitamins was prepared as shown in Table 2. Each mouse received 4 g of pellets and 4 ml of vitamin solution daily. The experimental group was fed the same pellets, but the solution of vitamins they received contained 240 mg vitamin E/l instead of 60 mg/l. Thus, Group 2 received 4 times as much vitamin E as Group 1.

The mice were inspected for a palpable tumour one month after injection of the carcinogen, and then once weekly. The mice which developed tumours were marked with fuchsin

Table 1. Composition of the experimental diet without vitamin supplements.

Wheat meal	40,00 %
Barley	2.00 %
Soyabean meal	13.00 %
Fish meal	15.00 %
Salt	1.00 %
Limestone	0.75 %
Sugar	2.00 %
Magnesite	0.25 %
KJ	3.92 mg/kg
$ZnSO_4 \times 7\,H_2O$	1187.33 mg/kg
MnO_2	166.58 mg/kg
$CoSO_4 \times 7\,H_2O$	1.43 mg/kg
$FeSO_4 \times 7\,H_2O$	188.60 mg/kg
$CuSO_4 \times 7\,H_2O$	549.45 mg/kg

Table 2. Composition of vitamin solution.

Vitamin	Amount/l drinking water
Vitamin A (retinol)	7000 IU
Vitamin D_3	300 IU
α-tocopherol	60 mg
Vitamin K_1 (Konakion Roche)	1.5 mg
Thiamine dichloride	4.0 mg
Riboflavin	5.0 mg
Vitamin B_6	6.0 mg
Nicotinic acid	10.0 mg
Calcium D(+) pantothenate	12.0 mg
Vitamin B_{12}	5.0 μg

or methylen blue solution. The date of the appearance of the initial tumour was recorded. The size of the tumour was recorded on first palpation, and then weekly until death.

The experiment was terminated when the last animal with a tumour died. The results were analysed with respect to the incidence of tumours, the length of the latent period and the length of survival with tumour.

Experiment 2

Experiment 2 was en exact repetition of Experiment 1. It was carried out to confirm the result of the first experiment.

Results

Experiment 1

In Group 1, tumours occurred in 16 mice; 2 mice died intercurrently and 2 survived without tumour. In Group 2, which received 4 times as much vitamin E as Group 1, tumours occurred in all 20 mice. Group 2 showed a slightly higher incidence of tumours, yet the difference between the groups was not significant. The influence of increased dose of vitamin E on the duration of latent period is shown in Table 3.

Table 3. Latent periods of tumours induced by 20-methylcholanthrene in the control group and in the group receiving high-dose vitamin E.

Group of mice	Latent periods of tumours in days
Group 1 (controls)	77, 84, 91, 91, 98, 98, 105, 112, 112, 119 119, 126, 175, 179, 182, 231
Group 2 (high-dose vitamin E)	77, 77, 77, 77, 77, 77, 84, 84, 91, 91, 91, 98, 98, 105, 105, 119, 119, 119, 156, 217
The average latent period:	Group 1: 124.93 days Group 2: 101.95 days.

The average latent period in Group 1 was 124.93 days, and in Group 2, receiving increased dose of vitamin E, only 101.95 days.

It is evident that a moderately increased dosage of vitamin E used in this experiment markedly shortened the latent period of tumours, i.e. it markedly enhanced tumorigenesis induced by 20-methylcholanthrene. The difference in the length of the latent periods between Group 1 and Group 2 is, however, not statistically significant ($p > 0.05$).

The average survival time with tumour was 35 days in Group 1 and 38.1 days in Group 2. The difference between both groups was not significant.

Experiment 2

In Group 1, 17 mice developed tumours; 1 mouse died intercurrently and 2 survived without tumour. In Group 2, which received 4 times as much vitamin E as Group 1, tumours occurred in 18 mice; 1 mouse died intercurrently and 1 survived without tumour. The influence of increased doses of vitamin E on the duration of latent period is shown in Table 4.

The average latent period in Group 1 was 107.94 days, and in Group 2 receiving increased doses of vitamin E only 89.05 days.

Table 4. Latent periods of tumours induced by 20-methylcholanthrene in the control group and in the group receiving high-dose vitamin E.

Group of mice	Latent periods of tumours in days
Group 1 (controls)	65, 72, 79, 79, 86, 93, 99, 99, 106, 113 113, 127, 127, 134, 141, 147, 155
Group 2 (high-dose vitamin E)	65, 65, 72, 72, 72, 72, 72, 86, 86, 93, 99, 99, 99, 106, 106, 106, 113, 120
The average latent period:	Group 1: 107.94 days Group 2: 89.05 days.

In the second experiment a moderately increased dosage of vitamin E markedly shortened the latent period of tumours, i.e. it markedly enhanced tumorigenesis induced by 20-methylcholanthrene. Again, the difference in the length of the latent periods between Group 1 and Group 2 was not statistically significant.

The average survival time with tumour was 40.62 days in Group 1 and 34.5 days in Group 2. The difference between the groups is not signifficant.

Discussion

In our study an enhancement of tumorigenesis in mice given a moderately increased amount of vitamin E was observed. The degree of enhancement was, admittedly, not statistically signifficant, but it was observed in two independent experiments, suggesting that the observed difference in the duration of latent periods between control and experimental mice was not coincidental. At any rate, our findings do not support the view that excess vitamin E has an inhibitory effect on tumorigenesis, but, on the contrary agree with the experimental results of several authors who observed a similar tendency to enhancement of tumorigenesis, or even a statistically signifficant enhancement due to high doses of vitamin E.

Temple and El-Khatib[1] studied the effect of vitamin E on the development of colon tumours in mice treated with 1.2-dimethylhydrazine. Compared with mice fed the control diet, those given vitamin E had a higher colon tumour incidence. This effect, which was stronger in females, was due to an increased incidence of adenomas.

Toth and Patil[2] also observed an enhancing effect of vitamin E on murine intestinal tumorigenesis induced by 1.2-dimethylhydrazine dihydrochloride. Vitamin E acetate (dl-α-tocopheryl acetate) at a 4% dose level enhanced tumour induction in the duodenum, cecum, colon, rectum and anus. The increased incidence of tumours was statistically significant.

Glauert et al.[3] studied the effect of dietary vitamin E on the development of altered hepatic foci and hepatic tumours induced by peroxisome proliferator ciprofibrate. They found that the incidence of hepatic tumours and the number and volume of altered hepatic foci were increased in rats fed larger amounts of vitamin E. The authors concluded that increasing dietary vitamin E enhances ciprofibrate-induced hepatocarcinogenesis.

Rockwood Telford[4] observed an enhancing effect of vitamin E (α-tocopherol) on tumorigenesis in mice injected with dibenzanthracene. She studied the effect of hypo- and hypervitaminosis E on the growth of lung tumours in mice and noted that the incidence of lung tumours was greatest in the hypervitaminosis E groups and so was the average number of lung tumours per animal. The hypovitaminosis group, in contrast, had the smallest number of tumours per animal.

Okishio[5] noted that supplementing basal diet with vitamin E markedly increased the incidence of tar carcinoma in rabbits.

Reddy and Tanaka[6] studied the interactions of selenium deficiency, vitamin E, polyunsaturated fat, and saturated fat on azoxymethane-induced colon carcinogenesis in male rats. They observed that the multiplicity of colon adenocarcinomas was increased by excess vitamin E in the diet.

Devor et al.,[7] who studied carcinogenicity of fecapentaene-12-diacetate on skin painting in mice, found an increased incidence of tumours, yet the difference observed was not statistically significant, when DAFP-12 was co-administered with vitamin E.

Some authors noticed no effect of high doses

of vitamin E on tumorigenesis in mice or rats treated with 3, 4, 5, 10-dibenzpyrene or 7, 12-dimethylbenzanthracene.[8, 9, 10]

In contrast to these reports, several authors interpreted their experimental data as supporting the hypothesis that high doses of vitamin E protect against carcinogenesis. The conclusions of some of these studies, e.g. those by Haber and Wisler,[11] Cook and MacNamara,[12] Kurek and Corvin,[13] however, are not very convincing: they compared the effect of diets rich in vitamin E with a diet deficient in vitamin E, or a diet containing relatively small amounts of this vitamin. In our opinion, the results obtained indicate that vitamin E deficiency increases the susceptibility of animals to tumour formation and do not suggest that high doses can protect against it.

Our view is supported by several studies[9, 14, 15] demonstrating that vitamin E deficiency increases the incidence of tumours.

Only a small number of experimental studies support the view that high doses of vitamin E have a protective effect on tumorigenesis.[16, 17, 18, 19, 20]

Some of these studies, however, were performed under special conditions. So Harman[16] supplemented the diet of rats with a very large amount of polyunsaturated fat (20% by weight of corn oil). Shamberger and Rudolph[17] applied vitamin E topically concomitantly with the tumour-promoter, croton oil. In chemoprevention of cancer, however, only oral consumption of a potentially anticarcinogenic substance is to be considered.

In our opinion the results of epidemiological studies, which are highly conflicting, do not indicate that high dose vitamin E could be used as a chemopreventive agent against cancer. The finding that subjects with serum levels of vitamin E in the lowest quintile are at a higher risk of developing cancer than persons with levels in the highest quintile[21, 22, 23] does not justify the conclusion that excess doses of vitamin E are beneficial, as another interpretation of these observations can also be that vitamin E deficiency or relative (marginal) deficiency have an adverse effect.

One should take care to avoid vitamin E deficiency. The best way to supply the organism with an adequate amount of vitamin E (and of other vitamins) is undoubtedly to eat a balanced, mixed diet containing sufficient amounts of vegetables and fruits.

Although the intake of supplements of high doses of vitamin E for chemoprevention of cancer does not seem justified, normal (physiological) amounts of vitamin E in a balanced diet certainly play a role in the protection against cancer as confirmed by the adverse effect of vitamin E deficiency.

Acknowledgement

We are indebted to Prof. M. Štruklec from the Faculty of Veterinary Medicine in Ljubljana for the preparation of experimental diet for mice and to Prof. Š. Adamič from Medical Faculty in Ljubljana for statistical analysis.

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Radiol Oncol 1992; 26: 233-8.

The development of radiology in Republic Macedonia

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The author presents in chronological order the development of radiology in the Republic of Macedonia, describing all the difficulties which generally go hand in hand with such a development. Based on the available literary data, the state in this branch of medicine till the establishment of the Institute of Radiology and afterwards is presented.

Key words: radiology-trends; Macedonia

The development of radiological service in Republic Macedonia can be regarded as a long, laborious and slow process.

Far back in 1895, Wiliam K. Roentgen by his discovery of X-rays enriched the humankind and medical science with a powerful diagnostic aid. The available literature shows that some countries soon made use of that new facility and thus contributed to the development of radiology, the youngest of medical disciplines.

According to the chronology of further development, the first radiogram of Mrs Roentgen's hand was not the only event which fascinated the world in that December. Already in the following year, the new discovery found its practical application in pediatric diagnostic radiology which represented the youngest branch in radiology. Thus, on January 17, 1896 in Berlin Klingerbert and Slaby presented a fracture of the radius, whereas ten days later radiographic presentation of osteomyelitis, and in February of the same year the first radiogram of a fetus *in utero* could be seen.[1]

Unexpectedly, the first roentgen apparatus did not appear in Skopje, but in Bitolj in 1921. It was owned by chief of the General Hospital, Dr. P. Avramović. Also the second X-ray machine was installed in Bitolj as a property of Dr. Osmanlija who had studied in Chicago and set up a private practice after his return from America. According to the results of investigation by D. Ivanovski, registered radiol. technician there were no other roentgen machines available in Macedonia at that time.[2]

Skopje got its first X-ray machine in 1935; it was installed in Zem hospital. This was a four-wave Tuto Helioscope which had served to several generations of radiologists and radiotechnicians for taking radiograms, digestive tract examinations, bronchoscopies and other all until it was replaced by a more advanced unit. The first machine was situated in an old wooden hut of a former anti-malaria dispensary, without any protection of the building or personnel.

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UDC: 615.3(497.17)

In the following period, from 1936 to 1937, two new X-ray machines – probably semi-wave – were installed; both were the property of our first primarius and radiologist Dr. I. Atanasov.

In the impoverished post-war period, a rapid development of radiological service could not be expected. The first attempts reflected in the establishment of centers intended for the treatment of tuberculosis the incidence of which was at that time very high. Thus, the antituberculosis service in the village Lešok near Tetovo obtained its first X-ray machine, a "Picker 2" from UNICEF in 1948. From then on, a more rapid development of antituberculosis service was associated with more X-ray machines being installed in the centers in Strumica, Gostivar, Bitola and Titov Veles. All those centers were assisted by the Anti-tuberculosis service of SR Macedonia and its leading center in Skopje at the Institute of Breast Diseases and Tuberculosis.

In 1947, together with the foundation of Medical Faculty in Skopje, some other institutions – among them also the Institute of Radiology – were established. Thus the roentgen department of Zem hospital became an institute, though in name only. There were no major changes made with respect to economy or personnel. Radiology did not partake in the rapid development observed in other institutions. This could be partly ascribed to the insufficiency of radiologic personnel at the level of whole Yugoslavia, and partly to the lack of financial means needed for the purchase of expensive equipment. The establishing of Medical Faculty as early as two years after the liberation was not in favor of the needs of Radiological Institute which required a substantial financial support. Therefore, due to the lack of equipment, the professional staff there was mainly involved in routine work. Within the first years of its existence, the Institute of Radiology was situated in four single-story rooms within the frame of Surgical Clinic. The previously mentioned machine was purchased in 1935 and has been fully redeemed. In order to prevent the machine from falling apart, the parts often had to be tied with a rope. The dark room was rather primitive without the essential conditions for quality work.

The second machine was an American version of Phillips PX-200 unit with a Dynamix X-ray tube. It was of massive construction with wide footing, and was used for tomographic imaging. The possibility of height adjustment by lifting enabled the machine to be used also for other radiologic investigations requiring sitting or standing position of the patient. Quality radiograms could be obtained by that machine due to its good technical characteristics. In 1967 it was handed over to the Medical Center in Ohrid.

Despite the mentioned deficiencies, the Institute of Radiology managed to function relatively successfully. The only radiologist on staff was Prim. I. Anastasov who had speicalized by Prof. Smokvina in Zagreb. He was joined by a young coworker Dr. Tevčev, and an unqualified radiological technician who was trained to handle an X-ray machine as well as to work in the dark room. The staff included also 2 clerks. The first resident was Dr. Kotnik from Slovenia who worked at the Clinic of Surgery. Later on, another physician – resident (volunteer) and a year later yet another joined the staff.

Though slowly, the Institute of Radiology began to face brighter perspectives. The young physicians insisting on the Institute's physical expansion, managed to obtain two additional rooms for out-patient service and an examination room for radiotherapy patients (a part of the cabin belonging to the Secondary Medical School situated near the Clinical Hospital). By voluntary work of the staff, two machines that had been staying inactive for a long time were adapted for use. Later on, the Institute acquired two more midwave units for out-patient purposes.

In the following years, the Institute managed to obtain a new X-ray machine – Super DH 4-wave with 2 working places adapted for tomography, which greatly improved the quality of work.

In 1955, Assist. Prof. Dr. Tadžer was appointed acting director of the Institute, and two

years later the staff was joined by Assist. Prof. Dr. S. Stavridis, urologist.

The year 1957 was important for further development of the Institute as it acquired new facilities for diagnostic and radiotherapeutic department together with a new machine.

A year earlier, an apparatus for radiotherapy was installed at the Institute of radiology. This was a Multivolt with 180 kV power, which was used by Prim. Dr. K. Popović. Thus, radiotherapy on in-patient basis was started. By then, radiotherapy moved to the place of the future mycotic centre of SRM. Beside the old apparatus, a new unit for deep irradiation therapy, i.e. Stabilipan with convergent rotation and 200 kV power, was obtained. The in-patient radiotherapy ward comprised 40 beds. Thus, the treatment could be performed under permanent monitoring of the physician.

In 1956, diagnostic radiology got place in the former rheumatic center of the newly built Clinical hospital. Thus, the conditions for work had been significantly improved. A few diagnostic units, as well as a dark room and a doctor's office were formed. At the same time a new Tridoros III machine with two working places was installed; one place was used for planigraphy whereas the other remained empty.

After having obtained the title of assistant professor, in the beginning of 1958 Dr. D. Tevčev was appointed the acting director of the Institute. This represents a milestone in further development of the Institute which reflects in a number of changes and improvements occurring in the years 1958–1961.

The Radiotherapy Department obtained a Picker machine for surface therapy and a Chaul for contact irradiation. The 652 mg of radium from Military Medical Academy that had been stored there were returned to the owner as they were found unsuitable for use.[3] Diagnostic radiology: the second working place with a coordinating chair for angiography was filled with a unit for angiography according to Venclih and Pesler, and a new 4-valve Siemens machine was purchased. In this period the staff was enhanced by a number of young physicians interested in radiology. As a result, the majority of specialists at the Institute obtained the required education. The problem of insufficient number of radiotechnicians and their training remained to be solved.

In such situation a new approach to solving the urgent problems of radiotherapy patients was developed. As our Institute was on the list of larger centers for orthovoltage therapy, the government of SR Macedonia endorsed a financial support for extending and reconstruction of the radiotherapy department. The ward and department for telecobalt therapy was completed by courtesy of the Federal Commission for Nuclear Energy. By that time, the available in-patient facilities comprised 110 beds, and adequate conditions for machine installation had been attained. The new radiotherapy department was put into use on May 25, 1963.

Development of radiological service in the central parts of Macedonia

Tetovo, precisely the village Lešok, was the first to obtain a Picker 2 machine donated by UNICEF in 1948; it was used exclusively for diascopy. The activity of this center has been closely connected with the Institute of Tuberculosis in Skopje. In the same timed, *mid-wave* machines were installed in Strumica, Gostivar, Bitola and Titov Veles.

In 1950, a new machine – "Morava" type, or precisely "Grafoskop" with a radiologist and radiotechnician – was brought to Tetovo from Karlovac.

Bitola had well organized radiological service with an experienced radiologist Assist. Prof. Dr. S. Levi. Later he was joined by another radiologist Dr. D. Mitrevsky and a few radiotechnicians. Next to the Institute of Radiology in Skopje, presently this high-tech equipped institution staffed by competent radiological expert and technicians represents one of the leading radiological centers in the country.

Kumanovo. Radiological service there was organized in 1957 by radiologist Dr. B. Malinski. Within a short period of time the necessary technical staff was educated and new facilities

and equipment obtained which all contributed to very good professional results.

Strumica. Far back in 1954, the first mid-wave X-ray machine "Morava" was installed in General Hospital there. The machine was handled by general physicians as there were no adequately trained radiotechnicians available. A specialist in radiology and a radiotechnician joined the staff in 1956, whereas in 1960, another young specialist Dr. I. Trajkov and two radiotechnicians were employed.

Struga. Radiological service in this place by the Ohrid lake was started in 1956 by K. Galabovski, radiotechnician.

Similarly, also in other towns of Macedonia, i.e. in Prilep, Ohrid, Titov Veles and Štip, the development of radiological service was started in the '60s. In Gostivar the activity started in 1955.

Catastrophic earthquake affecting Skopje on June 26, 1963

Heavy consequences due to the earthquake comprised also damage on the new building of the Medical Faculty in Skopje, which had been built by the help of our emigrants abroad. The building was damaged to the point which rendered any further work with machines and patients impossible. The personnel, like other inhabitants of Skoje, were housed in tents in the close vicinity of the damaged building. Among the casualties of the earthquake was also the head of diagnostic radiology Assist. Prof. Dr. Levi, a very competent and respected physician. Nevertheless, the whole personnel, i.e. physicians as well as technicians, showed great deal of responsibility in dealing with the problem of primarily surgical patients under those abnormal conditions. In the following days help from other republics and federal government started arriving; as a result, radiographies were performed on a portable X-ray machine. The help offered by the Clinical Center in Ljubljana comprised also a registered radiotechnician.

After normalization of conditions in the town, reconstrucition works on the damaged buildings of Clinical Hospital were undertaken. Both radiotherapy and radiodiagnostic departments were damaged to the point which rendered any work there impossible. The department of radiotherapy was completely destroyed.

In the beginning of 1963, on the initiative of professional board of the Institute, with consent of the Ministry of Health of SR Macedonia and the Medical Faculty, it had been concluded that the Institute of Radiology was the most suitable institution to take over the coordination with other clinics, with respect to organization of oncological serviced. Accordingly, on May 19, 1963, the Institute was named the Institute of Radiology and Oncology, which implied that it was entrusted with a number of new important responsibilities.

Institute of Radiology

The resonstruction of buildings within the frame of Medical Faculty represented a milestone in the development of the Institute of Radiology. The process was greatly accelerated by favourable conditions offered by the new building, thus starting the "golden era of radiology". Thanks to the inventiveness and ability of the then director Prof. Dr. Tevčev, sufficient financial means for purchasing of the most up-todate equipment had been collected, and the necessary new staff educated and trained for handling the machines.

In the year 1967, a new building designed specially for the needs of our service amidst the clinical block was built on the previous parking place. The front and side walls of the building were decorated by beautiful mosaics representing a roentgen tube. The rooms were comfortable, with large and bright waiting rooms full of flowers. The administrative part which is situated in the front section of the Institute is followed by waiting rooms from the side and behind. The largest – central part of the Institute is dedicated to the diagnostic services, which have been divided into two parts as follows: One is intended for diagnostic of the digestive tract, urinary tract, lung and skeleton with a centrally situated dark room. On the

other side there is angiodiagnostics, pediatric radiology, gynecological diagnostics and breast disease diagnostics. CT (1) is positioned in the corner, and there is another modern CT unit (2) on the other side. This part also disposes of a dark room. In the very centre of the Institute there is a large working place intended for results interpretation. The equipment comprises two large negatoscopes, one on each side; three non-stop present typists enable the work to be continued without interruption throughout the day.

On its 20th anniversary in 1967, the Institute had the following machines and equipment: seven 6-wave units (Gigantos, Tridoros and Super 100). Apart from these, there were also two 4-wave units installed. The machines were equipped with 3 Pantoscopes II, 1 Simmetrix, 1 universal planigraph, an Odelca camera, 4 Bucky tables, and one Baracetti craniograph. There were also in Elema Shelander's catheterization table, a Venclih-Pesler's table for abdominal and peripheral angiographies, one komograph and one Tele-pleoscope, as well as an apparatus for lymphographies. Other equipment comprised 5 electronic amplifiers with 5 monitors and an AOT for fast serial imaging in two directors. There were three ceiling stands and one stand for whole spine imaging as well as an automatic contrast injector according to Gidlund available. The diagnostic unit had a 16-mm camera and a 70 mm camera for digestive tract imaging. Additional equipment for pediatric diagnostics comprised protection suits in different sizes for imaging of children in standing position. Dark rooms were equipped with automatic development chambers.

Between the rooms for diagnostics and the waiting rooms there were long corridors with rooms for doctors and radiotechnicians. On the first floor there were teaching staff offices.

Teaching staff

The first professor[4] at the Chair of Radiology was at the same time also the first specialist in radiology who lectured to the students of medicine in the years 1951–1956. This was our first primarius and director of the Institute Dr. I. Anastasov.

At that time our Institute had three assistants: Prim. Dr. K. Popović, radiotherapist and chief of the later established radiotherapy department, Assist. Dr. D. Tevčev and Asist. Dr. S. Levi, who took active part in the education program.

In 1957, newly elected Asist. Prof. Dr. D. Tevčev was appointed the chairman of the Chair of oncology. On next elections in 1961, Dr. S. Levi received the title of Assist. Prof. whereas Dr. D. Antevski and Dr. M. Grunevski became Teaching Assistants. In 1967, the Institute's education base was implemented by new teaching personnel: Prof. Dr. D. Tevčev, Prof. Dr. J. Novak, Assist. Dr. K. Popović, Assist. Prof. Dr. D. Antevski and Assist. Prof. M. Grunevski. In 1970 Dr. N. Grivčeva-Janošević, presently Prof. of Radiology, was appointed Teaching Assistant. In 1975 the Chair had 12 newly elected teaching assistants and 4 young assistants. By the end of 1987, there were 6 professors (3 in the field of diagnostics, the remaining 3 being radiotherapists), 2 assist. professors, and 21 teaching assistants.

Institute of Radiotherapy and Oncology

In the beginning the development was parallel with that of our Institute. In 1957, a new building comprising a ward with 40 beds was allocated to radiotherapy. The period from the catastrophic earthquake in 1963 to 1979 represents a phase of constant development and staff education. The accelerator with the adjacent auxiliary rooms was installed in the bunker built in the basement of the Institute. By that year, the Institute's staff comprised five young residents, one graduated engineer of electronics, one graduated physicist and three pathologists.

Presently, the Institute has 170 beds. The average annual turn over is 53.000–54.000 patient days, and 6.000–6.500 outpatient visits. The total number of personnel is 125.

This would be a brief description of the

development of radiology in the Republic of Macedonia over the past few decades. We can conclude that the way has often been difficult, but nevertheless successful.

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Radiol Oncol 1992; 26: 239-42.

The role of physicist in radiology

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What the pharmacist is for chemotherapy in medicine, the physicist is for radiology and nuclear medicine. The duty of the radiological physicist is to ensure adequate radiological protection in roentgen diagnostic, roentgen and high energy source therapy and in the use of radioactive isotopes. He is furthermore responsible for dosimetry in all forms of radiological therapy, and together with physicians, as a member of the team, he takes part in routine and research work. The physicist's role in radiology is envisaged by the Recommendations of the International Agency for the use of Nuclear Energy (IAEA) and by various legal provisions.

Key words: radiology-manpower; physician's role

Present role of physicist in radiology results from a historic alliance between physics and medicine, originating from the time when the word *"medicus"* was a synonym for *"physicus"*, and when the Greek word *"physics"* referred to natural science in general, including the knowledge on human body physiology, health and disease.

The development of medicine and physics have been all the time parallel. Thus, discoveries in physics have always had a great impact on medicine. Likewise, new advances in medicine often played a decisive role in the development of physics.

It was the genius *Linceo,* physicist *Galilei,* one of those who first attempted to measure the human body temperature and established its outstanding stability. And who was the first to study the entity of viscosity of flowing liquids? The physician *Poisseille* in his blood circulation studies.

It is also indisputable that *Sir John Gilbert,* the physician to the Queen Elizabeth I, discovered the existence of electric particles, whereas another physician *Galvani* is famous for his discovery of galvanic electricity which represents a milestone of a new epoch in physics and medicine. For physics, these discoveries can be regarded as the origin of all knowledge on electricity and electric currents, as well as of the electrotechnical science without which the idea of the present modern life would have been inconceivable. For medicine, the same discoveries represent the basis a great deal of

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UDC: 616.8:616-073.75:614.23

The presented is somewhat upgraded text of an article enti-tled "The Role of Physicist in Radiology" by the same author, published in the Annals of Clinical Hospital "Dr. M. Stojanović" 10; 3-4: 220–3, 1971.

modern physiology, electrodiagnostics, electrotherapy and a number of other methods and devices indispensable in up-to-date medical theory and practice have been built upon.

Physicians *Mayer* and *Helmholtz* discovered the fundamental law of energy. The latter – a physician and physicist in one person – also significantly contributed to the development of physics in teh field of electrodynamics, thermodynamics, mechanics and optics, as well as to medicine where his findings and standpoints pertinent to physiology have maintained their indisputable value till present days.

Further development of physics and new discoveries associated with the famous names of Roentgen, Rutherford and Curie, greatly influenced the development of medicine in our century by promoting new, powerful means for the needs of diagnostics, therapy and medical scientific research.

Without knowledge of physics, many branches of medicine, particularly those prevailingly involved in the study of physical entities in living organisms (e. g. physiology) would have remained unexplained. Disorders in normal physical functioning, on the other hand, can be regarded the domain of pathophysiology and clinics. Circulation and respiration along with a number of other entities are associated with the role of liquids and gasses in the body. Statics and locomotion also are mechanical phenomena. Generation of body temperature, thermoregulation and the effect of environmental factors influencing the temperature, can be mostly explained as caloric physical phenomena. Neither can function of the eye be explained without optics, nor function of the ear without acoustics. As electrophysiology and physical medicine owe their existence to physics, also microbiology and bacteriology could not exist without microscopes and other optic devices and methods. The same applies to histology and a number of other medical branches and specialities which increasingly make use of highly perfected though more and more elaborate machines, technical devices and methods, all of which are based on the principles of physics.

Here a special place is taken by rentgenology, radiology and nuclear medicine. It is there that the most advanced physics and medicine have managed to merge into one.

Long time ago the physician was not just a diagnostician and a therapist but also a pharmacist. He prescribed as well as prepared the medications. In fact, this can be seen even today at places where medicine is underdeveloped. Scientific development of medicine, however was bound to bring about certain changes in this respect: apart from physicians there were chemists who specialised in drug preparation. These were the beginnings of not only pharmacology in medicine, but also pharmacy as a special branch exceeding the scope of medicine in the narrow sense of the word. Nowadays the role of pharmacists is indisputable, and no one would even think of having a physician instead of a pharmacologist as the head of a pharmacy, even when this is a hospital affiliated service. Self-evidently, this field is strictly the domain of a pharmacologist who has been adequately qualified for it.

A similar situation can be seen today in radiology which has developed from rentgenology, as well as in nuclear medicine. The tendency to free the physician of everything that might interfere with his very responsible and complex work in these specialities is becoming increasingly pronounced. As a result, a new profile of worker has been introduced in radiological and nuclear medical centers. This is the physicist whose role in the protection against ionizing radiation has been gaining in its importance during the last 40 years. The physicians, having learnt from drastic experience of severe professionale overexposure to X-rays, were forced to undertake the necessary measures to protect themselves and their coworkers, particularly since the introduction of more intensive sources of radiation, such as e.g. Cobalt units, betatron, and different accelerators, as well as diagnostic and therapeutic applications of different high-activity radionuclides. It has soon become apparent that the protection of patients as well as their surrounding is very important and indispensable.

The protection, however, was not the only

problem that remained to be solved. By stronger and stronger radiations sources of high-intensity beams coming into use, the question of exact determination of therapeutic doses, and associated with that the risk and responsibility, have become very urgent.

Should the measuring instruments be infallible, everyone could measure radiation beams and study the dose distribution by means of some "infalible" method. However, such measuring instruments unfortunately do not exist. Errors may therefore occur with every method. One might believe that all this elaborate work could be done by the computer. But, regardless its versatile usefulness, the latter device is only an electronic calculator. Its work is as reliable as the data that are entered into it, and the data can only be obtained by measuring.

Should the physician be expected to do all that, he would be alienated from his essential medical tasks in the same way as if he were to prepare drugs for his patients. Such a situation would be both impossible and unprofessional, if nothing else because of the very turnover of patients and the number of procedures to be carried out. All in all, this would be a glaring anachronism.

The present role of the physicist in radiology and nuclear medicine can therefore be compared to that of a pharmacologist, i.e. specialised medical chemist, in classical medicine for the needs of chemotherapy. The pharmacologist, however, works in a pharmacy, whereas the place of physicist is aside of the physician, in the same institution, with the same patients, making a constituent part of the same working team.

As it is indisputable that the physician specialised in radiology or nuclear medicine should be familiar with the essentials of physics that form the basis of the methods used, also the radio-physicist in expected to acquire the needed specialisation, or at least a corresponding postgraduate education. In some countries, a physicist can obtain the qualification and the title of specialist. As our legislation has not fully foreseen for this possibility, different institutions take different approaches to solving the problems of professional education, all in accordance with their comprehension and possibilities. Often the solutions were sought in collaboration with individual nuclear institutes, university departments for medical physics or by referring of selected candidates for fellowship programs to different internationally recognized centers. A radiophysicist is expected to be familiar with at least the basics of certain branches of medicine, such as e.g. anatomy, cytology, biophysics, but above all with radiology and the diagnostic and therapeutic aspects of nuclear physics.

This is best reflected in staff profiles within particular institutes and university hospitals. These will have to employ, with respect to the scope of work and the type of equipment, at least one (or more) radiophysicist. In an attempt to maintain an adequate professional level and to keep abreast with recent advances in the appointed profession, and particulary in order to promote the necessary scientific research, the need for a special Department of radiophysics within the frame of the Institute of Radiology and the Institute of Nuclear Medicine has been widely recognized. Such a department of radiophysics should be responsible for radiation protection associated with all radio-diagnostic and radiotherapeutic procedures as well as with the use of radionuclides. Apart from that, the Department should take care of dosimetry related to all types of radiotherapy performed, and – in collaboration with physicians of the relevant institution – should prepare irradiation protocols and take part in routine as well as the research work.

Here it should be pointed out that such an approach is in accordance with the recommendations of the International Agency for the Use of Nuclear Energy (IAEA), according to which the activity of radiophysicists is one of the prerequisites for working with radiotherapeutic equipment such as telecobalt units, betatrons and others in hospitals and other medical centers. These recommendations having the power of law, have been incorporated into relevant legislations of all countries, likewise also in our country. Thus, prior to being granted a permis-

sion for work with high-intensity radiotherapeutic equipment, the applying institution should state – apart from the names of the physicians who would work with the machines – also the name and qualification of the person who would have the task of an attending radiophysicist.

Therefore, the role of radiophysicist in radiology includes a close collaboration in all radiology-related activities, particularly in those pertinent to therapy. The physician and the physicist form an insaparatle team based on mutual trust, sharing care, effort, difficulties, success as well as failure, and above all a great responsibility for their mutual work.

Radiol Oncol 1992; 26: 243-7.

Report on the seminar "Advances in Nuclear Medicine"

September 6–12, 1992, London

The one-week seminar on advances in nuclear medicine, which was held under the auspices of the British Council, was prepared in collaboration with 35 invited speakers – top experts from Great Britain, the Netherlands, Belgium and Germany. I attended the course together with 15 other participants from different countries of Africa, Australia, Asia and Europe. On one side, we had the opportunity to become students again while on the other, all of us having considerable working experience, we were able to take part in the discussions with our teachers during lectures and joint lunches; thus, at moments, the course turned into a workshop. We also visited a radio-pharmaceutical company in Amersham.

Positron emission tomography (PET)

On the first day we attended lectures on technical back-ground and clinical applicability of PET, and also saw how that method was used in practice in two hospitals, i.e. Guy's and St Thomas's. PET has been introduced into clinical practice only in the '90s, after development of a cyclotron for clinical use which enabled direct production of ultrashort-life carbon, nitrogen and oxygen radionuclides. As all organic molecules consist of these elements it is possible to test theoretically all biochemical processes in the organism *in vivo*. All we need is a sufficiently fast radiopharmaceutical laboratory process which would take a few minutes to label the marker substance that will be introduced into the patient's body either perorally, parenterally or by inhalation. A special device, the so-called positron emission tomograph, monitors changes in the concentration of labelling substance on the images of investigated body sections and thus enables *in vivo* measuring of biochemical reactions in any part of the human body. The measured volumes can be very small ($1\,cm^3$). The method is called also autoradiography *in vivo*.

Hospital cyclotron, a product of Siemens company, is installed in St. Thomas's Hospital and provides with radionuclides not only its own department, but also PET department in a half an hour distant Guy's Hospital. Ultrashort living radionuclides ^{11}C, ^{13}N, ^{15}O and ^{18}F have an extremely short half life which represents an advantage for the examined patient whose exposure to radiation is thus greatly reduced. On the other side, however, the methods using ultrashort living radionuclides are very pretentious for the staff, as they require – apart from a cyclotron and a positron emission tomograph – also a radiochemical laboratory which enables radiopharmaceuticals to be labelled and produced within a few minutes time.

Superposition of PET-obtained tomograms, with images obtained by single photon emission tomography (SPECT), x-ray computer tomography (CT) and tomography by means of magnetic resonance (NMR) were the topics presented by DJ Hawkes. Information on the structure and functioning attainable from one and the same body section should prove its diagnostic value in the future.

Neurological use of PET was the first which can be attributed to the fact that small prototypes of machines were able to image relatively small body parts, such as eg. the head. Whole body evaluation was made possible only by modern machines. Of radiopharmaceuticals in neurology, ^{18}F-Fluorodeoxyglucosis is used most frequently for evaluation of regional cerebral metabolism. $^{11}CO_2$ or ^{15}O-labelled water

are used for the examination of regional blood supply in the brain. By means of different ^{11}C-labelled ligands receptors in the brain can be presented, and labelled neurotransmitters, eg. ^{18}F-DOPA, are used as well.

Cardiological use of PET was the next. There the central problem to be studied was cardiac ischemia and myocardiac infarction. The existing techniques in nuclear medicine, including thallium scintigraphy and ventriculography, were unable to draw a clear distinction between parts of the myocardium with different stages of damage. After an infarction, some parts of the myocard may still be viable and normally vascularized though immobile, i.e. the so-called "stunt myocardium". These parts will normally recover during the rehabilitation process. More affected parts are immobile and poorly vascularized though still viable (i.e. "hibernating myocardium"); these can be saved by timely revascularization. By means of PET it is possible to differentiate the above two forms of damage from the third one, i.e. ultimate necrosis.

Normally vascularized and normally oxygenated parts of the myocardium are imaged using ^{11}C-labelled fatty acids which are indicators of the aerobic metabolism. Poorly vascularized parts of the cardiac muscle are presented selectively by means of ^{18}F-Fluorodeoxyglucosis, since in the presence of ischemia, myocardiac cells draw energy from glycolysis and the latter radiopharmaceutical is the indicator of the anaerobic metabolism.

Oncological use of PET. An answer to the initial question "Where is the tumor?" is provided by scintigraphy using ^{18}F-Fluorodeoxyglucosis which is an unspecific tumor marker *in vivo*. Namely, for the difference from healthy tissues where aerobic glycolysis is prevailing, tumors are characterised by anaerobic glycolysis. The areas with anaerobic glycolysis can be imaged on tomograms, which helps to detect primary and secondary tumor sites, as well as to follow the effects of therapy and to differentiate benign (e.g. inflammation, radiotherapy-related scars) from malignant lesions etc.

This question is followed by another one: "How fast can the tumor cells multiply?" The answer is provided by ^{11}C-Thymidine which is used for measuring the doubling time of tumor cells. And further, proteosynthesis in tumors is measured by PET with ^{11}C-Methionine.

The third question: "Has the tumor got hormone receptors?" is explained by means of scintigraphy with ^{18}F-Estradiol which is able to image the presence of estrogen receptors in breast cancer.

And finally, the question "Will the treatment with fluorouracile be effective?" can be answered by ^{18}F-Fluorouracile which is used for studying the kinetics of this cytotoxic drug, and for predicting the treatment result.

Radiopharmacy

On the second day, K.E. Britton presented the strategy of the development of new radiopharmaceuticals. The former methods by which new markers were discovered more or less by chance, have been improved by a new approach: based on detailed molecular analyses, a computer model of substrate or receptor against which an antibody or ligand should be developed is made. In the second stage, the computer draws the structure of an unknown molecule whose structure best matches the ligand and is expected to specifically bind to it with all electron clouds in three dimensions. The development of this new molecule is a task of genetic engineering.

The situation concerning registration of new radiopharmaceuticals in European Community was presented by C.D.R. Hewat, a member of the group of experts preparing these regulations. In Europe, drug handling regulations have been in use for 600 years already. Regulations on handling radiopharmaceuticals, however, are in effects only in the United States. There the procedure for registration of a new radiopharmaceutical through the Food and Drug Administration takes from 3 to 5 years. In Europe, some kind of such regulations exist in Great Britain only, whereas all the other European countries are without them. Therefore, an attempt has been made to adjust the

American and British model for use in European Community legislation. This work was started in 1989 already, but as it is associated with numerous problems, no imminent results can be expected by 1993.

The lectures that followed were concerned with quality control, automatization in radiopharmacy etc. Present tendency is that one central radiopharmaceutical laboratory would produce individual doses of radiopharmaceuticals for all investigations of individual patients in different units of nuclear medicine in nearby hospitals.

Tumor imaging

The third day was dedicated to the diagnostics of tumors by means of standard radiological investigations, computer tomography (CT), ultrasonography (US), and tomography with nuclear magnetic resonance (NMR); these techniques were compared with the methods used in nuclear medicine. Whereas the former investigations have the potential of exact imaging of the structure of pathologically changed and healthy parts of the body, the latter techniques are able to show the functioning of these particular body parts. Thus, the already known methods using Gallium (^{67}Ga-citrate), five-valent Technetium dimercaptosuccinate (99 m Tc-V-DMSA), radio-Iodine (^{131}I-NaI), meta-Iodobenzylguanidine (^{131}I-MJBG), Thallium (^{201}Tl-chloride), as well as different immunoscintigraphies generally performed by means of a gamma camera for single photon emission tomography (SPECT) were presented.

Immunoscintigraphy has several drawbacks. In response to the use of radionuclide labelled murine antibodies against tumor markers, after the first diagnostic application the patient's body starts to produce antimurine antibodies (HAMA, human antimouse antibody) which, as a result, jeopardize the second immunoscintigraphy. On the repeated application of diagnostic doses of approximately 1 mg of mice antibodies, the patients do not develop clinical signs of oversensitivity or shock, though the scintigram shows that their hepatic and spleenic macrophage system promptly eliminates the antigen-antibody complex from the circulation. This is indicative of a subclinical form of oversensitivity, whereas the clinical form is probably only the peak of the iceberg. According to a study carried out in Graz, many of older people have antimurine antibodies present in their blood though they have neither been exposed to nor have they even heard of radioimmunoscintigraphy.

Receptor scintigraphy using radiopharmaceuticals which bind to the receptors on tumor cells is very encouraging. For example, some tumors which have cell receptors for somatostatin can be treated with a somatostatin analogue Octreotide which inhibits their growth. Scintigraphy with Octreotide that has been previously labelled with radioactive Indium (^{111}In) is helpful in determining the receptor status and prognosticating the treatment results.

Tumor therapy

V.J. Lewington's presentation dealt with the therapy of pain with radioactive Strontium (^{89}Sr) in osteoblastic bone metastases most frequently originating from prostatic carcinoma. Her calculations were aimed to prove that the costs of teleradiotherapy and analgesics were higher than the costs of radioactive Strontium based therapy; besides, a significantly better analgesic effect was achieved by the latter method in comparison with the previously mentioned methods of therapy. She also mentioned two new radiopharmaceuticals used for the same purpose, i.e. Samarium (^{153}Sm-polyphosphate) and Rhenium (^{186}Re-polyphosphate).

Differences in the analgesic effect of the above radiopharmaceuticals appear probably as a result of differences in their kinetics, scope of beta particles and half life of nuclides.

C.A. Hoefnagel presented a report on metabolic radiotherapy of neuroblastomas, feochromocytomas, paragangliomas, carcinoids and medullary thyroid cancer with metaiodobenzylguanidine (^{131}I-MJBG). The procedure is very

simple. The author claims that the main device needed in the treatment of small children are videocassettes which help the treated child keep quiet during the four hour infusion of the radiopharmaceutical, as well as during the following few days of "imprisonment" in the hospital room. Grandparents are the only company allowed.

^{131}I-MJBG is used as a preoperative treatment for stage IV neuroblastoma. A decrease in tumor volume was confirmed in 35 % of 273 such patients. The treatment success was even greater in malignant feochromocytomas where a more than 50 % tumor regression was reported in 56 % of the patients.

C.A. Hoefnagel performed treatment with ^{131}I and ^{125}I labelled MJBG. ^{131}I is a beta-ray emitter with a medium span of 1.5 mm. Taking into account that an average cell diameter measures 15 μm, and that the radiopharmaceutical collected in the secretion granules of tumor cells radiates to 1.5 mm distance, where the therapeutic radiation effect is expressed, we can calculate that the number of skiped cells is 100. Thus the tumor volume is important if the electrons emerging from its border are to hit the cells in its middle. Micrometastases cannot be destroyed with ^{131}I.

The other radionuclide of Iodine, i.e. ^{125}I, has just the opposite characteristics. This nuclide disintegrates by electron capturing, it emits soft gamma radiation which is of no therapeutic significance; instead, Auger's electrons were used for therapy. The energy and span of Auger's electrons of ^{125}I are so small that the shoots from the secretion granules do not reach the nucleus within the same cell. Nevertheless, Hoefnagel reported a decrease in tumor mass even after the therapeutic application of ^{125}I-MJBG particularly in patients with massive tumor infiltration in the bone marrow. It saves normal hematogenous cells in the immediate vicinity of tumor cells by means of therapy with low-energy beta particles.

Quality assurance

On the fourth day exposure of population to ionizing radiation due to medical diagnostic and therapeutic procedures was discussed, as well as the exposure of health care personnel on wards. Lectures on diagnostic value of investigations were followed by A.J. Coakley's presentation. He spoke about the ways to assess and improve the quality of work of physicians, nurses, technicians, clerks etc. Quite a new topic entitled "Audit in Nuclear Medicine" was defined as a "systemic critical analysis of the quality of medical care including diagnostic and therapeutic procedures, and the analysis of material consumption, working results and the quality of patient's life". I have learnt that in Great Britain they have a system which enables a retrospective analysis of the work performed every week; every member of the medical staff spends two hours a week over a white paper entitled "Working for Patients."

New investigations in non-malignant diseases

The fifth day was dedicated to new nuclear medicine procedures among which was the most interesting lecture of M.B. Pepys who presented a new scintigraphic method for the detection and follow up of amyloidosis. He claimed that at least a trace of amyloid, that homogeneous, transparent, wax-like matter between the cells of different organs, will be present in everyone of us. In some pathological conditions the collecting of amyloid in the intercellular space is stronger and may result in the appearance of clinical symptoms, depending on the site of amyloid collection: if the substance occupy Langerhans' islands in the pancreas, the disease is called diabetes of old age, whereas an excessive compilation of amyloid in some areas of the brain is called Alzheimer's disease. Amyloidosis is therefore a relatively frequent condition, though it is rarely recognized in living patients. The only diagnostic method known so far is a histologic analysis of the tissue sample, and even then the pathologist fails to detect the

disease unless the specimen has been stained with Kongo red. The new approach to diagnosis of amyloidosis by means of scintigraphy is the only simple investigation for this condition *in vivo*.

A radiopharmaceutical for scintigraphy of amyloidosis has been obtained from a pre-stage of amyloid, a protein that is normally produced in the liver, is present in the serum and form fibriles in the intercellular matter where it stays permanently. This substance, which is called serum component of amyloid P, is labelled with ^{123}I and injected into the investigated patient. Scintigrams taken with a planar gamma camera, were showing amyloid deposits in the body from the technical point of view the resolution of images was excellent. The radiopharmaceutical is not commercially available yet.

Single photon emission tomography (SPECT)

Tomographic gamma camera has been well established as a basic tool in scintigraphy, so that no particular novelties in this field have been presented. The presented reports were concerned with quality assurance, reconstruction and filtering of scintigraphic sections, three-dimensional tomography and different technical details that could be of great interest to a majority of engineers.

Conclusion

The participants were given an overview of the trends in nuclear medicine on the verge of the twenty-first century; we were able to compare the latest advances elsewhere with the situation in our own countries, and got some ideas for improvement of the quality of our work.

Prim. Janez Šuštaršič, MD
Institute of Oncology
Ljubljana

Radiol Oncol 1992; 26: 248-9.

Book review

X-ray diagnosis of endocrine disease

Author: Professor Ljubomir Djankov, ptt. D

Printed in »Medicine and Physical Education« – Sofia, Bulgaria 1990 p. 331 Lv.

The author of the monograph, professor Lj. Djankov, a very distinguished and eminent radiologist, Head of the Endocrinological Center affiliated to the Medical Academy of Sciences in Sofia, member of the European Radiological Association, member of the German Association of Radiologists, author of well supported articles, is also a member of the Academy of Medical Sciences in Sofia.

Contributions and opinions in this book have been given by distinguished radiologists like: the radiologists of Bulgaria, Professor Hoyk (Stuttgart), Professor E. Willich (Heidelberg), Dr. Krae (Wirtzburg), Professor Buhman (Moscow) and others.

The monograph represents a link of the generally known diagnostics and conventional radiological diagnostics and in the special part of the book he outlines the modern radiodiagnostics, starting from macroradiography, contrast diagnostics with positive and negative contrasts, computed tomography, all the way to magnetic resonance.

Ultrasound, and radionuclide diagnostics are also applicable in endocrine diseases.

Besides the above autlined methods, interventional (therapeutic) radiology is also included.

In the second special part ot the book, the author described endocrine diseases from a radiological point of view, covering and analysing a part of clinical symptomatology, too, and outlining them as follows:

– Hypotalamical-hypophysis diseases

– Diseases relating to tumors of the hypophysis

and: the group of hypothalamo-adenohypophyseal diseases.

The diseases caused by the hyperfunction of the adenohypophysis have been radiologically diagnosed and analysed in details (acromegaly, hypophyseal-gigantism, Cushing's as well as the syndrome of hypergalactia).

The dysfunctions of the hypophysis and adenohypophysis have been autlined and well documented with adequate photographs.

Hypothalamo-hypophyseal nanism, panhypopituitarism is described together with its evolution of the disease as »empty sella« syndrome.

Hypotalamo-neurohypophyseal diseases have also been analysed in details as well as diabetes insipidus. The pinealopathies diseases of pinealis have been analysed in a special chapter of this book.

Besides the anatomical data, an outline of tumor pathology of the gland has been given. The bibliography, which is always given in footnotes below every chapter of the book, complements all partially expressed thoughts so that one could have complete insight into the analysed problem.

The thyroid gland has been studied thoroughly. Besides the anatomical structure and physiology of the gland a survey of the goiter has been given with special emphasis on the problem of tumors of this endocrine gland.

On the othes side, the hyperfunction-hyperthyroidism has been analysed in details in rela-

tion to the hormonal dependence on the thyroid gland and the hypophysis. The hypothyroidism and hyperthyroidism have been fully described in the other chapter of the book.

The parathyroid gland has been thoroughly studied in the second chapter of this book as well as her hyper-and hypofunction.

Thymus-problem baby has been presented thoroughly with its anatomical variables as well as with its tumors.

The suprarenal gland its pathology m. Cushing, sy. Conn, adrenogenital syndrome, all the way to the tumor evolution of this important gland, have been paid attention to.

The endocrine glands of male: hyporhism and primary or secondary hyorhism as well as the problem of crytorhism, with changed status of teh sex, is very effectively show with adequate schemes.

The female gonads have their own place in this book.

A survey has been given firstly of the primary hypogonadism, followed by the secondary hypogonadism with its causes and consequences, as well as a detailed, thoroughly observed problem of ovarial hyperandrogeny.

The syndrome of Stein-Levental (sclerosis of ovary) has been very successfully documented.

The second hapter of this book reviews the always acute problem of the intersex, so that sy. Turner, Noonam sy., sy. Klinefelter complete this part with real and false hermaphroditism.

With a schematic review and comparative studies of other authors dealing with thiw problem, the required effect has been attained.

At the end to the book, attention has been paid to the group of endocrine pancreatic diseases-with an analysis of the normal anatomy, physiology, as well as the tumor processes in this important gland; a survey of hyperinsulism has been given as well with regard to the diabetic process with the changes filed on the skeleton-diabetic osteoartropathy.

Finally, a word or two about the technical equipment: satisfactory level of equipped monograph, with quality technical schemes and drawings. Photographs are very successfully done, technically clear.

The text is easy to read and a very high professional radiological level has been attanined.

The topics outlined in this book represent an up to date problem of multidisciplinary nature: primary radiological, endocrinological, genetic, surgical, pediatric, oncological, orthopedic, neuropathological, neurosurgical, patho-histological, urological and other disciplines which could not have been listed.

The book covers 160 pages, is easy to read and it could be used as a valvable literature to all general physicians as well as to specialists in their daily practice.

Professor Dr. Nada Grivčeva-Janošević, ptt. D.
Institute of Radiology
School of Medicine, University of Skopje,
Macedonia

Radiol Oncol 1992; 26: 250.

Book review

Atlas of cancer incidence in Slovenia 1978 – 1987

Authors: ***Vera Pompe-Kirn, Maja Primic-Žakelj, Anuška Ferligoj, Janez Škrk***

Design: Monika Fink-Serša and Mateja Zorman; Language reading: Velimir Gjurin; Charts: Geodetic Institute of Slovenia, Ljubljana; 106 pages, circulation: 2000 samples; Printed by "Tiskarna ljudske pravice"; Publisher: Institute of Oncology, Ljubljana

Atlas of Cancer Incidence in Slovenia was published in 1992 by the Institute of Oncology in Ljubljana. The maps present the data collected from cancer registration forms, death certificates and autopsy reports by the staff of the Cancer Registry of Slovenia during the appointed 10-year period.

The book comprises 23 four-color maps in Slovenia presenting 17 most frequent cancer sites by sex. The text is divided into 9 chapters as follows: Foreword, Abstract, Introduction, Some Characteristics of Slovenian Communities, Methods of Data Processing, Incidence by Cancer Site, Conclusion, Appendix, and Literature.

The core of the book consists of four-color maps of Slovenia together with a transparency with the names of Slovenian communities. The highest and the lowest incidence values are colored with dark shades of red and green, median are yellow, whereas the communities without particular cancer cases are white. All communities, except for those united under Maribor region, are presented separately. The data on the maps provide a detailed information, however, the large number of communities (60) poses a question how to evaluate the incidence in small, closely packed geographic units with generally small numbers of population. This was perhaps the reason why the authors decided to join all the communities of Maribor region into a single unit, though, they remained inconsistent in other similar cases, e.g. the coastal communities. For the future it would therefore seem sensible to present the data by regions, with incidence rates in 3 colors only, so that both higher and lower values would be presented by the same number of colors.

The maps are accompanied by a comment briefly describing the trends of incidence of particular cancers in Slovenia, pointing out their correlation with age and distribution by communities; risk factors and recommendations for possible decrease of incidence are mentioned as well. In the latter comment, however, more stress is laid on bad life habits than on environmental factors. Therefore, it might be useful if the maps of incidence were accompanied also by maps of air, water and land pollution.

The Atlas is the first such publication in Slovenia, and certainly contains a valuable information essential in dealing with almost all problems pertinent to different aspects of human life. Thus, the data should be useful so for highly qualified professionals as well as for lay ecological movements, and certainly, they should be regarded as indispensable in health care policy planning. It would be welcome if every inhabitant of Slovenia would get a chance to see the book. The style of writing is attractive and easy to follow, the text logically completes the information given on the maps. The explanations are written in such a way they catch the reader's attention and give him a clue to think further. Last but not least, the book represents an achievement also from the technical point of view: its form, design and language are on a high professional level, so that this valuable handbook can be listed among the top achievements in recent medical publishing. Few critical points given above should by no means decrease its value and importance.

Atlas of Cancer Incidence in Slovenia is available in book-shops as well as at the Institute of Oncology in Ljubljana.

Tomaž Benulič M.D.

Notices

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

Molecular biology

The ESO course "An introduction to molecular biology for clinicians" will be offered in Orta San Giulio, Italy, *April 19–21, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Paediatric oncology

The ESO training course for Central and Eastern Europe will take place in Grossenzersdorf, Vienna, Austria, *April 19–24, 1993.*

Contact European School of Oncology – Vienna Office, Arztekammer Fuer Wien, Weihburggasse 10–12, 1010 Vienna, Austria; or call +4322251501280. Fax: +43 222 51 501 240.

Breast cancer

The ESO training course for Central and Eastern Europe will be offered in Grossenzersdorf, Vienna, Austria, *April 26–30, 1993.*

Contact European School of Oncology – Vienna Office, Arztekammer Fuer Wien, Weihburggasse 10–12, 1010 Vienna, Austria; or call +4322251501280. Fax: +43 22251 501 240.

Secretaries in oncology

The ESO training course for non-oncologists, will be offered in Venice, Italy, *April 28–30, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Tumor & virus

The 20th meeting of European Tumor Virus Group will be held in Innsbruck, Austria, *May 3–7, 1993.*

Contact M.P. Dierich, Institute for Hygiene, Leopold-Francens-University, Fritz-Pregl-Str. 3, A-6010 Innsbruck, Austria. Fax: +43512 507 3599.

Chest tumours

The ESO course will be offered in Orta San Giulio, Italy, *May 3–7 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Breast cancer

The ESO training course "Controversies in breast cancer" will be held in New York, USA, *May 6–7, 1993.*

Contact CME office-MSKCC/1275 York Avenue, 10021 New York, USA; or call +1 212 6396754. Fax: +1 212 7173140.

Stereotactic radiotherapy & surgery

The international conference and course will be held in Amsterdam, The Netherlands, *May 6–8, 1993.*

Contact Ms. A. Sol, International Conference & Course on Stereotactic radiotherapy/surgery, Free University Hospital, VU Ziekenhuis, Afd. Radiotherapie, Postbus 7057, 1007 MB Amsterdam, The Netherlands; or call +31 20 548 6163/548 6164. Fax: +31 20 548 6160/548 6161.

Oncology

The ESO seminar "Gynaecological and breast tumours: diagnostic and prognostic factors" will take place in Venice, Italy, *May 10–11, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Annual European brachytherapy GEC-ESTRO meeting

The meeting will take place in Padova, Italy, *May 12–14, 1993.*

Contact the ESTRO Secretariat – University Hospital St. Rafael, Radiotherapy Department, Capucijnenvoer 35, 3000 Leuven, Belgium; or call +32 16 21 22 13. Fax: +32 16 21 22 28.

Oesophageal cancer

The ESO training course will be held in Moscow, Russia, *May 12–18, 1993.*

Contact European School of Oncology – Moscow Office, Moscow Cancer Research Centre, Kashirskoye Shosse 24 – 115478 Moscow, Russia; or call +7 95 3241184/3241564. Fax: +7 95 2302450. Tlx: 411015 knife.

Melanoma

The ESO alumni club refresher day titled "Melanoma: new tools in early diagnosis and education" will be offered in Vienna, Austria, *May 17, 1993.*

Contact European School of Oncology – Vienna Office, Arztekammer Fuer Wien, Weihburggasse 10–12, 1010 Vienna, Austria; or call +43 222 51 501 280. Fax: +43 222 51 501 240.

Radiology & Oncology '93

The annual congress of the British Institute of Radiology will take place in Glasgow, Scotland, U.K., *May 17–19, 1993.*

Contact The British Institute of Radiology, 36 Portland Place, London, WIN 4AT, U.K.; or call +44 71 436 7807. Fax: +44 71 255 3209.

Gynaecological oncology

The ESO course will be held in Orta San Giulio, Italy, *May 17–21, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Cancer

The "84th Annual Meeting American Association for Cancer Research" will take place in Orlando, Florida, USA, *May 19–22, 1993.*

Contact Amer. Assoc. Cancer Res., Meetings Mailing List AACR, Public Ledger Building, 6th and Chestnut Streets, Suite 816, Philadelphia, Pa 19106, USA.

Dosimetry

The IAEA symposium on measurement assurance in dosimetry will be held in Vienna, Austria, *May 24–27, 1993.*

Contact International Atomic Energy Agency, P.O. Box 200, A-1400 Vienna, Austria.

Physics in clinical radiotherapy

The biennial meeting including a joint ESTRO/EPOMP session on safety in radiotherapy will take place at *May 28–30, 1993.*

Contact the ESTRO Secretariat – University Hospital St. Rafael, Radiotherapy Department, Capucijnenvoer 35, 3000 Leuven, Belgium; or call +32 16 21 22 13. Fax: +32 16 21 22 28.

Cancer control

The ESO international conference "Cancer in the Balkans and Middle East: which educational priorities?" will be held in Athens, Greece, *June 2–3, 1993.*

Contact European School of Oncology – Athens Office, 2 Adrianiu St. & Papada ST., 11825 Athens, Greece; or call +30 1 6496 620. Fax: +30 1 6924 372.

Malignant lymphoma

The ESO course, organised in conjunction with the 5th international conference on malignant lymphoma in Lugano, will be offered in Orta San Giulio, Italy, *June 6–8, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Familial cancer

The ESO training course will take place at *June 15–16, 1993.*

Contact European School of Oncology – Brussels Office, Avenue Mounier, 83, 1200 Brussels; or call +32 2 7724 621. Fax: +32 2 7726 233.

Radiosurgery

The 1st congress of the International Stereotactic Radiosurgery Society will be offered at *June 16–19, 1993.*

Contact Congress Secretariat, ISRS '93, Stockholm Convention Bureau, P.O. Box 6911, S-102 39 Stockholm, Sweden.

Conservative treatment in oncology

The 1st international symposium will take place in Lyon, France, *June 17–19, 1993.*

Contact Prof. J.P. Gerard, Centre Hospitalier Lyon-Sud, 69310 Pierre Benite, France; or call +33 78 5084 81. Fax: +33 78 2868 63.

Medical oncology

The ESO training course for pharmaceutical product managers, will be offered in Nice, France, *June 21–24, 1993.*

Contact European School of Oncology, Via Venezian, 18 20133 Milan, Italy; or call +39 2 70635923 or 2364283. Fax: +39 2 2664662.

Radiation oncology

The International Congress ICRO'93 will be held in Kyoto, Japan, *June 21–25, 1993.*

Contact Mitsuyuki Abe, Profesor and Chairman, Department of Radiology, Faculty of Medicine, Kyoto University, Shogoin-kawaharacho, Sakyo-ku, Kyoto 606, Japan; or call +81 75 751 3417. Fax: +81 75 771 9749.

Chemotherapy

The 12th international congress of chemotherapy will be offered in Stockholm, Sweden, *June 27 – July 2, 1993.*

Contact Stockholm Convention Bureau, P. O. Box 6911, S-102 39 Stockholm, Sweden.

Announcement

As one of the authors (M. Koršič[3]) has been omitted in the article entitled "Medulloblastoma, results of treatment at the Institute of Oncology, Ljubljana" published in Advances in Radiology and Oncology. Radiologia Iugoslavica 1992, pages 167–47 we are publishing the correction:

Medulloblastoma, results of treatment at the Institute of Oncology, Ljubljana

Petrič-Grabnar G, Župančič N, Klun B, Umek B, Stare J, Kopač Š, Koršič M, Kragelj B, Cindro L, Škrbec M, Jereb B

Berta Jereb, MD, PhD
Professor of Oncology

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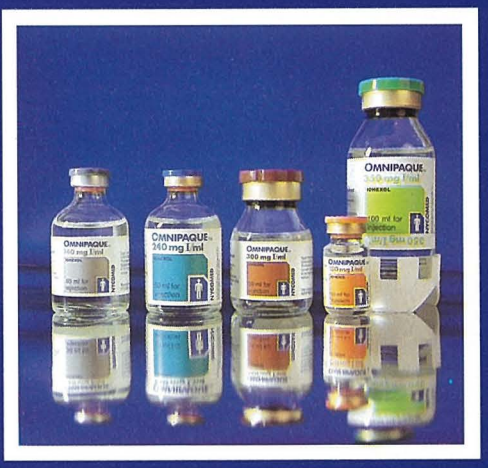

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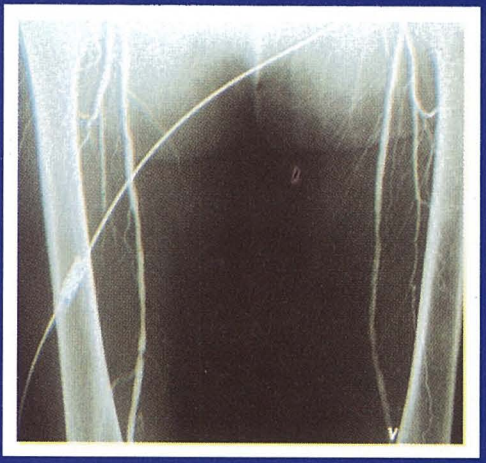

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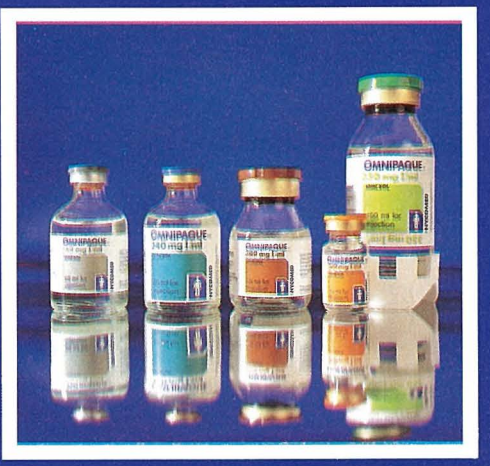

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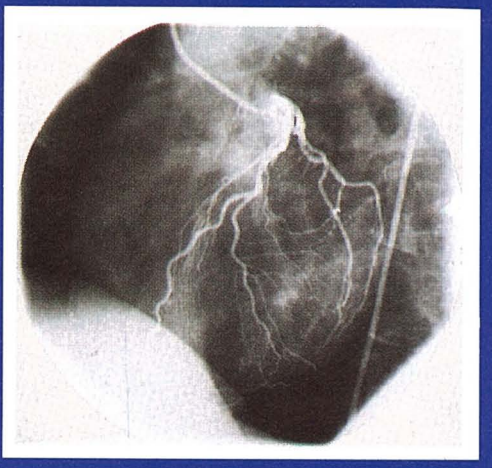
- smanjena učestalost i intenzitet subjektivnih reakcija bolesnika u usporedbi s konvencionalnim ionskim kontrastnim sredstvima
- izuzetno rijetka pojava alergijskih reakcija
- visokokvalitetni angiogrami



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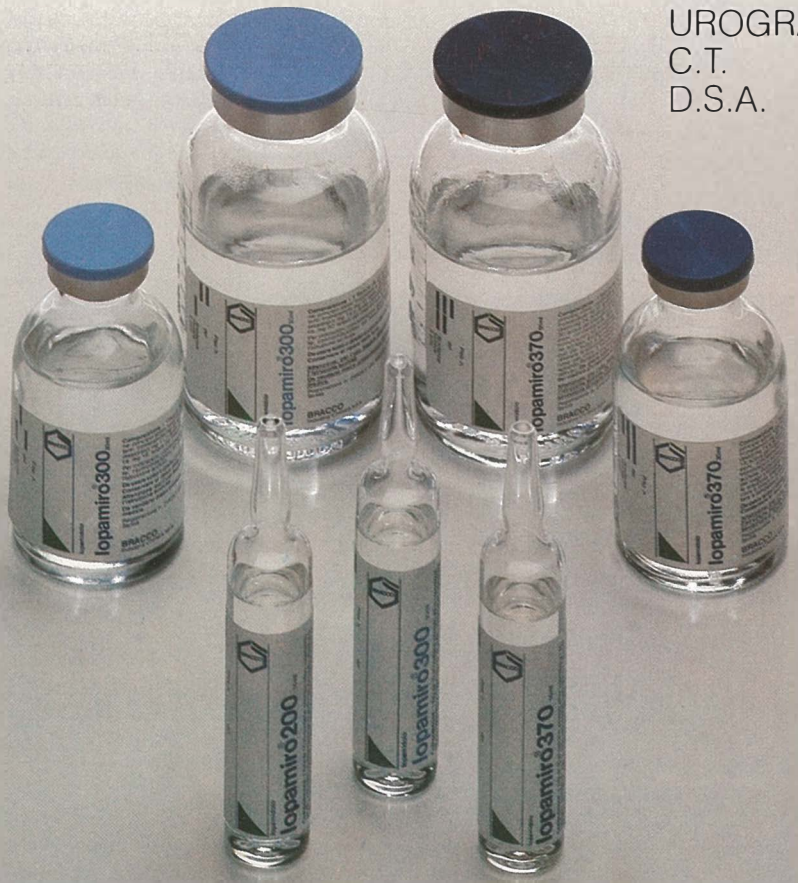

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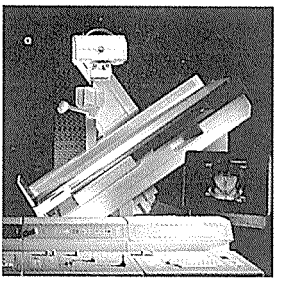

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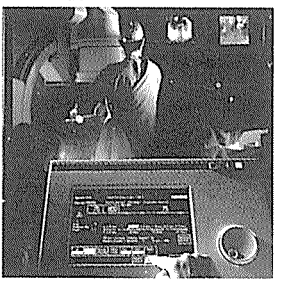

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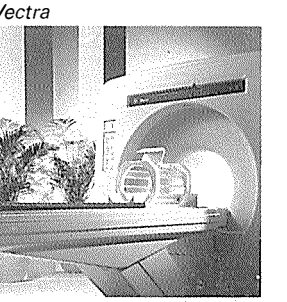

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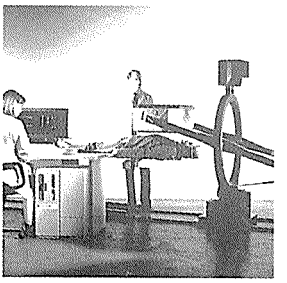

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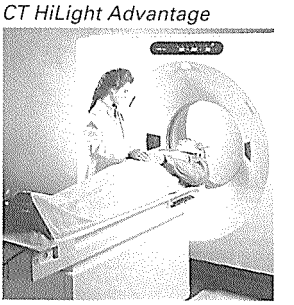

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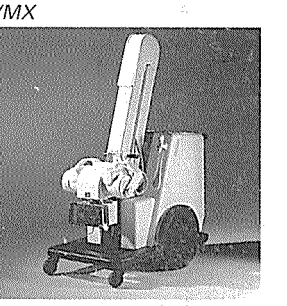

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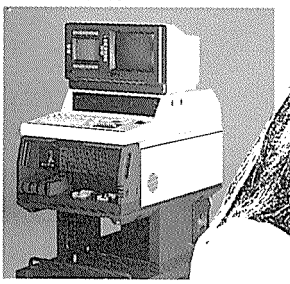

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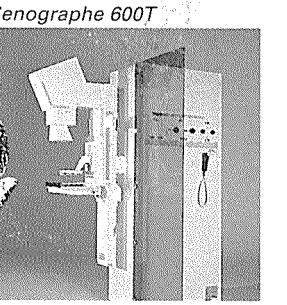

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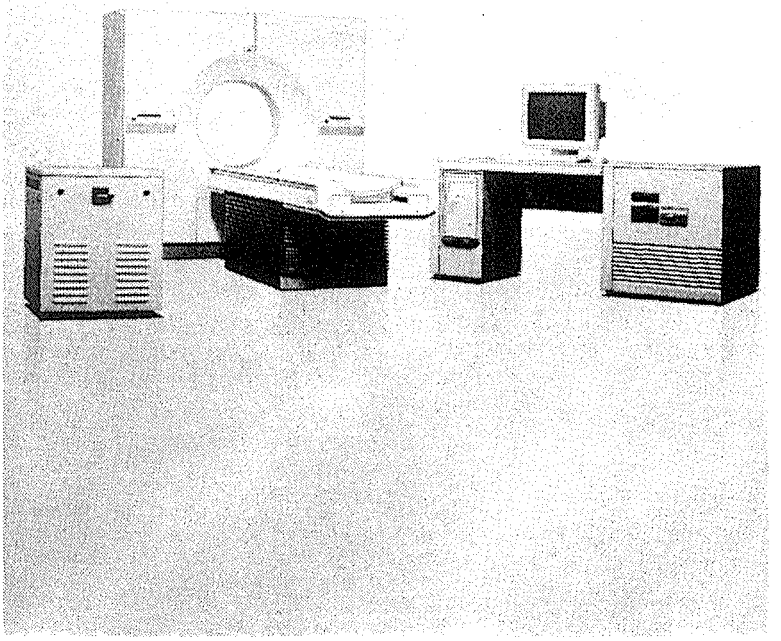

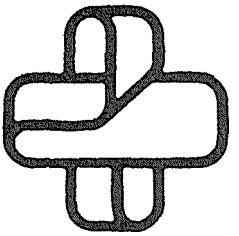

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The publication of the journal is subsidized by the Ministry of Science and Technology of the Republic Slovenia.

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Inštitut za diagnostično in intervencijsko radiologijo, UKC Ljubljana

Klinika za otorinolaringologijo in maksilofacialno kirurgijo, UKC Ljubljana

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