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IN MEMORIAM

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Color doppler for the evaluation of puncture site complications after percutaneous coronary interventions

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Femoral access site complications (FASC) after percutaneous coronary interventions (PCI) may be frequent, difficult to identify, and associated with significant morbidity. To refine our catheterization technique, we performed duplex color flow imaging (DCFI) in 42 consecutive patients undergoing diagnostic coronary arteriography (Group A) or PCI (Group B). In all patients, arterial (6-9F) and venous femoral sheaths (8F) were inserted by the Seldinger technique followed by the IV bolus of heparin (3000-10000 U). In Group A, the sheaths were removed immediately after the procedure. In Group B, heparin infusion (1000 U/hr) was started after PCI, and the sheaths were removed the following morning. DCFI was performed the day after catheterization using the 7.5 MHz linear phased-array transducer. Abnormal physical (groin swelling, new bruit) and ultrasound findings (hematoma, pseudoaneurysm, AV fistula) were recorded in 11 patients (26.2 %) and 15 patients (35.7 %), respectively. In patients with groin swelling or new bruits, DCFI revealed hematomas, pseudoaneurysms, or AV fistulas. FASC correlated with age >65 years ($p < 0.05$), sheath size ($p < 0.01$), and heparin dosage ($p < 0.01$). In conclusion, FASC occur often after PCI, and can be easily identified by DCFI. Risk factors include advanced age, large sheaths, and more aggressive heparin administration. Early detection using DCFI will minimize the morbidity associated with FASC.

Key words: angioplasty, transluminal, percutaneous coronary-adverse effects; coronary angiography-adverse effects; femoral vein-ultrasonography.

Introduction

Femoral access site complications (FASC) following percutaneous coronary interventions (PCI) add morbidity to the procedures and increase costs by prolonging hospital stay. FASC have been reported with increasing frequency, partly due to older patients with more extensive peripheral vascular disease, as well as owing to the widespread use of anticoagulant/fibrinolytic therapy, and larger size vascular sheaths.[1-11] Hematoma is the most common finding and represent a simple collection of blood with no communication with the punctured vessel.[12] Pseudoaneurysm results from leakage of blood into the soft tissues around the femoral artery, with subsequent fibrous encapsulation and failure of the defect in the vessel wall to heal.[13] AV fistula is an abnormal communication between the artery and the vein, occurring when a needle tract crosses both the artery and the vein and is dilated during catheterization.[14, 15] While hematoma is almost always spontaneously resorbed, pseudoaneurysm and AV fistula represent potentially unstable lesions, which may predispose to more serious sequelae. They may give origin to emboli; and may cause local infection, vascular thrombosis, or pressure effects and might rupture or cause high-output cardiac failure.[16] Several previous reports emphasized the limitations of physical findings, such as pulsatile groin mass, enlarging ecchymosis, abnormal puncture site pain and a new audible bruit in the clinical setting of peripheral vascular inju-

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ries.[17,18] Nowadays, duplex color flow imaging (DCFI) is believed to be the leading noninvasive, highly specific and sensitive modality for the diagnosis, planning of therapy and follow-up of potential FASC.[19–23] It allows for simultaneous 2D imaging of anatomic structures and Doppler study of blood flow, thus eliminating the need for invasive radiological procedures.[20–23]

In order to refine our current catheterization technique, FASC were prospectively evaluated in our group of patients following diagnostic coronary arteriography or PCI. The aims of this study were threefold: 1) to detect the frequency and nature of femoral access site complications in our group of patients; 2) to access the utility of clinical signs in the diagnosis of vascular complications as verified by DCFI findings; 3) to identify clinical and procedural factors that would predict the likelihood of these complications in our catheterization laboratory.

Materials and methods

Catheterization procedures

42 consecutive patients undergoing diagnostic coronary arteriography (Group A, 22 patients) or PCI with PTCA and stenting (Group B, 20 patients) at the Department of Cardiology, University Medical Center, Ljubljana, were enrolled in the prospective study between October 12, 1995 and February 20, 1996. Cardiac catheterizations were performed by four skilled interventional cardiologists. In all patients, arterial (Group A, 6F; Group B, 9F) and venous femoral sheaths (8F) were inserted using the Judkins approach by the double-wall Seldinger technique, followed by IV administration of a heparin bolus (Group A, 3000 U; Group B, 10000 U). In Group A, the sheaths were removed immediately after the diagnostic procedure. In Group B, heparin infusion (1000 U/hr) was started after PCI and the sheaths were removed the following morning 4 hrs after the discontinuation of heparin. The patients were maintained on bed rest for 6 (Group A) or 12 hrs (Group B) thereafter.

Clinical detection of vascular complications

Following the removal of sheaths each patient was examined for evidence of prolonged bleeding, subcutaneous ecchymosis, groin swelling, access site pain, vessel thrombosis and new femoral bruit.

Vascular imaging

DCFI was routinely performed in all patients with the Acuson computed color Doppler sonography system (Acuson 128, Acuson Corporation, Mountain View, Canada) employing the 7.5 MHz linear phased-array transducer. The greatest diameter and the site of the peripheral vascular complications were recorded. An echo-free mass with no communication with the vascular structures was considered to be a hematoma. Pseudoaneurysm was identified as an extravascular hypoechogenic cavity communicating with the femoral artery by a sinus tract, displaying "to and fro" signal on pulsed Doppler examination (Figure 1a). AV fistula was characterized by demonstrating a communication between the femoral artery and vein with a unidirectional continuous AV shunt representing typically, high diastolic flow in the arterial waveform proximal to the fistula and increased turbulent flow with arterial pulsation in the draining vein (Figure 1b).

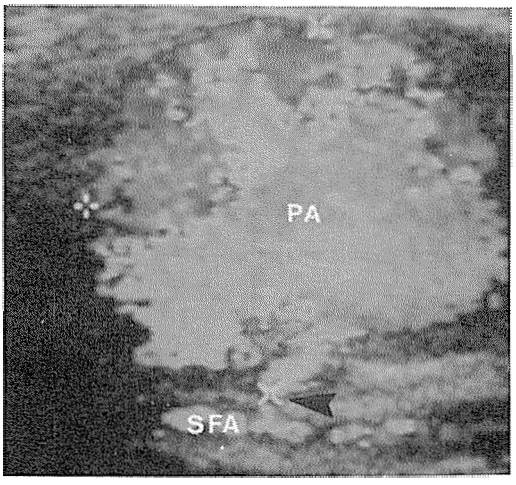

Figure 1a. A longitudinal color and pulsed Doppler image of the pseudoaneurysm (PA) at the ventral aspect of the superficial femoral artery (SFA) showing the cavity communicating with the artery by a sinus tract (arrow), and characteristic "to and fro" waveform.

Clinical data

The recorded baseline clinical variables included patient age, gender, height, weight, body mass index (BMI), pulse pressure during catheterization, risk factors for atherosclerotic disease and the presence of femoral and aorto-iliac artery disease. The procedural parameters included the type of cath-

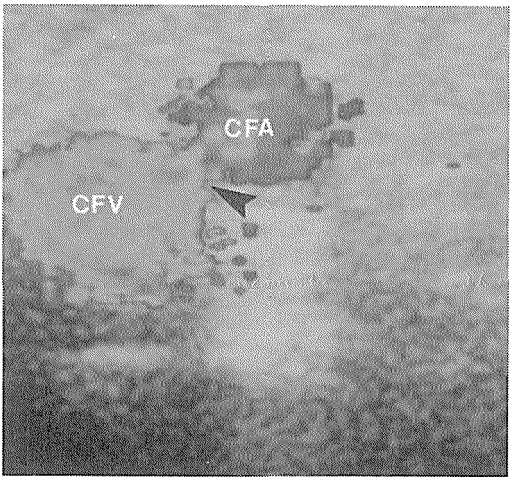

Figure 1b. A transverse color and pulsed Doppler image of the AV fistula between the common femoral artery (CFA) and the common femoral vein (CFV) showing a communicating channel (arrow), and continuous, unidirectional, turbulent waveform.

eterization procedure, the size of indwelling vascular sheaths, the number of consecutive ipsilateral punctures, and the length of bed rest prior to ambulating. The amount of heparin administered during and after the procedure was also documented.

Statistics

Numeric continuous data were analyzed as the mean ±1 SD, and categorical parameters were expressed as proportions. Differences in the distribution of selected characteristics between patients with DCFI-detected vascular complications and those without them were examined by the two-tailed Student t-test and the Chi-square test for continuous and categorical variables, respectively. Univariate logistic regression was then performed to identify individual factors predicting the likelihood of vascular complications. Statistical significance was defined as a p value <0.05. All analyses were performed with the SPSS release 6.0 statistical package.

Results

Diagnosis

In 42 consecutive patients undergoing diagnostic coronary arteriography or PCI no major FASC, such as severe groin/abdominal hemorrhage, access site infection, sepsis or limb loss were observed. Abnormal physical and ultrasound findings were observed in 11 (26.2 %) and 15 (35.7 %) patients, respectively (Table 1a). In 11 patients clinically suspected of having FASC, 7 hematomas, 1 pseudoaneurysm, and 3 AV fistulas were confirmed by DCFI. 4 (9.5 %) additional patients with no local signs of FASC were found to have a significant vascular pathology on routine DCFI examination. One from 8 hematomas (12.5 %), 2 from 3 pseudoaneurysms (66.6 %), and 1 of 4 AV fistulas (25.0 %) would be missed solely on clinical grounds.

Clinical assessment

Physical findings at the access site in 15 patients with the DCFI-confirmed FASC are detailed in Table 1b. In patients with large groin swelling measuring ≥7 cm, DFCI revealed 4 hematomas, but 1 pseudoaneurysm and 1 AV fistula. Though femoral

Table 1a. Clinical and DFCI findings in patients following diagnostic coronary arteriography (Group A) and PCI (Group B).

Patients	Swelling ≥ 7 cm	New bruit	Hematoma	Pseudoaneurysm	AV fistula
Group A (n = 22)	4 patients (18.2 %)	2 patients (9.1 %)	4 patients (20.0 %)	1 patient (4.5 %)	1 patient (4.5 %)
Group B (n = 20)	2 patients (10.0 %)	3 patients (15.0 %)	4 patients (18.2 %)	2 patients (10.0 %)	3 patients (15.0 %)
Total (n = 42)	6 patients (14 %)	5 patients (12 %)	8 patients (19.0 %)	3 patients (7.1 %)	4 patients (9.5 %)

Table 1b. Physical findings at the access site in 15 patients with DCFI-confirmed diagnosis of femoral artery injury following diagnostic coronary arteriography or PCI.

Patients (n=15)	Hematoma	Pseudoaneurysm	AV fistula
Ecchymosis	6/8 patients	1/3 patient	0/4 patient
Groin swelling	4/8 patients	1/3 patient	1/4 patient
Pulsation	0/8 patient	1/3 patient	0/4 patient
Tenderness	8/8 patients	3/3 patients	4/4 patients
New bruit	1/8 patients	1/3 patient	3/4 patients

arterial pulsations were transmitted from the femoral artery in all patients, a more marked pulsation that extended over the femoral artery boundaries was observed in only 1 patient with pseudoaneurysm. New bruits were detected in both patients with pseudoaneurysm (33.3 %) and AV fistula (35.0 %), but they were also recorded in 1 (12.5 %) patient with hematoma. The bruit associated with a pseudoaneurysm was systolic in nature; on the other hand, the bruits present in patients with AV fistula were described as continuous in 2 patients, and as "long-systolic" in 1 patient. Subcutaneous ecchymosis was associated with hematoma in 6, and with pseudoaneurysm in 1 patient. Mild to moderate tenderness at the local puncture site was present in all patients.

DCFI characteristics

A total of 15 FASC included 8 hematomas (53.3 %), 3 pseudoaneurysms (20.0 %) and 4 AV fistulas (26.6 %). Most of hematomas were graded as small and measured 2.6 ± 0.6 cm in diameter. Pseudoaneurysms had an average dimension of 2.5 ± 0.5 cm and were located within 1 cm from the involved arterial segment. 2 pseudoaneurysms occurred at the ventral aspect of the superficial femoral artery, and one at the dorsal aspect of the common femoral artery in close proximity to its bifurcation. AV fistulas were located in superficial femoral artery in 3 cases, and in the common femoral artery in 1 case. They were considered to be hemodinamicaly unimportant, since no signs of venous hypertension or proximal arterial dilatation were observed during DCFI examination.

Risk factors

FASC were more likely to result from PCI as compared to diagnostic coronary angiography (45.0 % versus 27.2 %, $p < 0.05$). A comparison of baseline and procedural variables between patients with DCFI-confirmed vascular complications and patients without complications are shown in Table 2. The studied groups did not differ as concerns sex, obesity, underlying predisposing risk factors and distribution of aorto-iliac artery disease. In both groups, blood coagulation tests before catheterization were within normal range. Pre-treatment with aspirin or dipyridamol did not influence the risk of FASC in this study. Among all patients, the strongest predictors of FASC were advanced age ($p < 0.05$), the use of large-size indwelling sheaths ($p < 0.01$) and higher dosage of heparin ($p < 0.01$). Univariate logistic regression was used to identify the clinical and procedural factors predicting the likelihood of FASC (Table 3). A dose-dependent regimen of heparin administration remained a statistically significant risk factor in all entities. While advanced age significantly contribute to hematoma formation, the use of large-size sheaths predicted the likelihood of AV fistula formation.

Management

All peripheral vascular lesions were managed non-operatively. Transfusion of 3 U of blood was ad-

Table 2. DFCI confirmed FASC as a function of clinical and procedural characteristics in patients undergoing diagnostic coronary arteriography or PCI.

Characteristic	Complications (n = 15)	Controls (n = 27)	P
Age (years)	65.4±10.0	56.2±11.6	0.013
Age > 65 years	40.0 %	25.9 %	0.029
Male gender	66.6 %	59.2 %	NS
BMI (kg/ m^2)	26.5 ±2.8	25.9 ±4.3	NS
Obesity (BMI >25 kg/m^2)	40.0 %	37.0 %	NS
Hypertension	66.6 %	62.9 %	NS
Pulse pressure (mm Hg)	65.4 ±19.9	65.2 ±19.9	NS
Diabetes mellitus	3.3 %	7.4 %	NS
Hypercholesterolemia	53.3 %	48.1 %	NS
Current smoking	33.3 %	59.2 %	NS
Peripheral vascular disease	26.6 %	25.9 %	NS
Aspirin or dipyridamole before catheterization	80.0 %	85.1 %	NS
Heparin during catheterization (10.000 U vs 3.000 U)	73.3 %	29.6 %	0.006
Continuous heparin overnight (1000 U/h)	73.3 %	29.6 %	0.006
Sheath dimension (9 F vs 6 F)	66.6 %	33.3 %	0.005
Consecutive number of ipsilateral arterial puncture	2.1±1.8	1.8 ±1.2	NS

ministered to only 1 patient with moderate hemorrhage into the retroperitoneal space. Most hematomas resorbed within a few days or weeks, depending on their size. One pseudoaneurysm showed spontaneous resolution as documented by the follow-up DCFI. Two stable pseudoaneurysms were successfully treated by DCFI-guided external compression. All AV fistulas appeared hemodinamicaly unimportant and were followed-up closely by DCFI.

Discussion

The reported incidence of FASC after diagnostic coronary arteriography varies widely, from less than 1 % to as much as 20 %.[1-3, 7-10] When PCI are included the figure is higher (6.1-24 %), possibly owing to the introduction of new devices, increased anticoagulation and larger sheath size.[4-6, 11] Furthermore, owing to the difference in definition there is a wide discrepancy in the reported incidence of FASC, in particular those of hematoma (0.6-12.3 %) and bleeding (0.1-20.0 %).[1, 4-6, 8] Our 26.2 % incidence of FASC detected clinically ranks among the highest reported rates. It was mostly contributed to small stable hematomas, that would be excluded in other studies. The incidence of pseudoaneurysms (2.3 % clinical detection; 7.1 % DCFI) compares favorably with previously reported (0.5-5.2 clinical detection; 5.8–9.0 % DCFI).[12, 13] Our incidence of AV fistulas (7.1 % clinical detection; 9.5 % DCFI) was higher as compared to other studies (0.05-0.1 % clinical detection, 0.3-5.2 % DCFI)[14, 15, 21] and may be related to our common practice to perform the double-wall Seldinger technique and routine ipsilateral arterial and venous catheterization. However, in contrast to other reports, no major FASC, such as severe hemorrhage, access site infection, sepsis, limb loss or even death were observed in our study.

Our current methods for the detection of FASC included a routine clinical and DCFI examination. Clinically, FASC were suspected in 11 patients, but DCFI-confirmed in 15 patients. Four patients (9.5 %) with significant vascular pathology would be missed on clinical grounds alone. Accordingly, we believed that clinical examination alone is not sufficient in order to detect all FASC. Although several physical signs have been used to detect FASC, clinical examination alone may not reliably distinguish between different entities. The rate of diagnostic accuracy of any single physical sign detected in our study was low. In patients with groin swelling, DCFI revealed hematomas, as well as pseudoaneurysms and AV fistulas. Although pulsatility of the mass appeared to be suggestive of pseudoaneurysm, it was present in only one case. As expected, new bruits suggested both pseudoaneurysm and in AV fistula, but simple hematoma did also cause a bruit due to extrinsic compression of the neighboring artery. Furthermore, a quality of bruit did not reliable identify its etiology.

The early recognition and prompt treatment of unstable vascular lesions are necessary to prevent further morbidity.[16, 24] Apart from progressive expansion and pain no objective criteria exist that would prospectively identify those pseudoaneurysms that will rupture and those that will spontaneously thrombose.[22, 23] In the present study, two stable pseudoaneurysms were successfully treated by DCFI-guided manual compression. Thus, we obviated the need for surgical interventions, and prevented spontaneous rupture in those patients followed conservatively.

The incidence of FASC was significantly higher after PCI than after diagnostic coronary arteriography as confirmed previously.[4, 6-8] FASC were most closely associated with the use of large-diameter sheaths and higher amount of heparin administration. Significantly higher complication rate observed in patients of advanced age may be due to a somewhat delayed process of healing, and seems to implicate a rigidity and poor retractability of underlying vessels.

Conclusion and future outlook

FASC occur frequently after PCI and can be easily identified by DCFI. Diagnosis based on clinical examination alone is rather inaccurate. An exact

Table 3. Univariate logistic regression for the identification of individual clinical and procedural factors predicting the likelihood of hematoma, pseudoaneurysm and AV fistula.

Characteristic	Hematoma	Pseudoaneurysm	AV fistula
Advanced age	$p < 0.03$	NS	NS
Periprocedural regimen of heparin	$p < 0.05$	$p < 0.04$	$p < 0.02$
Sheath dimension	NS	NS	$p < 0.04$

diagnosis facilitates the choice of treatment and prevents further morbidity. Based on our initial experience, DCFI-guided compression seems to be a useful alternative to surgical closure of pseudoaneurysm. Risk factors, identified in our study include advanced age, large sheaths, and large amount of heparin administration. Monitoring of adjunctive anticoagulant therapy, and careful patients selection may reduce the morbidity and increase the safety of these procedures. It seems advisable to use a single-wall puncture technique, to avoid routine venous puncture, and to alternate the access site with repeat catheterization. As indicated by our study, meticulous attention to catheterization details will minimize complications related to the access, while early detection and management will reduce the morbidity associated to complications.

References

1. Gwost J, Stoebe T, Chesler E, Weir EK. Complications of coronary arteriography from the collaborative study of coronary artery surgery (CASS). *Circulation* 1979; **59**: 1105–11.
2. Skillman JJ, Kim D, Baim DS. Vascular complications of percutaneous femoral cardiac interventions. *Arch Surg* 1988; **123**: 1207–12.
3. Babu SC, Picorrellil GO, Shash PM, Stein JH, Clauss RH. Incidence and results of arterial complications among 16,350 patients undergoing cardiac catheterization. *J Vasc Surg* 1989; **10**: 113–6.
4. Kaufman J, Moglia R, Lacy C, Dinerstein C, Moreyra A. Peripheral vascular complications from percutaneous transluminal angioplasty: A comparison with transfemoral cardiac catheterization. *Medical Sciences* 1989; **297**: 22–5.
5. Oweida SW, Roubin GS, Smith RB, Salam AA. Post-catheterization vascular complications associated with percutaneous transluminal coronary angioplasty. *J Vasc Surg* 1990; **12**: 310–5.
6. Muller DW, Podd J, Shamir KJ. Vascular access site complications in the era of complex interventions. *Circulation* 1992; **82**: 510.
7. Mullet DW, Shamir KJ, Ellis SG, Topol EJ. Peripheral vascular complications after conventional and complex percutaneous coronary procedures. *Am J Cardiol* 1992; **69**: 63–8.
8. Fransson SG, Nylander E. Vascular injury following cardiac catheterization, coronary angiography, and coronary angioplasty. *European Heart Journal* 1994; **15**: 232–5.
9. Ricci MA, Trevisani GT, Pilcher DB. Vascular complications of catheterizations. *The American Journal of Surgery* 1994; **167**: 357–78.
10. Bogart DB, Bogart M, Miller JT, Farrar MW, Barr K, Montgomery MA. Femoral artery catheterization complications: A study of 503 consecutive patients. *Cathet Cardiovasc Diagn* 1995; **34**: 8–13.
11. Omoigui NA, Califf RM, Pieper K, Keller G, O'Hanesian MA, Berdan LG, Mark DB et al. Peripheral vascular complications in the coronary angioplasty versus excisional atherectomy trial (CAVET). *JACC* 1995; **26**: 922–30.
12. Altin RS, Flicker S, Naidech HJ. Pseudoaneurysm and arteriovenous fistula after femoral artery catheterization: Association with low femoral punctures. *AJR* 1989; **152**: 629–31.
13. Mitchell DG. Femoral artery pseudoaneurysm: diagnosis with conventional duplex and color Doppler US. *Radiology* 1987; **165**: 687–90.
14. Heystraten FMJ, Fast JH. Arteriovenous fistula as a complication of the Seldinger procedure of the femoral artery and vein. *Diagn Imag* 1983; **52**: 197–201.
15. Thadani U, Pratt AE. Profunda femoral arteriovenous fistula after percutaneous arterial and venous catheterization. *Br Heart J* 1971; **33**: 803–5.
16. Mills JL, Wiedman JE, Robinson JG, Hallet JW. Minimizing mortality and morbidity from iatrogenic arterial injuries: the need for early recognition and prompt repair. *J Vasc Surg* 1986; **4**: 22–7.
17. Messina JL. Clinical characteristics and surgical management of vascular complications in patients undergoing cardiac catheterization. *J Vasc Surg* 1989; **13**: 593–600.
18. Cohen GI, Chan KL. Physical examination and echo Doppler study in the assessment of femoral arterial complications following cardiac catheterization. *Cathet Cardiovasc Diagn* 1990; **21**: 137–43.
19. Reneman RS. Cardiovascular applications of multi-gate pulsed Doppler systems. *Ultrasound in Med and Biol* 1986; **12**: 357–70.
20. Coughlin BF, Pausther DM. Peripheral pseudoaneurysm: evaluation with duplex US. *Radiology* 1988; **168**: 339–42.
21. Igidbashian VN, Mitchell DG, Middleton WD, Schwartz RA, Goldberg B. Iatrogenic femoral arteriovenous fistula: diagnosis with color Doppler imaging. *Radiology* 1989; **170**: 749–51.
22. Mitchell DG. Femoral artery pseudoaneurysm: diagnosis with conventional duplex and color Doppler US. *Radiology* 1987; **165**: 687–90.
23. Sheikl KH. Utility of Doppler color flow imaging for identification of femoral arterial complications of cardiac catheterization. *Am Heart J* 1989; **117**: 623–8.
24. Kirsh JD, Reading CC, Charboneau W. Ultrasound-guided compression and repair of postangiographic femoral arteriovenous fistulas. *Mayo Clin Proc* 1993; **68**: 612–3.

Radiol Oncol 1996; 30: 171-6.

Routine versus selective intraoperative cholangiography during open cholecystectomy?

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In the last 20 years, 3653 patients suffering from biliary calculous disease have been operated on in the Karlovac County General Hospital, 511 (14 %) of them with common bile duct exploration (CBDE). A total of 436 selective Intraoperative Cholangiographies was performed and, on the basis of the obtained results, CBDE was performed in 271 (53 %) cases. Intraoperative cholangiography (IOC) was indicated but not performed in 71 (14 %) cases because of medical, technical and other reasons, mainly subjective. In 47 (9 %) patients CBDE was performed without previous IOC because of clear clinical findings in 112 (24 %) cases, CBDE was performed on the basis of the surgeons's clinical estimation, without IOC. Preoperative and intraoperative criteria were used. The preoperative criteria (CR I) included obstructive jaundice, biliary panceatritis and cholangitis in recent history as well as positive findings of intravenous biligraphy (IVB) or ultrasonic tomography (UST). The intraoperative criteria included an enlarged CBD, a wide cystic duct or the presence of small multiple stones in the gallbladder. Positive IOC findings occured in 287 (63,5 %) and negative in 141 (33 %) cases. The findings in eight cases were insufficient for analysis. False positive IOC findings occured in 24 (5,2 %) and false negative IOC findings in 22 (5 %) cases of all 436 IOC's. By using selective IOC we recorded 69 (1,7 %) missed stones and 63 (13 %) negative, unnecessary CBDE's. Only one complication in the form of a CBD lesion was recorded. In average, IOC extended operative time for about 30 minutes and increased the operative cost for 62 %.

Key words: cholecystectomy; intraoperative period; intraoperative cholangiography, retained stones, negative common bile duct exploration, cryteria

Introduction

In 1932. Mirizzi published his first experiences of intraoperative cholangiography (IOC) used for detecting unsuspected common bile duct (CBD) stones. This method was widely accepted a few decades later. The purpose of IOC was to detect as many unsuspected CBD stones as possible, and to reduce the percentage of unnecessary common bile duct exploration (CBDE).

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The method decreased unnecessary morbidity and mortality due to CBDE and reoperations.[1,2] In the 1960s, the method was accepted by a great number of surgeons. The increased cost of the procedure, extended operative time, increased danger of possible intraoperative infections, unnecessary exposure to x-ray radiation as well as the need for additional, expensive x-ray equipment were its disadvantages. Because of the above mentioned reasons, a group of surgeons preferred a selective use of IOC.

They reported almost identical results to those obtained by routine IOC.[2-6] The selective use of IOC reduces the total cost of the procedure as well as the above mentioned complications and problems. IOC detects other changes in the CBD as well

as in the papilla Vateri. We use pre-operative and intraoperative criteria. Laparoscopic cholecystectomy tries to maintain all successfull intraoperative diagnostic methods confirmed in open cholecystectomy, including IOC. The most recent papers discuss the use of selective IOC during laparos-copic cholecystectomy.[7-9]

Material and methods

From 1974 to 1994, 3653 patients with calculous biliary disease underwent open cholecystectomy. During the procedure, 511 patients underwent CBDE. Patients with malignant diseases of the biliary tract with or without stones were excluded. IOC was performed in 436 patients on the basis of the preoperative or intraoperative criteria. The mean age of the patients was 56 (18–84). There were 31 % male and 69 % female patients.

The preoperative criteria were determined as follows:

1. *Filling defects and ultrasonic echo in the CBD* were considered as: positive findings as well as a wide CBD with an internal diameter larger than 10 mm.

2. *A wide CBD* with the contrast slowly emptying into the duodenum during *IVB* was considered a positive criteria, too.

3. *Jaundice in recent history*-bilirubin (Bil) > 50 umol/L, alkaline phosphatase (AP) > 100 u/L three months prior to the procedure.

4. *Pancreatitis in history*-data related to biliary pancreatitis a year prior to the operation.

5. *Cholangitis*-biliary colics, fever and transitory jaundice six months prior to the operation.

The intraoperative criteria established on the basis of the intraoperative findings were as follows:

1. *Enlarged CBD* with an external diameter larger than 12 mm. The size of the CBD was determined by means of a 12-mm olive Bakes probe;

2. *Enlarged cystic* duct (CD) with an external diameter larger than 4 mm;

3. *Presence of small stones in the gallbladder;* Small multiple stones were detected either by palpating the emptied gallbladder (needle bile aspiration) or by examining the content of the extracted gallbladder.

In addition to the above mentioned criteria, CBDE with no previous IOC was performed in patients with the following:

1. *Palpable stones in CBD;*

2. *Presence of progressive obstructive icterus* at the time of the operation (Bil > 100 umol/L, AP > 150 u/L);

3. *Enlarged CBD* with an external diameter larger than 15 mm.

In some cases IOC was not performed despite the positive criteria. Technical and medical disadvantages were the main reasons, as well as the fact that, at the beginning, some surgeons in the Hospital refused to accept the procedure. IOC was performed through a square incision on the lateral side of the cystic duct. A polyethylene venous 4–6 F gauge catheter or a metal Storz cannula was inserted. During the examination all unnecessary metal instruments were removed from the operating field. A mobile »SIEMENS« C-arm image amplifier was covered with a special sterile cover. Before the contrast injection the bile tree was flushed with 20–40 ml of warm Normal Saline.

Possible air bubbles were aspirated. The contrast, Telebrix, Biligraphin, Biliscopin, Omnipaque, Ronpacon was diluted to 30 % dilute solution, so that the contrast would not obscure possibble small stones. Diascopy was performed with 10 ml of the contrast and the contrast flow was followed through the papilla Vateri. Two films 24 x 30 cm size and additional 20 ml contrast medium was used. While the films were being developed we completed cholecystectomy to shorten operative time. After the examination, the complete sterile operative kit was replaced. The duration of the examination was recorded on an anaesthesiological sheet. The additional costs were calculated on the basis of the cost of x-ray films, contrast medium, syringes, catheters and additional sterile material. The cost of anaesthesia and the medical radiology team's fee were taken into account while the cost of operating theatre and the surgical team's fees were not determined and, therefore, were left out.

Results

Of 3653 patients undergoing cholecystectomy, 436 (12 %) underwent selective IOC. Of 511 CBDEs performed, 271 (53 %) were performed on the basis of positive selective IOC findings.

The number and percentage of the positive and negative IOC findings and the distribution of the false negative and false positive finding are given in Figure 1. In performing selective IOCs we were guided by preoperative and intra operative criteria.

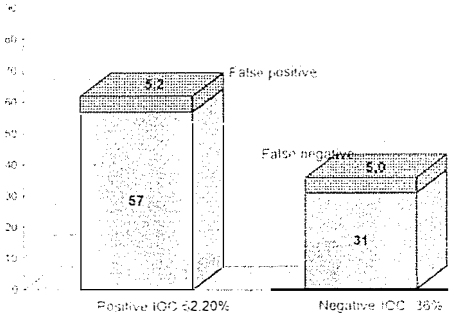

Figure 1. Relations between positive and negative IOC findings. False negative and false positive findings is present too. Eight (1,8 %) insuffitient IOCs was insuffitient for use.

More than 60 % of the patients fulfilled more than one criterion. In Table I we emphasized only one criterion, the one that had been recorded in the files first. In 22 patients the first criterion was not clearly indicated and in 9 patients IOC was performed on the basis of unknown preoperative criteria. The most common combination not given in Table I was a wide CBD accompanied by jaundice and/or pancreatitis in history. A positive IVB or UST finding was the most common preoperative criterion used in 37 % (129/350). Over one third of the positive CBDE results was due to pancreatitis. The most common combination of the intraoperative criteria was a wide CD with small stones in the gallbladder. Nevertheless, the most common intraoperative criterion was a wide CBD – 74 % (58/78).

As the paper shows, IOC should have been performed in 71 (14 %) cases, but, because of the reasons mentioned earlier, it was not performed. The results in this group were very bad as shown in Table 2.

The procedure extended operative time for approximately 30 minutes. In cases with a preoperative indication, operative time was extended for a little more than 20 minutes and in the cases with an intraoperative indication, it was extended for more than 45 minutes.

The IOC cost can not be shown in figures in our circumstances, but we have estimated that the cost of cholecystectomy with IOC is 62 % more expen-

Table 1. Preoperative and intraoperative criteria distribution and results of IOC Criteria for IOC.

CRITERIA FOR IOC	IOC	IOC pos (%)	IOC neg (%)	CBDE pos (%)	CBDE neg (%)
Preoperative (CR I)	350	227 (65 %)	123 (35 %)	208 (92 %)	19 (8%)
Positive IVB*	55	34 (62 %)	21 (28 %)	31 (91 %)	3 (9%)
Positive UST*	42	23 (55 %)	19 (45 %)	21 (91 %)	2 (9%)
Positive IVB or UST*	32	26 (81 %)	6 (19 %)	24 (92 %)	2 (8%)
Jaundice	82	63 (77 %)	19 (23 %)	59 (94 %)	4 (6%)
Pancreatitis	85	43 (51 %)	42 (49 %)	40 (93 %)	3 (7%)
Cholangitis	23	17 (74 %)	6 (26 %)	16 (94 %)	1 (6%)
Miscellaneous	22	17 (77 %)	5 (23 %)	13 (76 %)	4 (24%)
Unknown	9	4 (44 %)	5 (56 %)	4 (100 %)	0
Intraoperative (CR II)	78	60 (77 %)	18 (23 %)	56 (93 %)	4 (7%)
Wide CBD > 12 mm	58	47 (81 %)	11 (19 %)	44 (94 %)	3 (6%)
Wide CD > 4 mm	9	7 (78 %)	2 (22 %)	6 (86 %)	1 (14%)
Small stones in	11	6 (55 %)	5 (45 %)	6 (100 %)	0
Total**	428	287 (67 %)	141 (33 %)	264 (92 %)	23 (8%)

IOC – intraoperative cholangyography, CBDE – common bile duct exploration (choledochotomy), IVB – intravenous biligraphy, UST – ultrasonic tomography, CBD – common bile duct, CD – cystic duct.
* In preoperative calculous biliary desease diagnostics we used IVB till 1984, from 1984 to 1989, the combination of IVB and UST and since 1989 we have been using UST in most cases.
** The quality of 8 IOC's was not suitable for analyses.

Table 2. Retained stones and negative CBDE data.

	Crit I	Crit II	IOC was not necessary	CBDE without IOC	Simple cholecystectom	Total
Cholecystectomy	350	78	47	71	3106	3653
Retained stones	29 (8 %)	4 (5 %)	2 (4 %)	21 (30 %)	13 (0,4 %)	69
Negative CBDE	19 (5 %)	4 (5 %)	3 (6 %)	29 (40 %)	8 (0,25 %)	63
	48 (13 %)	8 (10 %)	5 (10 %)	50 (70 %)	21 (0,65 %)	132

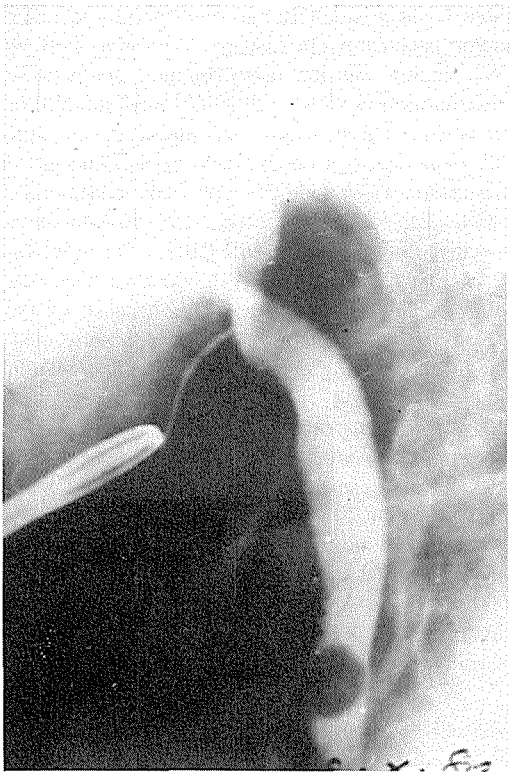

Figure 2a. Prepapillary stone detected by IOC. CBDE was performed, the stone was extracted and T – tube inserted.

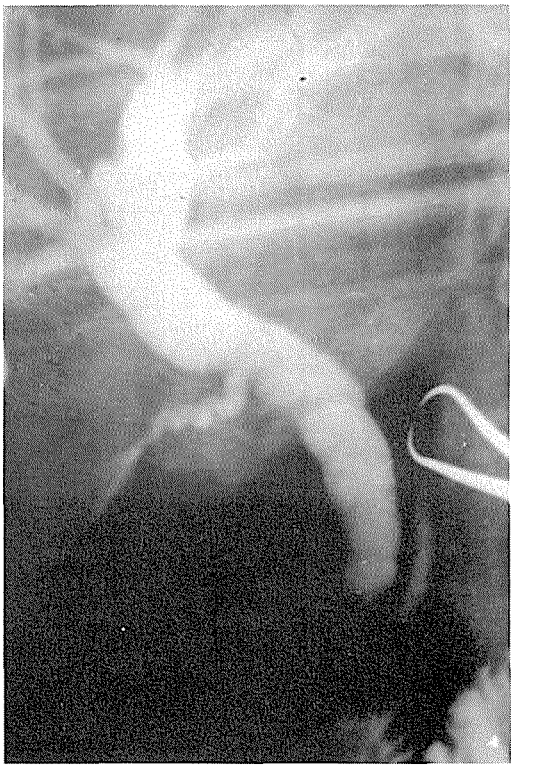

Figure 2b. Papillary stenosis with suprastenotic dilatation of the complete biliary tree. Latero-lateral choledochoduodenostomy was performed.

sive than simple cholecystectomy using the points and their value given in the so called »Blue Book«.

Discussion

IOC reduces the number of retained stones as well as the percentage of unnecessary CBDEs. Selective IOC has proved its value in conventional cholecystectomy. Recently, its use has been taken into consideration in laparoscopic cholecystectomy.[8, 9] CBDE increases morbidity and mortality rate three of four times when compared with simple cholecystectomy.[10–20] Stirnemann[14] reports that mortality in biliary reoperations is 8.8 % and in CBDE with cholecystectomy only 2,8 %. Lennert[15] reports two deaths in negative CBDE, and Sheridan et al[11] noted 39,3 % complications in the patients who had had negative, unnecessary CBDEs, including two deaths, too.

On the basis of the data given in Table 3 we can seen that an attempt to avoid retained stones can lead to an increased percentage of negative CBDE. In their comparative reports, Clavien and Strassberg[17] using routine IOC report an irrelevant percentage (0,2 %) of retained stones or no stones at all, but their reported negative CBDEs were 27 % and 39 % respectively. Sheridan et al[11] reported 2 % retained stones and 22,3 % negative CBDEs respectively. Morgenstern and Berci[16] conclude that 1 % of retained stones at routine IOC is an optimal percentage. On the other hand, Gerber and Apt[21] showed 500 consecutive cholecystectomies without any IOC. They recorded only one retained stone. Therefore, our results of 1.7 % of retained stones and 13 % of negative CBDE could be considered satisfactory. We have been using the IOC criteria for a long time of which we reported earlier.[22] Gregg[3] divided the indications of common duct stones into three groups: *minimal* – 4 % of positive findings, *moderate* – 21 positive findings and *maximal* – 91 of positive findings. He has concluded that IOC should be performed in only 7–8 % of patients. Wilson et al[5] divide cholecystectomies into two

Table 3. References of reported cases in avaliable literature.

Refer	Author	Country	Year	Cholecisectomy No.	IOC %	Residual stones %	Negative CBDF %
14	Strinemann	Swiss	1984	346	100	1.2	18.6
16	Morgenstern & Berci	USA	1992	1200	95	0.8	
17	Clavien	Swiss	1992	602	91	0.2	26.8
17	Strassberg	Canada	1992	650	89	0	39.3
19	Den Besten & Berci	International	1986	1072	83	4.5	18.5
20	Moreaux	France	1994	5000	83	1.56	0.5
2	Shively	USA	1990	579	81		21.5
5	Wilson	Austral	1986	272	51	0.36	18
11	Sheridan	United Kingdom	1987	1962	10	1.9	14
3	Gregg	USA	1986	1035	1.9	2.5	16.5
	Present Report	Croatia	1994	3653	12	1.7	13.3

groups: *»Would explore«* and *»Would not explore«*. There were 49 % of positive findings in the first group and only 4 % of missed stones in the second group. Pace et al[6] divide the IOC criteria into *CR+* and *CR–*. They had 95.7 % of normal fin dings in the CR– group and 71 % of positive findings in the CR+ group. In this way, they avoided unnecessary CBDE in 55 % of patients. The greatest percentage of positive findings (63 %) occured in the group with an elevated serum Bilirubin level as the criterion, while in the group where the criterion was preoperative cholangitis there were even 82 % of IOC findings. Our results show that preoperative jaundice gave 77 % of positive IOC findings while preoperative pancreatitis gave positive results in only one third of patients and this coresponds with other reports. The most common preoperative criteria are preoperative positive IVB or UST findings.[23, 24]

In addition to the presence of CBD stones we take into account the internal diameter of CBD too. In our report a wide CBD was criterion in 73 % of cases and filling defects in 70 % of IOCs and in 56 % of CBDEs positive. Although different authors consider an 8–15 mm CBD enlarged, we take a 10 mm internal diameter as a positive preoperative criterion, while a 12 mm external diameter is taken as a positive intraoperative criterion. Intraoperative criteria were determined only in 20 % of cases. Fourty-seven (9 %) patients underwent CBD without previous IOC. Twenty-eight (8.5 %) patients had palpable stones in the CBD. Gregg[3] palpated only 7 (13.7 %) stones in 51 patients with CBD stones. Stirnemann[14] reports that stones can be palpated only in the middle third of the CBD, the palpation certainty being only 10 %. Our report shows that in the group of 71 patients where IOC was clinically indicated but not performed, 21 (30 %) retained stones and 29 (49 %) negative CBDEs were recorded. Different authors report different extensions of operative time. Thompson and Bennion report a 7-minute extension of operative time, Gregg a 23-minute, Shively a 10-minute and Paulino-Netto a 27-minute extension of operative time.[2,3, 25, 26]

Our results show an average extension of operative time of 30 minutes. The majority of the authors take the age of patients as a positive criterion but we have not noticed any incidence of CBD stones related to the patients' age. The cost of the procedure varies from USD 125 to USD 400 in different authors. Taylor[27] states that routine IOC in all cholecystectomies carried out in 1987 would have cost additional 90 million dollars. According to Skilling,[28] the cost of one detected unsuspected CBD stone is USD 6,612. According to Gregg,[3] 200 cholangiograms and 12 CBDEs have to be carried out to prevent one recurrent stone, at a cost of at least USD 80,000. Pace[6] reports that 2135 routine IOCs must be performed to detect one unsuspected CBD stone. Our investigation has shown that each IOC increases the cost of simple cholecystectomy for 62 %. If we compare our results with those given in literature we can conclude that we have chosen good criteria for selective IOC. It is a method of choice of intraoperative diagnostics in classical open as well as in laparoscopic cholecystectomy. It decreases the total cost of the procedure giving good results in detecting CBD stones during cholecystectomy. In this way, unncessary CBDEs, which increase morbidity and mortality rate, are avoided.

References

1. Stark ME, Longthry CW Routine operative cholangiography with cholecystectomy. *Surg Gynecol Obstet* 1980; **151**: 657–8.
2. Shively EH et al. Operative cholangiography. *Am J Surg* 1990; **159**: 380–5.
3. Gregg RO. The case for selective cholangiography. *Am J Surg* 1988; **155**: 540–5.
4. Taylor TV, Torrance B, Rimmer S, Hillier V and Lucas SB. Operative cholangiography: Is there statistical alternative; *Am J Surg* 1983; **145**: 640–3.
5. Wilson TG, Hall JC, Watts J, Mc K. Is operative cholangiography allways necessary? *Br J Surg* 1986; **73**: 637–40.
6. Pace BW, Cosgrove J, Brener B, Margolis IB. Intraoperative cholangiography revisited. *Arch Surg* 1992; **127**: 448–50.
7. Lorimer JW, Fairfull-Smith RJ. Intraoperative cholangiography is nor essential to avoid duct injuries during laparoscopic cholecystectomy. *Am J Surg* 1995; **169**: 344–7.
8. Sackier JN, Berci G, Philips E, Caroll B, Shapiro S, Par-Partlow M. The role of cholangiography in laparoscopic cholecystectomy. *Arch Surg* 1991; **126**: 1021–6.
9. Soper NJ, Dunnegan DL. Routine versus selective intraoperative cholangiography during laparoscopic cholecystectomy. *World J Surg* 1992; **16**: 1133–40.
10. Crumplin MKH et al. Menagement of gallstones in a district general hospital. *Br J Surg* 1985; **72**: 428–32.
11. Sheridan WG, Williams HOL, Lewis MH. Morbidity and mortality of common bile duct exploration. *Br J Surg* 1987; **74**: 1095–9.
12. Trede M, Schaupp W. Ein Pladoayer fur die Cholecystetomie-Gold-Standard der Gallensteintherapie. *Chirurg* 1990; **61**: 365–9.
13. McShery ChR. Cholecystectomy. The Gold-Standard. *Am J Surg* 1985; **158**: 174–88.
14. Stirneman H. Gallengangrevision: Ja oder Nein; *Chirurg* (1984); **55**: 162–7.
15. Lennert KA, Muller U. Wie ist das Risiko der operativen Behandlung der Choledocholithiasis. *Chirurg* 1990; **61**: 376–8.
16. Morgenstern, Wong L, Berci G. Twelve hundred open cholecystectomies before the laparoscopic era: A standard for comparison. *Arch Surg* 1992; **127**: 400–3.
17. Clavien PA, Sanabria JR, et al. Recent results of elective open cholecystectomy in a North American and a European center. *Ann Surg* 1992; **216**: 618–26.
18. Schriefers KH, Gok Y, Bernhard JCh-Wandel von. Diagnostic und Indicationen in der Gallenstein chirurgie. *Chirurg* 1988; **59**: 185–9.
19. Den Besten L and Berci G. The current status of biliary tract surgery: An international study of 1072 consecutive patients. *World J Surg* 1986; **10**: 116–22.
20. Moreaux J. Prospective study of open cholecystectomy for calculous biliary disease. *Br J Surg* 1994, **81**: 116–9.
21. Gerber A, Apt MK. The case against routine cholangiography. *Am J Surg* 1982; **143**: 375–7.
22. Pajić M. Stefanović M, Tonković V. Vrijednost intraoperativna kolangiografija. *Acta Chir Iug* 1982; **29**: 1: 55–60.
23. Baškot A, Pavan G, Polović A. Kritički osvrt na vrijednost ultrazvuka u dijagnostici koledokolitijaze. Stručni sastanek Hrvatskog društva radiologa, Karlovac 20. 10. 1995.
24. Fučkar Ž. Gallbladder and biliary tree. In: Kurjak A, Fučkar Ž, Gharbi HA eds. *Atlas of abdominal and small parts sonography*. Zagreb: MB, 1990: 155–68.
25. Thompson JE, Bennion RK. A simple, costeffective medhod for operative cholangiography. *Am J Surg* 1989; **158**: 461–2.
26. Paulino-Neto A. A rewiev of 391 selected open cholecystectomies for comparison with laparoscopic cholecystectomy. *Am J Surg* 1993; **166**: 71–3.
27. Taylor TV. Editorial comment. *Am J Surg* 1990; **159**: 385.
28. Skillings, Villiams JS, Hinshaw JR. Costeffectivness of operative cholangiography. *Am J Surg* 1979; **137**: 26–31.

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Effects of verapamil on cardiac uptake of radiolabeled doxorubicin and iodo-doxorubicin in rabbits

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Since verapamil has been shown to increase cellular concentrations of anthracyclines in resistant tumor cells, this study was designed to investigate the effect of verapamil on myocardial accumulation of radiolabeled doxorubicin (DOX) and iodo-doxorubicin (IDOX) in rabbits, and to estimate the risk of increasing anthracycline-related cardiotoxicity. After intravenous administration of either I-123 DOX or I-123 IDOX alone, and in combination with a single dose of 0.3 mg or 3 mg verapamil/kg body weight scintigraphic imaging was performed up to 100 min p.i. and cardiac uptake of the radiolabeled anthracyclines was calculated by ROI-technique in percent of total body activity. Cardiac uptake was decreasing in a monoexponential manner for both DOX and IDOX, and there were no significant differences due to verapamil in either dosage. However, cardiac uptake of DOX was nearly 2-fold higher than of IDOX confirming the lower cardiotoxic potential of IDOX. In conclusion, our results in rabbits do not show a significant increase of myocardial accumulation of anthracyclines following intravenous injection of verapamil suggesting no increased risk of cardiotoxicity for a combined therapy of DOX or IDOX and verapamil.

Key words: heart radionuclide imaging; doxorubicin; verapamil; myocardium-drug effects; rabbits

Introduction

Anthracyclines like the widely used doxorubicin (DOX) or the more lipophilic derivative iodo-doxorubicin (IDOX) are efficient and well-established anticancer drugs in various tumors, e.g. breast or lung cancer.[1-5] However, drug resistance to anthracyclines is a well-known phenomenon limiting effective anti-cancer treatment. Multidrug resistance related to an overexpression of transmembranous glycoprotein p170 decreases the intracellular concentration of several antineoplastic drugs including anthracyclines such as DOX or IDOX by actively enhancing their efflux out of the cells.[6-9]

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Recently, the so-called chemosensitizers have been shown to modulate the effects of p170 glycoprotein on drug efflux; e.g. calcium channel-blockers like verapamil increase the intracellular concentration of anthracyclines in resistant tumor cells by reducing their efflux via p170 glycoprotein, thus, enhancing cytotoxicity.[10-13] Since clinical studies testing anthracyclines in combination with verapamil also suggested an improved therapeutic efficacy of this antineoplastic regimen,[14, 15] a potential increase of toxic side effects of anthracyclines to normal tissue has special interest.[11] In particular, an increase of the well-known cardiotoxicity[16-18] of anthracyclines would be of great clinical impact.

The aim of this study, therefore, was to evaluate the impact of verapamil on in-vivo myocardial uptake of radiolabeled DOX and IDOX in rabbits in order to estimate the potential risk of increasing cardiotoxicity.

Materials and methods

The anthracycline antibiotics doxorubicin and its derivative 4'-deoxy-4'-iododoxorubicin (Farmitalia, Italy) were radioiodinated with I-123 (Amersham, Braunschweig, Germany) by electrophilic substitution by the Iodogen method as recently published in detail.[19–21] Radiochemical purtiy as confirmed by Sep-Pak RP-C 18 cartridges (Millipore, Eschborn, Germany) was more than 98 % in all cases.

Six 3-month old male New Zealand white rabbits weighing approximately 2.5–3 kg were investigated in two subsets of three animals each. One subset was treated with I-123 labeled DOX, the other with I-123 labeled IDOX. In both subsets the animals first recieved the radiolabeled anthracycline alone, then in combination with low-dose verapamil after one week, and thirdly in combination with high-dose verapamil after another week. In each animal 40 MBq of I-123 labeled DOX or IDOX were administered via an intravenous butterfly catheter in a central ear vein. Verapamil (Knoll, Ludwigshafen, Germany) was administered slowly 5–10 min prior to injection of the radiolabeled anthracycline. Thereby, a dose of 0.3 mg verapamil per kg body weight intravenously applied was considered as low-dose, 3 mg per kg body weight as high-dose injection.

Immediately after tracer application, simultaneous planar whole body images from anterior and posterior views with a zoom factor of 1.2 were acquired initially in five 1-min intervals and then in 5-min intervals up to 100 min p.i. using a double head gamma camera system (Bodyscan, Siemens Gammasonics) equipped with high resolution parallel hole collimators for low energy. In order to avoid artefacts due to movements the animals were anesthesized with thiopental (Trapanal®; Byk Gulden, Konstanz, Germany) during scintigraphy. Cardiac uptake of radiolabeled DOX and IDOX in percent of total body activity was calculated for each time interval by conventional ROI-technique.

Quantitative data are given as mean ± one standard deviation. Two-tailed students t-test was used to evaluate differences, with $p < 0.05$ considered to be statistically significant.

Results

Time-to-uptake curves of cardiac uptake of I-123 labeled DOX, DOX in combination with low-dose verapamil (DOX/LD) and DOX in combination with high-dose verapamil (DOX/HD) are shown in Figure 1. The corresponding curves of IDOX, IDOX in combination with low-dose verapamil (IDOX/LD) and IDOX in combination with high-dose verapamil (IDOX/HD) are depicted in Figure 2.

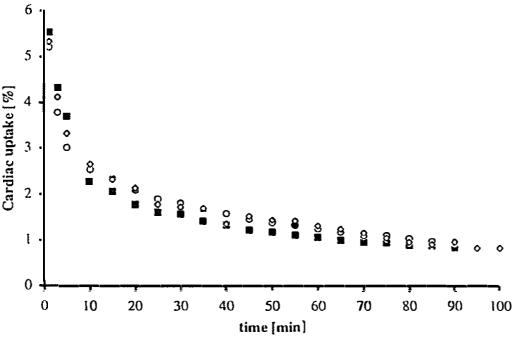

Figure 1. Cardiac uptake in percent of total body activity of I-123 DOX (filled squares), I-123 DOX in combination with low-dose verapamil (open circles) and I-123 DOX in combination with high-dose verapamil (open diamonds) in rabbits up to 100 min p.i.. Symbols represent means, standard deviation bars are omitted for clearness.

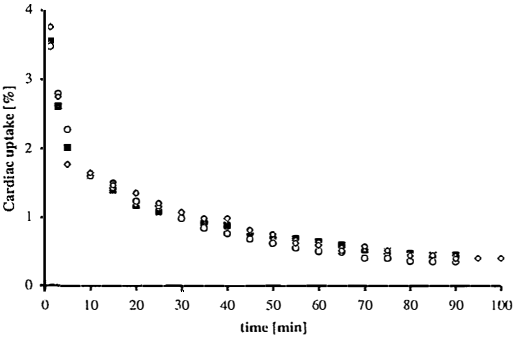

Figure 2. Cardiac uptake in percent of total body activity of I-123 IDOX (filled squares), I-123 IDOX in combination with low-dose verapamil (open circles) and I-123 IDOX in combination with high-dose verapamil (open diamonds) in rabbits up to 100 min p.i.. Symbols represent means, standard deviation bars are omitted for clearness.

Cardiac tracer uptake was decreasing in a roughly mono-exponential manner during measurement from 0–100 min p.i. for both iodine-123 labeled DOX and IDOX. Verapamil in either low-dose or high-dose administration did neither significantly affect the myocardial time-to-uptake curves of DOX (Figure 1) nor of IDOX (Figure 2). Although both DOX/LD and DOX/HD values were slightly higher than DOX values, there were no significant differ-

ences between these curves ($p > 0.05$). Furthermore, there were no significant differences between DOX/LD and DOX/HD and between IDOX/LD and IDOX/HD ($p > 0.05$).

However, myocardial uptake of DOX was significantly higher ($p < 0.05$) as compared to IDOX. DOX values were nearly twice as high as the corresponding values of IDOX during the whole time period. Similiar results were obtained for DOX/LD and IDOX/LD as well as for DOX/HD and IDOX/HD confirming the higher cardiac accumulation of DOX.

Discussion

Since an effective anti-cancer treatment with cytotoxic agents like the widely used anthracyclines is often hampered by multidrug resistance, drug combinations with chemosensitizers have been investigated in order to restore drug sensitivity in resistant cancer cells. Recently, calcium channel-blocking agents like verapamil have been shown to effectively improve the cellular uptake of anthracyclines by reducing their efflux in p170 glycoprotein-associated multidrug resistant cancer cells both in experimental animals and in first clinical studies.[10–15] However, since a severe and dose-related cardiotoxicity is a well-known and treatment-limiting side effect of anthracyclines,[16–18] it is necessary to evaluate whether verapamil would also increase the toxicity of anthracyclines in normal tissues.

In experimental studies, a 30 % increase of DOX concentrations in normal rat myocardial cells perfused with verapamil has been reported, as well as a higher incidence and severity of degenerative changes in cardiac tissue of mice treated with verapamil and doxorubicin.[22–24]

Our results in rabbits, however, did not confirm significant differences of cardiac accumulation of I-123 labeled DOX as compared to either DOX in combination with low-dose (0.3 mg/kg body weight) or with high-dose (3 mg/kg body weight) verapamil. Moreover, there were no significant differences between radiolabeled IDOX and IDOX in combination with low-dose or high-dose verapamil.

This may probably be due to the dosage and the different ways of administration of verapamil. In experimental studies perfusion of isolated myocardial tissue with verapamil in a constant concentration will reach continuously higher and more effective plasma levels as compared to single intravenous bolus injections or oral application of verapamil as used in clinical settings.[25] Therefore, plasma concentrations of verapamil as achieved in this study – even using a high-dose regimen of 3 mg verapamil per kg body weight – may be too low to effectively modulate p170 glycoprotein function of myocardial cells resulting only in a small increase of intracellular anthracycline concentration. Similar observations with no increase in both tumor cytotoxicity and toxic side effects have been reported from a clinical phase II study.[25] The major problem thereby is most probably the dose-limitation of verapamil because of its severe acute cardiovascular toxicity when plasma concentrations reach those required for successful reversal of multidrug resistance in vitro.[26, 27]

Furthermore, in normal cells without overexpression of p170 glycoprotein, e.g. cardiomyocytes, verapamil may decrease the efflux of anthracyclines only slightly so it could not be detectable by scintigraphic means. Similar results are reported for normal human bone marrow cells in which myelotoxicity of anthracyclines was not increased by verapamil.[28]

Another important modifying factor to be considered is the labeling of DOX and IDOX with I-123. Adding iodine by the Iodogen method,[19–21] physicochemical and, thus, biological properties of the molecule may be altered resulting in different pharmacokinetics of the labeled drugs as compared to nonlabeled derivatives. Therefore, further investigations are necessary to define changes in biokinetics of iodinated DOX and IDOX as compared to the unlabeled drugs.

Total cardiac activity measured by scintigraphic means, i.e. ROI-technique, includes both myocardial uptake and cardiac blood pool activity. Therefore, our results of cardiac accumulation, as presented in this study, do not exclusively depend on myocardial uptake. However, it has been shown that less than 0.4 % of the injected dose of either DOX or IDOX is detectable in the plasma within a few minutes after administration.[29] This is in accordance to a fast blood clearance of DOX and IDOX as shown by a rapidly clearing activity from the large vessels and the lungs. The decreasing bloodpool activity has been demonstrated by a quick decrease of cardiac uptake in the first two minutes, too. Therefore, cardiac activity appears to be mainly related to myocardial uptake after two minutes, thus, confirming our results that single-dose verapamil has no major impact on myocardial uptake of both DOX and IDOX.

DOX showed a nearly 2-fold higher cardiac accumulation as compared to IDOX. This holds true either alone or in combination with verapamil. Although IDOX is the most lipophilic derivative of common anthracyclines,[30] cardiac accumulation in our study was significantly lower suggesting a less cardiotoxic potential of IDOX. This is consistent with several preclinical and clinical studies reporting a reduced cardiotoxicity of IDOX as compared to DOX.[30-32] Thus, this scintigraphic finding confirms the reliability of the experimental setup chosen and suggests no major differences in pharmacokinetics of the labeled drugs as compared to non-labeled derivatives.

Conclusion

The results in rabbits did not confirm a significant increase of in vivo cardiac accumulation of anthracyclines following a single bolus injection of verapamil. Therefore, no increased risk of cardiotoxicity for treatment of DOX or IDOX in combination with verapamil is suggested so far. The lower cardiac accumulation of IDOX confirmed its lower cardiotoxic potential as compared to DOX.

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References

1. Sessa C, Calabresi F, Cavalli F, Cerny T, Liati P, Skovsgaard T, Sorio R, Kaye SB. Phase II studies of 4'-iodo-4'-deoxydoxorubicin in advanced non-small cell lung, colon and breast cancers. *Ann Oncology* 1991; **2:** 727–31.

2. Mross K, Mayer U, Hamm, K, Burk K, Hossfeld DK. Pharmacokinetics and metabolism of iodo-doxorubicin and doxorubicin in humans. *Eur J Clin Pharmacol* 1990; **39:** 507–13.

3. Mross K, Mayer U, Langenbuch T, Hamm K, Burk K, Hossfeld D. Toxicity, pharmacokinetics and metabolism of iododoxorubicin in cancer patients. *Eur J Cancer* 1990; **26:** 1156–62.

4. Mross K, Mayer U, Zeller W, Becker K, Hossfeld DK. Pharmacodynamic and pharmacokinetic aspects of iodo-doxorubicin. *Oncology Res* 1992; **4:** 227–31.

5. Mross K. New anthracycline derivatives: what for? *Eur J Cancer* 1991; **27:** 1542–4.

6. Pastan I, Gottesman M. Multiple drug resistance in human cancer. *N Engl J Med* 1987; **316:** 1388–93.

7. Lemontt JF, Azzaria M, Gros P. Increased mdr gene expression and decreased drug accomulation in multidrug-resistant human melanoma cells. *Cancer Research* 1988; **48:** 6348–53.

8. Evans CH, Baker PD. Decreased p-glycoprotein expression in multidrug-sensitive and -resistant human myeloma cells induced by cytokine leukoregulin. *Cancer Res* 1992; **52:** 5893–9.

9. Rao VV, Chiu ML, Kronauge JF, Piwnica-Worms D. Expression of recombinant human multidrug resistance p-glycoprotein in insect cells confers decreased accumulation of technetium-99m-sestamibi. *J Nucl Med* 1994; **35;** 510–15.

10. Bruno NA, Slate DL. Effect of exposure to calcium entry blockers on doxorubicin accumulation and cytotoxicity in multidrug-resistant cells. *J Natl Cancer Inst* 1990; **82:** 419–24.

11. Damiani D, Michieli M, Michelutti A, Melli C, Cerno M, Baccarani M. D-verapamil downmodulates p170-associated resistance to doxorubicin, daunorubicin and idarubicin. *Anti-Cancer Drugs* 1993; 4: 173–80.

12. Mross K, Hamm K, Hossfeld DK. Effects of verapamil on the pharmacokinetics and metabolism of epirubicin. *Cancer Chemother Pharmacol* 1993; **31:** 369–75.

13. Lehnert M. Reversal of multidrug resistance in breast cancer: many more open questions than answers. *Ann Oncology* 1993; **4:** 11–3.

14. Durie BGM, Dalton WS. Reversal of drug-resistance in multiple myeloma with verapamil. *Br J Haematol* 1988; **68:** 203–6.

15. Miller TP, Grogan TM, Dalton WS. P-glycoprotein expression in malignant lymphoma and reversal of clinical drug resistance with chemotherapy plus high-dose verapamil. *J Clin Oncol* 1991; **9:** 17–24.

16. Nilles M, Wehr M, Köhler F. Adriamycin-Kardiomyopathie. *Medwelt* 1984; **35:** 103–8.

17. Casper ES. The cardiotoxic effect of epirubicin and doxorubicin (adriamycin). *Clinical Trials J* 1987; **24** (Suppl 1): 57–66.

18. Neri B, Cini-Neri G, Bandinelli M, Pacini P, Bartalucci S, Ciapini A. Doxorubicin and epirubicin cardiotoxicity: experimental and clinical aspects. *Int J Clin Pharmacol* 1989; **27:** 217–21.

19. Fraker PJ, Speck JC. Protein and cell membrane iodinations with a sparingly soluble chloroamide, 1,3,4,6-tetrachloro-3α,6α-diphenylglycoluril. *Biochim Biophys Res Comm* 1978; **80:** 849–57.

20. Salacinski PRP, McLean C, Sykes JE, Clement-Jones VV, Lowry PJ. Iodination of proteins, glycoproteins and peptides using a solid-phase oxidizing agent, 1,3,4,6-tetrachloro-3α,6α-diphenyl glycoluril (iodogen). *Analytical Biochemistry* 1981; **117:** 136–46.

21. Wolf H, Marschall F, Scheffold N, Clausen M, Schramm M, Henze E. Iodine-123 labelling of atrial natriuretic

peptide and its analogues: initial results. *Eur J Nucl Med* 1993; **20:** 297–301.

22. Monti E, Paracchini L, Piccinini F. Effect of calcium inhibitors and calcium mobilizers on doxorubicin accumulation in rat myocardial tissue. *Pharmacol Res Commun* 1988; **20:** 369–76.

23. Sridhar R, Dwivedi C, Anderson J, Baker BP, Sharma HM, Desai P, Engineer FN. Effects of verapamil on the acute toxicity of doxorubicin in vivo. *J Natl Cancer Inst* 1992; **84:** 1653–60.

24. Santostasi G, Kutty RK, Krishna G. Increased toxicity of anthracycline antibiotics induced by calcium entry blockers in cultured cardiomyocytes. *Toxicol Appl Pharmacol* 1991; **108:** 140–9.

25. Mross K, Bohn C, Edler L. Randomized phase II study of single-agent epirubicin ± verapamil in patients with advanced metastatic breast cancer. *Ann Oncol* 1993; **4:** 45–50.

26. Hamilton G, Thayer G, Baumgartner G. Calcium antagoniststs as modulators of multi-drug resistant tumor cells. *Wien Med Wochenschr* 1993; **143:** 526–32.

27. Van Kalken CK, van der Hoeven JJ, de Jong J, Giaccone G, Schuurhuis GJ. Beprifil in combination with anthracyclines to reverse anthracycline resistance in cancer patients. *Eur J Cancer* 1991; **27:** 739–44.

28. Busch FW, Schmittele U, Ehninger G. Toxicity of novel anthracycline derivatives towards normal bone marrow progenitor cells is not increased by verapamil. *Blut* 1990; **60:** 219–22.

29. Mross KB, Mayer U, Hamm K, Burk K, Hossfeld KD. Pharmacokinetics and metabolism of iodo-doxorubicin and doxorubicin in humans. *J Clin Pharmacol* 1990; **39:** 507–13.

30. Mross K, Langenbuch T, Burk K, Hossfeld DK. Iododoxorubicin, ein neues Anthrazyklin-Derivat. *Onkologie* 1990; **13** 345–51.

31. Villani F, Galimberti M, Lanza E, Rozza A, Favalli L Poggi P. Evaluation of cardiotoxicity of a new anthracycline derivative: 4'-deoxy-4'-iododoxorubicin. *Invest New Drugs* 1988; **6:** 173–8.

32. Villani F, Galimberti M. Early cardiac toxicity of 4'-iodo-4'-deoxydoxorubicin. *Eur J Cancer* 1991; **27:** 1601–4.

Radiol Oncol 1996; 30: 182-8.

Scatter correction in hippuran clearance estimation with the modified Oberhausen technique

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The modified Oberhausen technique is widely used in the estimation of hippuran clearance. However, when using a gamma camera the slope of the retention curve may be influenced by scattered photons from the kidneys. Therefore, the aim of this study was to quantify renal scatter and to elucidate the underlying factors. Scatter was measured in a seperate energy window in 47 patients with fast and in 31 patients with prolonged reno-vesical transport. An excellent correlation between renal clearance obtained with and without scatter correction was yielded ($n = 76$; $r^2 = 0.993$, SEE = 10.7 ml/min/1.73 m^2). In two patients only, we underestimated renal clearance by 43 and 47 % when scatter correction was omitted (see Figure 1). As underlying factors we determined obstruction and concomitant impaired renal function. In conclusion, in these patients an underestimation of renal clearance in renal function studies should be kept in mind.

Key words: metabolic clearance rate; iodohipporic acid; scattered, radiation; hippuran clearance, modified Oberhausen technique, scatter correction

Introduction

Renal function scintigraphy with iodine-123-hippuran is an established quantitative method in nuclear medicine.[1-3] The classical definition of renal clearance for the single shot-technique and falling plasma concentration of radioiodine-hippuran is total body loss (dm) of the tracer per time (dt) devided by the corresponding plasma concentration (C_{Pl}), according to equation 1.

$$Cl = \frac{\frac{dm}{dt}}{C_{Pl}} \qquad (1)$$

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This approach is free of any assumption concerning compartment analysis, may be directly measured by diagnostic in nuclear medicine, and has become a clinically feasible method of reference.[3] The original method requires total body count detection with renal and urinary bladder shielding.[4, 5] For reasons of practicability this method was modified by using a gamma camera background region-of-interest.[6-9] The resulting time-activity-curve was assumed to be representative for the total body retention curve of the tracer. This assumption has not been confirmed by the original author and indeed, in a careful comparison proved to be not reliable enough for clinical patient care.[10] This may be due to scatter of renal count rate into the backround ROI which are in the same field of view of the gamma camera used. However, in routine patient management clearance estimation is not influenced, since the time-activity-curves of both renal and background ROI have a parallel time course in the time interval of interest from 12 to 24 min post injection.

On the other hand, in patients with obstuctive uropathy a time-dependent increase of count rate over both kidneys yields a non-parallel time course of the respective time-activity-curves. In consequence, scatter of the kidneys may artificially flatten the total body retention curve. This directly results in a falsely decreased radioiodine-hippuran clearance.

Therefore, the purpose of this study was to estimate and subsequently to compensate for any undesired effects of renal scatter on the background slope. Parts of the results have been published in brief recently.[11–13]

Materials and methods

Out of routine clinical patient care 78 patients were included consecutively. These patients were devided into two groups: 47 patients (20 female, 27 male, age: 48.5 ± 16.7 years) with normal or fast reno-vesical transport and 31 patients (10 female, 21 male, age: 49.4 ± 25.4 years) with prolonged reno-vesical transport. Renal scintigraphy was performed in all patients after a bolus injection of 40 to 80 MBq I-123-hippuran in a conventional manner. Serial images were acquired in a posterior view using a LFOV-gama-camera equipped with a LEAP-collimator (Gamma Diagnost Tomo, Philips, The Netherlands) up to 25 min p. i. The symmetric 10 % energy window was set on the photopeak of I-123, i. e. 144–176 keV. The clearance was derived according to equation 1 using the physiologic approach for clearance estimation, i. e. plasma concentration at 12 and 24 min p. i. and the slope of the camera background retention curve at the respective time were combined with the standard algorithm. The background ROI was positioned in the largest possible distance to the kidneys in the basal parts of the lungs.

In addition, during data acquisition a second energy window, set from 96 to 144 keV[14] was used to sample scatter information. Follwing standard data evaluation for renal clearance calculation, different fractions of the scatter images from 0 to 80 % were subtracted from the original photopeak of the background ROI.[7, 14-16] As a second method of scattter correction a constant fraction of 1 to 5 % of the activity of the renal ROIs was subtracted from the background ROI without measurement of scattered radiation.

In order to recognise both differences and both patient groups basing on scattered radiation and the success of the correction for scattered radiation, we introduced the slope S of the retention curve given by the logarithm of the retention value at 24 min (R_{24min}) devided by the retention value at 12 min (R_{12mn}), as given in equation 2. These slope values of both patient groups are not directly comparable since they are dependent of the respective clearance values. Therefore, slope values were normalised with the individual clearance of the respective patient. When starting from a one compartment model,[17] the slope of the retention curve is a direct measure for the respective clearance. Thus, an index derived by dividing the slope and the clearance (Cl_i) should be constant. Any deviation of this index between both patient groups should, therefore, be due to scattered radiation.

$$S = \ln\left(\frac{R_{24\,\mathrm{min}}}{R_{12\,\mathrm{min}}}\right) \tag{2}$$

For reasons of practicability we normalised the terived index I according to equation 3 with a factor F as given in equation 4 in order to yield values near unity without any dimension.

$$I = \frac{S}{Cl} \cdot F \tag{3}$$

$$F = \frac{\sum_{i=1}^{78} Cl_i}{\sum_{i=1}^{78} \ln\left(\frac{R_{24\,\mathrm{min}}}{R_{12\,\mathrm{min}}}\right)_i} \tag{4}$$

Data are given as mean ± one standard deviation. Curve fitting was quantified by the linear regression coefficient, r and the standard error of the estimate (SEE). The difference between both patient groups was calculated with a two-tailed t-test according to Wilcoxon for unpaired data, with $p < 0.05$ considered to be statistical significant.[18]

Results

Scatter correction with measurements of a scattered fraction

The effect of an increasing correction of a scattered fraction in the background ROI on the correlation of the calculated index and modified hippuran clearance according to Oberhausen in both patient groups is given in Table 1. Without scatter correction the indices of both patient groups are different from 1

Table 1. Effect of subtraction of different fractions (F in %) from the scatter window of the photopeak from the background-ROI on the indices (I) in both patient groups with fast or normal reno-vesical transport (A: n = 47) and in patients with prolonged reno-vesical transport (B: n = 31) and its effect on the correlation (r^2, SEE) to the modified Oberhausen clearance. The latter was 358.0 ± 84.4 and 253.0 ± 156.8 ml/min/1.73 m^2 in group A and group B, respectively.

	Group A (n = 47)			Group B (n = 31)		
F	I	r^2	SEE	I	r^2	SEE
0	1.075 ± 0.354	0.183	0.323	0.886 ± 0.479	0.228	0.428
20	1.067 ± 0.335	0.223	0.299	0.898 ± 0.460	0.275	0.399
40	1.043 ± 0.289	0.354	0.235	0.935 ± 0.429	0.404	0.337
60	1.026 ± 0.265	0.444	0.200	0.961 ± 0.427	0.465	0.318
70	1.001 ± 0.239	0.564	0.159	0.998 ± 0.452	0.487	0.329
80	0.944 ± 0.265	0.407	0.206	1.085 ± 0.607	0.348	0.498

with figures of above 1 in group A and figures of below 1 in group B. In consequence, the correlation between index and clearance is low with $r^2 = 0.183$ in A and $r^2 = 0.228$ in group B. With an increasing subtracted scatter fraction F the difference in both groups diminishes. The indices are converging to 1. In consequence, the correlation between index and hippuran clearance becomes gradually closer. An optimal subtraction is yielded by subtracting 70 % of the scatter window from the photopeak window in the background ROI. Consequently, the indices are almost 1 with r^2 reaching a maximum and SEE reaching a minimum. With increasing subtraction of 80 % the correlation worsens again. This is due to an overcorrection.

Scatter corrrection without measurement of scattered radiation

The effect of different scatter corrrections without direct measurement of the scattered fraction on the corrrelation of index and clearance values in both patient groups is given in Table 2. Varying degrees of the photopeak of the renal ROIs ranging from 1 to 5 % were subtracted from the photopeak of the background ROI. Without any scatter correction the indices of both patient groups are different from unity again. With an increasing subtraction F this difference reaches a minimum when subtracting 3 % of the scatter window from the photopeak window. In consequence, the indices in both patient groups are converging at 1 with r^2 reaching a maximum and SEE reaching a minimum. Again, an increase of subtraction to 4 and 5 %, respectively, worsens the correlation of calculated index and hippuran clearance indicating overcorrectin.

Since the best correlation of the calculated index and hippuran clearance is reached with a subtraction of 70 % of the scattered window of the background ROI, corresponding to an optimum compensation for scattered radiation, this method is usede for the following an calculations.

Influence of scatter correction on renal clearance estimation

The scatter corrected clearance (Cl_{SC}) is shown versus the modified Oberhausen clearance (CL_{OH}) in Figure 1. As could be expected, the clearance was singificantly higher in patient with normal or fast reno-vesical transport (squares) as compared to patients with prolonged reno-vesical transport (circles): 358.0 ± 84.4 versus 253.0 ± 156.8 ml/min/1.73 m^2. Correlation equations and correlation parameters with respective renal clearance values with and without scatter correction are given in table 3 for differ-

Table 2. Effect of substraction of different fractions (F in %) from the photopeak of the kidney-ROI from the background-ROI on the indices (I) in both patient groups with fast or normal reno-vesical transport (A: n = 47) and in patients with prolonged reno-vesical transport (B: n = 31) and its effect on the correlation (r^2, SEE) to the modified Oberhausen clearance. The latter was 358.0 ± 84.4 and 253.0 ± 156.8 ml/min/1.73 m^2 in group A and group B, respectively.

	Group A (n = 47)			Group B (n = 31)		
F	I	r^2	SEE	I	r^2	SEE
0	1.063 ± 0.308	0.407	0.241	0.904 ± 0.296	0.089	0.294
1	1.041 ± 0.283	0.449	0.213	0.938 ± 0.265	0.187	0.249
2	1.015 ± 0.257	0.500	0.184	0.977 ± 0.251	0.350	0.211
3	0.986 ± 0.232	0.551	0.157	1.021 ± 0.287	0.446	0.222
4	0.951 ± 0.216	0.543	0.148	1.074 ± 0.436	0.332	0.371
5	0.909 ± 0.240	0.343	0.197	1.138 ± 0.855	0.174	0.809

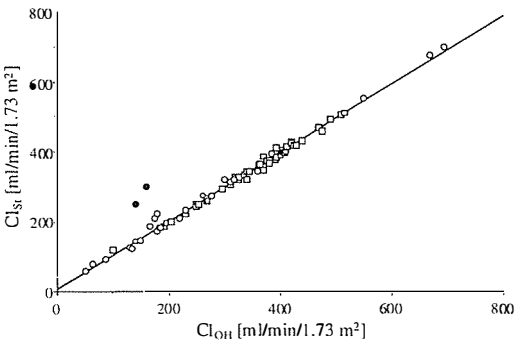

Figure 1. Scatter corrected (Cl_{St}) versus modified Oberhausen clearance (Cl_{OH}) in ml/min/1.73 m² in 47 patients with normal or fast (squares) and 31 patients with prolonged (circles) reno-vesical transport. Note, two patients with obstructive uropathy and concomitant decreased renal fuction (filled circles) in whom renal function would have been underestimated without scatter correction by 43.5 and 46.7 % respectively. For correlation equation see Table 3.

ent patient groups. In 47 patients with normal or rast reno-vesical transport (Table 3, group A) an excellent correlation of clearance values with and without scatter correction was yielded.

estimated by 43.5 and 46.7 %, respectively.

Without these two patients (table 3, group B without 2) correlation of scatter corrected clearance and Oberhausen clearance was as goood as in group A (r^2 = 0,993; SEE: 13.5 ml/min/1.73 m²).

Discussion

Pathophysiology

According to the delinition of renal clearance (see equation 1) both parameters of the fraction, i. e. slope of the retention curve and plasma concentration of radioiodine-hippurane, can be measured directly. This physiologic and compartment-free approach was proposed by Oberhausen[4,5] using a whole body retention curve with renal and urinary bladder shielding. In recent time this method was modified by using a large-field-of-view gamma camera.[8] However, this implies that both the renal and the background ROI are in the same field-of-view of the gama camera used. Therefore, scattered radiation from the kidneys into the background ROI is implicitly a more pronounced problem when com-

Table 3. Correlation of modified Oberhausen clearance with (Cl_{St}) and without (Cl_{OH}) optimal scatter correction (r^2, SEE in ml/min/1.73 m²) in different patient groups with fast or normal reno-vesical transport (A: n = 47) and patients with prolonged reno-vesical transport (B: n=31). with and without these both patients with obstructive uropathy and concomitant decreased renal function.

Patients	n	Correlation equation	r^2	SEE
GroupA	47	$Cl_{St} = 0.98 \cdot Cl_{OH} + 4.9$	0.990	8.3
Group B	31	$Cl_{St} = 0.96 \cdot Cl_{OH} + 22.4$	0.956	32.7
Group A plus B	78	$Cl_{St} = 0.95 \cdot Cl_{OH} + 19.6$	0.970	21.8
Group B without 2	29	$Cl_{St} = 0.99 \cdot Cl_{OH} + 6.5$	0.993	13.5
Group A plus B without 2	76	$Cl_{St} = 0.99 \cdot Cl_{OH} + 6.6$	0.993	10.7

In 31 patients with prolonged reno-vesical transport (Table 3, Group B) we found a very good correlation of the clearance values with and without scatter correction with al somewhat enlarged SEE (r^2 = 0.956; SEE = 32.7 ml/min) as well.

In two of 31 patients (Figure 1, filled circles) with prolonged reno-vesical transport and concomitant decreased renal function correlation between scatter corrected clearance and modified Oberhausen clearance was bad. The clearance values without scatter correction were 140 and 160 ml/min/1.73 m², respectively. On the other hand, when correcting for scattered radiation the clearance values were calculated as to 248 and 300 ml/min/1.73 m². Thus, without scatter correction clearance would have been underpared to a whole body counter as proposed by Oberhausen. In order to minimize this problem, the background ROI is positioned as far away from the kidney ROIs as possible.

However, even with these assumptions we could show that approximately 3 % of the photopeak of the renal ROIs become effective within the background ROI. This correponds to a correction of scattered radiation in the background ROI of about 70 % of scattered radiation measured in an energy window from 96 to 144 keV.[14] These observations are in good agreement with data reported in the literature.[14–16]

In our patients we found a very good correlation of renal clearance calculated with and without scat-

ter correction in all patients with fast or normal reno-vesical transport (see table 3, $r^2 = 0.990$). This holds true as well in 29 of 31 patients with a prolonged reno-vesical transport ($r^2 = 0.993$). However, in 2 patients with prolonged reno-vesical transport the hippuran clearance was underestimated by about 35 %. In these patients clearance values were not confirmed by an independent reference method.[19] Therefore, even clearance values after scatter correction may be underestimated. However, since we found very good correlation of the calculated clearance values with and without scatter correction ($r^2 = 0.993$) in the remaining 76 patients this may serve as an argument that we did not introduce artefacts with the scatter correction performed.

Two main factors could be shown to be important for the underestimation of renal clearance without scatter correction. The effect of a prolonged reno-vesical transport with a corresponding accumulation time of the time-activity-curves is easy to recognise since time-activity curves of renal and background ROIs are-non parallel. Moreover, the simultaneously decreased renal function is imperative for the underestimation of renal clearance as well. A scatter fraction of about 3 % of the photopeak of the renal ROI yields predominantly to an increase of late retention values. Therefore, a flat retention curve will be influenced more than a steep one. This implies that a reduced renal function will be influenced more than a normal renal function as could be expected from the so-called Oberhausen tables: a change of the fraction of retention values at 2 and 24 min p. i. (= E/D according to the Oberhausen tables) yields to less pronounced change in the slope of the retention curve in patients with normal renal function ($E/D \approx 0{,}5$) as compared to patients with markedly decreased renal function ($E/D \approx 0.9$).

Clinical applications

A markedly larger influence of scattered radiation has to be expected when positioning the background ROI in the near vicinity of the kidneys.[7] In patients with obstructive uropathy and decreased renal function hippuran clearance will be underestimated markedly. Therefore, in routine ptient management the background ROI will be positioned in the largest possible distance to the kidneys. However, this distance is limited by the field-of-view of the gamma camera used.

Since even under these conditions a scattered radiation fraction of about 3 % of the photopeak of the kidneys can be expected, this should be considered in patients with decreased renal function and obstructive uropathy. In these patients one should be aware of a marked underestimation of the clearance values calculated.

As could be shown in this paper the correction for scatter radiation can be performed *a posteriori* easily. However, this implies the acquisition of information related to scattered radiaton in a second energy window during routine renal scintigraphy. In daily patient management renal function scintigraphy can be corrected for scattered radiation if the calculated hippuran clearance and time-activity-curves of the kidneys suggest an underestimation of the hippuran clearance calculated.

Since the measured scatter fraction of the background ROI by the photopeak of the kidney ROIs of about 3 % is dependent on several factors, i. e. square of the distance of background ROI and kidney ROIs, body-weight this results in an enormous intra- and interindividual scatter. Therefore, its numeric value should be restricted to scientific work and, thus, should not be used for scatter correction in an individual patient.

Methodological considerations

In order to document an effective correction of scattered radiation we had to use a measure which is independent of the slope of the retention curve in an individual patient. Therefore, we started from the ordinates of the retention curves at 12 and 24 min as given by Oberhausen. These can be taken directly since the logarithm of this fraction is a direct measure for renal clerance when using a one-compartment model.[17] Normalising this slope by the individual renal clearance of the respective patient yields to an index which is independent of the individual renal function of the patient investigated. Since this index does not serve as a quantitative measure for the clearance itself and since we used this index simply to compare two patient-groups, the error introduced by a one-compartment model[17] can be neglected.

Thus, the differences of this index between two patient-groups indicate a lack of correlation of the slope of the retention curve and renal clearance. Since the only difference of these both patient-groups was the reno-vesical transport, difference of this index between both the groups is caused by

different effective fractions of scattered radiation. Therefore, the index introduced is a measure for scattered radiation.

Although the numeric values of the index derived from the individual patient exhibit a relative large scatter, we could introduce a measure for the effect of scattered radiation by the division of our patients in two groups with different reno-vesical transport. This is supported by the fact that the indices go systematically in one direction with increasing correction of the scattered fraction. This could be shown statistically significant ($p < 0.05$) by a modified t-test calculated from the single values of correlation coefficients.[18]

Since the introduced index is of basic importance in order to measure the degree of scatter correction its behaviour shall be discussed in detail. First, the index used was normalised at 1 for better readability. In patients with normal or fast reno-vesical transport scatter from the kidneys in the background ROI is not effective. Therefore the indexs is near unity. On the other hand, in case of effective scattered radiation from the kidneys into the background ROI in patients with prolonged reno-vesical transport the retention curve will be flattened artificially. Therefore, the index is below unity. In case of an overcorrection of the scattered radiation the index will be above unity.

According to the definition of clearance (see equation 1) both parts of the fraction will change in the same direction with changing clearance values. Thus, clearance values can be estimated from measurements of the plasma concentration of the tracer[20–25] or from calculations of the slope of the time-activity-curve of the background ROI[20–28] as well. With the clearance estimation by measurement of the plasma concentration of the radiopharmaceutical at any time after injection there won't be any problem with scattered radiation from the kidneys since no time-activity-curve from the background ROI is used for clearance estimation.[20–22, 25] On the other hand, this method implies that there is a comparable distribution of the tracer in all body compartments between all patients investigated. Therefore, clearance estimation by single measurements of plasma concentrations are not valid in patients with non-homogenous distribution of the tracer in the respective compartments. The same holds in principle for clearance estimation from the slope of the retention curves alone.[26–29]

These limitations do not hold for the clearance estimation method according to Oberhausen since both parts of the clearance equation do change in the same sense. Therefore, even if in an individual patient tracer distribution in the different compartments of the body vary numeric values of radioiodine hippuran clearance will be calculated correctly. Moreover, it was shown, that the background ROI used with a modified Oberhausen method, is representative for the background ROI of the partly shielded whole-body configuration.[8]

Conclusions

Scattered radiation yields to an underestimation of the calculated radioiodine hippuran clearance using the modified Oberhausen method in a few patients only. However, this is of importance in patients with obstructive uropathy and concomitant decreased renal function. The effective scattered radiation should be minimised *a priory* by the maximum possible distance of the background ROI with respect to the kidney ROIs. Scatter correction can be obtained easily *a posteriori* by using and additional energy window collecting scatter data during the acquisition of renal function scintigraphy.

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References

1. Blaufox MD, Fine E, Lee HB, Schar S. The role of nuclear medicine in clinical urology and nephrology. *J Nucl Med 1984*, **25:** 619–25.

2. Oberhausen E. Nuklearmedizinische Methoden in der Nephro-Urologie. *Münch Med Wschr* 1983; **125:** 465–7.

3. Oberhausen E, May P. Nuklearmedizinische Untersuchungen. In: Alken CE, Staehler W eds. *Klinische Urologie*. Stuttgart: Thieme, 1973: 76–92.

4. Oberhausen E. Bestimmung der Nierenclearance mit dem Ganzkörperzähler. In: Höfer R ed. *Nierenclearance*. Gelbe Reihe der Farbwerke Hoechst, 1968: 1–19.

5. Oberhausen E. Nuklearmedizinische Untersuchungen. *Radiologe* 1981; **21**: 548–52.

6. Fine EJ, Axelrod M, Gorkin J, Saleemi K, Blaufox MD. Measurement of effective renal plasma flow a comparison of methods. *J. Nucl Med* 1987; **28**: 1393–1400.

7. Kotzerke J, Wallburger M, Gettner U, Burchert W, Hundeshagen H. Vergleich zweier Algorithmen zur Bestimmung der renalen Ganzkörper-Clearance nach simultaner Akquisition mit dem teilabgeschirmten Ganzkörperzähler und der Gammakamera. *Nuc Med* 1990; **29**: 101–8.

8. Rohloff R, Hast B, Leisner B, Heinze HG. Bestimmung der ^{131}J-Hippuran-Clearance im Rahmen der Kamerafunktionsshzintigraphie der Nieren nach vereinfachten Modifikationen der Methode von Oberhausen. *Nucl Med* 1975; **13**: 303–20.

9. Sonntag A. Einfache nuklearmedizinische Nierenclearancemethoden im Vergleich. *Nucl Med* 1984; **23**: 155–60.

10. Buvat I, Benali H., Todd-Pokropek A, Di Paola R. Scatter correction in scintigraphy the state of the art. *Eur J Nucl Med* 1994; **21**: 675–94.

11. Clausen M, Bohuslavizki KH, Felber M, Schramm M, Wolf H, Brenner W, Eberhardt JU, Stauch C, Zimmermann JS, Henze E. Streustrahlenkorrektur der Retentionskurve bei der Nierenfunktionsszintigraphie mit einem Compton-Energiefenster. *Nucl Med* 1994; **33**: A26.

12. Clausen M, Bohuslavizki KH, Felber M, Schramm M, Wolf H, Czapp W, Brenner W, Eberhardt JU, Stauch C, Zimmermann JS, Henze E. Scatter corrrection in renal studies with radioiodinehippuran. In: Bergmann H, Sinzinger H eds. *Radioactive isotopes in clinical medicine and resarch.* Basel: Birkhäuser, 1995: 241–5.

13. Felber M, Clausen M, Schramm M, Wolf H, Bohuslavizki KH, Brenner W, Eberhardt JU, Stauch C, Henze E. Beeinflussung der Retentionskurve aus einer Hintergrund-ROI durch die Nierenaktivität bei der Funktionsszintigraphie. *Nucl Med* 1994; **33**: A59.

14. Jasszczak RJ, Greer KL, Floyd CE, Harris CC, Coleman RE. Improved SPECT quantification using compensation for scattered photons. *J Nucl Med* 1984; **25**: 893–900.

15. Gilardi MC, Bettinardi V, Todd-Pokropek A, Milanesi L, Fazio F. Assessment and comparision of three scatter correction techniques in single photon emission computed tomography. *J Nucl Med* 1988; **29**: 1971–9.

16. Ljungberg M, King MA, Hademenos J, Strand SE. Comparison of four scatter correction methods using monte carlo simulated source distributions. *J. Nucl Med* 1984; **35**: 143–51.

17. Rösler H. Die Bestimmung der o-^{131}J. Hippursäure Total-Clearance als Grundlage einer quantitativen Radionephrographie. *Dtsch Med Wschr* 1976; **92**: 881–5.

18. Sachs L. *Applied statistics A handbook of tecniques.* Berlin, Heidelberg, New York: Springer, 1984.

19. Sapirstein LA, Vidt DG, Mandel MJ, Hanusek MJ. Volumes of distribution and clearances of injected creatinine in the dog. *Am J Physiol* 1955; **181**: 330–5.

20. Piepenburg R, Bockisch A, Anfreas A, Düber C, Kann P, Maier G, Hahn K. ^{99m}Tc-MAG3-Nierenfunktionsszintigraphie ohne und mit Captopril zur Diagnostik der renovaskulären Hypertonie. *Fortschr Röntgenstr* 1993: **159**: 150–7.

21. Schaub T, Schweden F, Witsch U, El-Damanhoury H, Schild H, Thelen M. Computertomographie nach extrakorporaler Stoßwellenlithotripsie (ESWL) der Nieren Teil III Prospektive CT-Untersuchungen bei 105 Patienten und Drei-Jahres-Kontrolle bei 23 Patienten mit CT und seitengetrente ^{99m}Tc-MAG3-Clearance. *Fortschr Röntgenstr* 1993, **158**: 121–6.

22. Schaub T, Witsch U, El-Damanhoury H, Nägele-Wöhrle B, Hahn K. ^{99m}Technetium-Mercaptoacetyltriglycin (MAG3) zum Nchweis von Nierenveränderungen nach extrakorporaler Stoßwellenlithotripsie Eine prospektive Untersuchung bei 117 Patienten. *Fortschr Röntgenstr* 1992; **157**: 338–43.

23. Tauxe EN, Dubovsky EV, Kidd T, Diaz F, Smith LR. New formulas for the calculation of effective renal plasma flow. *Eur J Nucl Med* 1982: **7**: 51–4.

24. Tauxe EN, Maher FT, Taylor WF. Effective renal plasma flow estimation from theoretical volumes of distribution of intravenously injected ^{131}I-orthoiodo hippurate. *Mayo Clin Proc* 1971; **46**: 524–31.

25. Willich N, Heidenreich P, Renner D. Vereinfachte Verfahren zur Nierenclearancebestimmung Ergebnisvergleich der ^{51}Cr-EDTA-Slope-Clearance, J-Hippuranclearance, endogene Kreatininclearance. *Fortschr Röntgenstr* 1983: **138**: 553–7.

26. Sonntag A. MAG3-Clearance methodischer Aufwand und Ergebnisqualität. *Nucl Med* 1994; **33**: 68.

27. Winkler K, Fischer M, Buchinger HD, Hengst W. Vereinfachte Methode zur Bestimmung der Nierencleasrance. *Nuc Compact* 1979; **10**: 235–8.

28. Winter CC. *Radioisotope renography.* Baltimore: Williams & Wilkins, 1963.

29. Junges R. Der Influß der Meßmethode auf die Bedeutung der Nierenclearance. *Fortschr Röntgenstr* 1985; **142**: 212–4.

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Gastric emptying in rats with gastroduodenal disease induced by N-methyl-N-nitro-N-nitrosoguanidine and alcohol

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The rate of gastric emptying was measured with a dye dilution technique in rats treated with N-methyl-N-nitro-N-nitrosoguanidine and alcohol.
Gastric emptying was compared in rats with gastroduodenal inflammatory diseases and gastroduodenal neoplasms, and in those without gastroduodenal disease.
Gastric emptying was found to be significantly increased following the intragastric injection of liquid meal in rats with gastroduodenal diseases as opposed to the control group of healthy rats.
These findings suggest that an increased gastric emptying of liquids can be explained by abolition on the relaxation of the gastric wall in rats with gastroduodenal diseases.

Key words: gastric emptying; dye dilution technique; stomach diseases-chemically induced; N-methyl-N-nitrosoguanidine

Introduction

There is an increasing tendency to incriminate abnormalities in gastric emptying in the pathogenesis of gastroduodenal disease. Many disorders are associated with delayed gastric emptying without evidence of a structural gastric outlet obstruction.[1-4] Nevertheless, Nomiyama[5] found, by use of the acetaminophen absorption method, that gastric emptying in patients with early gastric cancer was rather rapid, if compared with emptying in healthy subjects. These differences may be caused by differences in the methods of the gastric emptying measurement and in the test meal used.[3, 6]

We supposed that liquids injected directly into the stomach by a sonde, would be emptied from a stomach with gastroduodenal disease more quickly than from a healthy stomach.[7]

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We tested this hypothesis using the dye dilution test for gastric emptying[8, 9] after treating Wistar rats with N-menthyl-N-nitro-N-nitrosoguanidine (MNNG)[10,11] and alcohol.

Materials and methods

Animals

We used 70 male Wistar rats weighing 150–200 g. The animals were fed pelleted Knapka food, and maintained in macrolon cages at a constant temperature (22±2 °C) and relative humidity (60±5 %). All the animals were given MNNG (Fluka Chemie, Switzerland) at a concentration of 100 mg/litre[10] in a drinking solution. We arbitrarily divided the experimental animals into two groups. One group had MNNG diluted in tap water, while the other, in a 12 % alcohol solution. The control group of 10 animals drank tap water. The experimental animals drank MNNG solution for 29 weeks; after that they drank tap water for an additional 29 weeks, at which time the experiment concluded.

The experimental animals were observed daily and weighed once every 4 weeks. Autopsies were performed on all except two animals.

At the end of the 58 experimental weeks, the gastric emptying tests were performed.

Gastric emptying studies

The technique of Mangel and Noegel[8, 9] was used with modifications. Studies were performed on all rats with the exception of the rats which spontaneously died during the experiment.

During fasting the rats were maintained in wire-bottomed cages to avoid copraphagy. The experiments were performed in a room with the same environmental conditions (temperature, noise and humidity) as those in the breeding area. All experiments were done in the morning.

The phenol red meal was prepared as follows: methyl cellulose was dissolved in water at about 80 °C and prepared in a final concentration of 1.5 %. The solution was stirred until dissolved, and phenol red (50 mg/100 ml) was then added to the stirring solution.

Three ml of phenol red solution, maintained at 37 °C, was administered orally to the rats. The animals were then killed 10 minutes (healthy rats) or 20 minutes (healthy rats and rats with gastroduodenal diseases) after the ingestion of the phenol red meal by means of CO_2 inhalation.

An incision was made for a middle laparotomy. The stomach was exposed and occluded at the pylorus and cardia. The stomach was then removed, cut along the greater curvature and washed out with 3 ml of 0,9 % saline. The gastric content was placed in 100 ml of 0,1 N NaOH with 0,9 % saline.

Trichloracetic acid (0,5 ml) (20 % t/vol) was added to 5 ml of the mixture. This sample was centrifuged at 2,500 rpm for 30 min. The supernatant was removed and 4 ml of 0,5 N NaOH added. Samples were then read on a colour spectrophotometer (MA 9502) at 560 nm.

The percentage of gastric remains was calculated as follows:

$$\% \text{ gastric remains} = \frac{\text{absorbtion value for stomach}}{\text{mean absorbtion value for test meal}} \times 100$$

Values were reported as means ± SE.

Statistical analysis was made using the Student's t test with a significance level criteria of 0,05.

Morphologic evaluation

The stomach and other visceral organs were examined macroscopically, fixed in a 10 % neutral formalin and routinely processed for histopathological studies. Gastroduodenal lesions were classified histopathologically into neoplastic (dysplasia, papilloma, squamous cell carcinoma, adenocarcinoma, sarcoma) and nonneoplastic (principally inflammatory) gastroduodenal diseases, following accepted histologic criteria.[12]

Statistical evaluation

The significance of the percentage difference of the gastric content 20 minutes after the test-meal was evaluated by using the Student's t test.[13]

Results

Body weight gains of rats in the different MNNG-treated groups are shown in Figure 1.

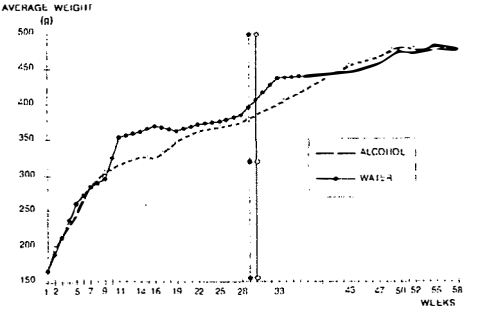

Figure 1. Weight gain in rats during different dietary periods.

One animal in the alcohol and two animals in the water group died from pneumonia and one animal in the alcohol group from an advanced gastric tumor. Autopsies were not done in two animals.

As shown in Table 1, tumors were found in 23 rats (from a total of 60 rats). The incidence of gastroduodenal carcinoma was greater in the experimental group drinking the tap water with MNNG, in contrast to the group drinking alcohol with MNNG.

The data on gastric emptying in rats with gastroduodenal diseases and those in healthy rats are summarised in Figure 2.

The gastric emptying in rats with gastroduodenal lesions with or without gastric or duodenal tumors

Table 1. Effect of Various Test Meals on Gastroduodenal Neoplasia Induced by MNNG in Male Wistar Rats*

Gastroduodenal Lesions	Treatment (Test Meals)		
	Ethanol**	Water***	Total
Displasia	4	0	4
Papilloma	1	1	2
Carcinoma	5	11	16
Sarcoma	1	0	1
Total	11	12	23

* Total No of rats were 60.
** 12.0 vol % of ethanol in tap water with MNNG.
*** Tap water with MNNG.

was approximately equal. Figure 2 also shows that the gastric emptying was significantly slower in the

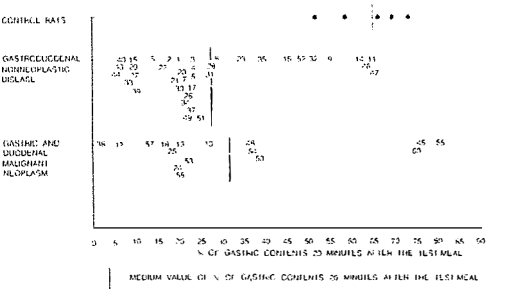

Figure 2. Distribution of the gastric content of the standard meal in the stomach of rats with and without gastroduodenal disease.

No	%	
1	20.2	Chronic superficial duodenitis.
2	18.2	Fibrosis of fundic mucosa. Chronic superficial duodenitis.
3	24.1	Chronic superficial duodenitis.
4	24.1	Chronic antral gastritis with focal fibrosis of mucosa and sub. mucosa.
5	22.9	Focal fibrosis of fundic and antral mucosa.
6	13.8	No pathological changes.
7	21.5	Chronic gastritis and focal fibrosis of antral mucosa. Focal dysplasia (grade II) of nonglandular (squamous) mucosa. Chronic superficial duodenitis.
8	29.6	Chronic superficial duodenitis and focal fibrosis of antral mucosa.
9	55.0	Focal regeneratory atypia of duodenal mucosa (in the vicinity of fibrosis).
10	27.1	Focal chronic gastritis of antral mucosa. Early adenocarcinoma of liver.
11	64.4	Mild chronic gastritis of antral and fundic mucosa.
12	(–)	No autopsy report.
13	20.0	Focal fibrosis of fundic mucosa. Focal dysplasia and invasive squamous cell carcinoma of nonglandular mucosa.
14	61.8	Mild chronic duodenitis with focal fibrosis of propria.
15	10.3	Chronic duodenitis. Chronic gastritis and chronic erosion of antral mucosa.
16	44.9	Focal fibrosis of submucosa of antral mucosa region. Chronic duodenitis.
17	24.4	Chronic gastritis of antral mucosa.
18	16.9	Moderate dysplasia of squamous mucosa. Chronic antral gastritis with focal fibrosis of submucosa. Early adenocarcinoma of antral mucosa.
19	(–)	Advanced sarcoma.
20	21.0	Chronic gastritis of antral mucosa. Liver cystadenoma.
21	19.6	Chronic gastritis of antral mucosa.
22	16.1	Focal fibrosis of antral and duodenal mucosa.
23	34.7	Chronic gastritis of antral mucosa.
24	19.6	Chronic gastritis of antral mucosa with focal fibrosis. Squamous cell papilloma of nonglandular mucosa. Adenocarcinoma (infiltrates muscularis propria) of antral mucosa.
25	17.7	Moderate dysplasia of squamous mucosa. Early invasive cell carcinoma of nonglandular mucosa.
26	23.5	Mild dysplasia of squamous mucosa.
27	9.6.	Chronic gastritis of antral mucosa with focal fibrosis.
28	27.8	Focal fibrosis of antral mucosa. Liver cystadenoma.
29	11.4	Focal fibrosis of antral mucosa.
30	20.2	Chronic gastritis of antral and fundic mucosa with focal fibrosis.
31	27.6	Chronic gastritis of antral mucosa with focal fibrosis. Liver hamartoma.
32	52.6	Chronic duodenitis.
33	10.2	Chronic gastritis of antral mucosa and erosion of fundic mucosa.
34	21.0	Chronic gastritis of antral mucosa with focal fibrosis of antral and duodenal mucosa.
35	38.8	Focal fibrosis of antral and fundic mucosa.
36	(–)	Advanced autolysis. No tumor.
37	22.9	Focal fibrosis of antral and fundic mucosa.
38	1.6	Chronic gastritis of antral mucosa. Moderate dysplasia of nonglandular mucosa. Early invasive squamous carcinoma.
39	10.9	Chronic gastritis of antral mucosa. Focal dysplasia of fundic mucosa.

No	%	
40	8.3	Chronic gastritis of antral mucosa. Chronic duodenitis.
41	(–)	Focal fibrosis of antral mucosa. Initial autolysis.
42	5.9	Chronic gastritis and focal fibrosis of antral mucosa. Chronic duodenitis. Advanced (Dukes B) adenocarcinoma of duodenum.
43	7.6	Chronic gastritis of antral mucosa. Papillary cystadenoma of liver.
44	6.5	Chronic gastritis of antral mucosa. Focal fibrosis of duodenal mucosa.
45	76.2	Adenocarcinoma of antral mucosa.
46	63.5	Focal fibrosis of antral mucosa. Gastritis cystica profunda of prepyloric region.
47	65.5	Focal fibrosis of antral and duodenal mucosa and antral submucosa.
48	36.6	Adenocarcinoma of antral mucosa (submucosal invasion).
49	22.4	Gastritiscystica profunda of antral mucosa. Cystadenoma of liver.
50	38.9	Chronic duodenitis. Adenocarcinoma of antral (prepyloric) mucosa (submucosal invasion).
51	25.0	Focal fibrosis of antral mucosa and submucosa and chronic erosion of antral mucosa.
52	48.3	Focal fibrosis of antral and fundic mucosa.
53	21.9	Focal fibrosis of antral mucosa. Adenocarcinoma of antral mucosa (submucosal invasion).
54	36.8	Chronic gastritis of antral mucosa. Advanced (Dukes B) adenocarcinoma of duodenum.
55	80.5	Chronic gastritis and focal fibrosis of antral mucosa. In nonglandular mucosa squamous papilloma and invasive squamous carcinoma (early). Advanced (Dukes B) adenocarcinoma of duodenum. Multiple papillary cystadenoma of liver.
56	(–)	No autopsy report.
57	12.7	Chronic gastritis of antral mucosa. Adenocarcinoma of antral mucosa (invasion of submucosa).
58	20.0	Adenocarcinoma of antral (prepyloric) mucosa (invasion of submucosa)
59	(–)	Chronic gastritis and focal fibrosis of antral mucosa.
60	75.0	Advanced (Dukes B) adenocarcinoma of distal duodenum.

healthy rats than in those with gastroduodenal lesions. ($P < 0{,}01$).

The time duration for gastric emptying in the control (healthy) animals is illustrated in Figure 3.

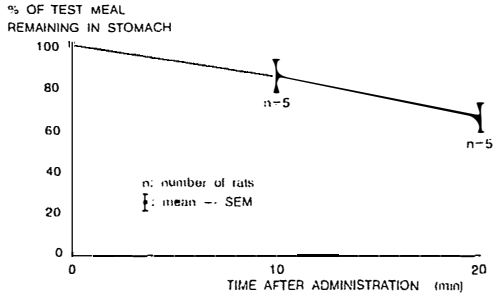

Figure 3. Gastric emptying in rats without gastroduodenal disease.

Discussion

In the present work we found a significantly faster gastric emptying in rats with gastroduodenal diseases, in comparison with the control group of healthy rats.

We show that there is not a great difference in the rates of emptying between the rats having the gastroduodenal neoplastic and those with inflammatory disease. This finding confirms the previous work of Nomiyama[5] who, using the acetaminophen absorption method, discovered that gastric emptying in patients with early gastric cancer was rather rapid, when compared with emptying in healthy subjects.

On the other hand, delayed gastric emptying has been demonstrated for a variety of infiltrative diseases.[1, 4, 14–16] This includes lymphomas, carcinoma, Whipple's disease, and diseases that produce granulomas in the gastric wall. In our study, all the animals with a prolonged gastric emptying with neoplasia had advanced carcinomas of the antrum and duodenum. On the other hand, the animals with shortened emptying generally had early gastric tumors.

Gastric mucosal abnormalities can affect gastric emptying. Diseases of the gastric musculature, including the inflammatory and endocrine myopathias, muscular dystrophies, and infiltrative disorders, can result in significant gastroparesis.[1] Most patients with gastroparesis have a delay in the emptying of solid food, but the rate of liquid emptying is preserved. This observation suggests that the factors that regulate the fundic tone are preserved longer in most patients with gastroparesis.[17] The proximal stomach has two remarkable motor properties that allow it to carefully regulate intragastric pressure during gastric filling, namely: receptive relaxation and accommodation.

The proximal stomach relaxes to receive the bolus of ingested food from the esophagus; hence the term receptive relaxation. Liquids entering the fun-

dus trigger vagally mediated initial receptive relaxation, so that the fundus plays a key role in the gastric emptying rate for liquids.[18]

The slight shortening of the time for gastric emptying could be accounted for as a result of the absence of the part of the receptive relaxation of the stomach when swallowing is eliminated.[19]

Accommodation to distension is a process whereby the stomach accepts increasing volumes without greatly increasing the intragastric pressure.

In the present work, an increased gastric emptying (especially the initial emptying) of liquids can also be explained by the abolition of the vagally mediated receptive relaxation, and/or of the change in the fundic tone as the intragastric injection of the liquid test meal occurs, that raises the intraluminal pressure, elevates the pressure gradient between the stomach and duodenum, and allows more liquids into the duodenum.[20]

This abnormally rapid gastric emptying, compared with the emptying in healthy rats, may be caused by differences in the gastric tonus.[9]

In healthy group, the proximal stomach accommodated easily to distension, keeping the intragastric pressure low as the stomach filled. On the contrary in the group with gastroduodenal disease, larger increases in pressure occurred during gastric distension. The gastroduodenal diseases impaired the stomachs' accommodation and led to greater increases in intragastric pressure with gastric filling. Moreover, the greater increases in pressure in those animals with gastroduodenal diseases led to the more rapid gastric emptying of liquids for most of the rats studied.

References

1. Chanduri TK, Fink S. Gastric emptying in human disease states. *Am J Gastroenterol* 1991; **86:** 533–8.
2. Griffith GH, Owen GM, Inset AP, Campbell H, Smith R. Gastric emptying in health and in gastroduodenal disease. *Gastroenterology* 1968; **51**: 1–7.
3. Tatsuta M, Liski H, Okuda S. Gastric emptying in patients with fundal gastritis and gastric cancer. *Gut* 1990; **31**: 767–9.
4. Shih WJ, Domstated PA, Deland FH. Technetium – 99 m triethelene tetramine polysterone resin gastric emptying studies in patients with various upper gastrointestinal diseases. *Clin Nucl Med* 1985; **10**: 494–7.
5. Nomiyama T. Gastric emptying in gastric cancer. In: Tsuneoka K, Miwa T, Sekiguchi T, eds. *Gastroduodenal motor disorder*. Tokyo: Bunhodo, 1985: 178–81.
6. Minami H, Mc Callum RW. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* 1984; **86**: 1592–610.
7. Azpiroz F, Maalagelada JR. Gastric tone measured by an electronic barostat in health and postsurgical gastroparesis. *Gastroenterology* 1987; **92**: 934–43.
8. Scarpignato CT, Capovilla T, Bertaccini G. Action of caerulein on gastric emptying of the conscious rat. *Arch Int Pharmacodyn* 1980; **246**: 286–94.
9. Mangel AW, Koegl A. Effect of peptides on gastric emptying. *Am J Physiol* 1984; **246**: (Gastrointest Liver Physiol 9): G342–G345.
10. Takahashi M, Hasegawa R, Furukawa F, Toyoda K, Sato H, Hayeshi Y. Effect of ethanol, potasium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initation with N-Methyl-N-Nitro-N-Nitrosoguanidine. *Jpn J Cancer Res (Gann)* 1986; **77**: 118–24.
11. Watanable H, Takahashi T, Okomoto T, Ogundigie PO, Ito A. Effect of Sodium Chloride and Ethanol on Stomach Tumorigenesis in ACI Rats Treated with N-Methly-N-Nitro-N-Nitrosoguanidine; A Quantitative Morphometric Approach. *Jpn J Cancer Res* 1992; **83**: 588–93.
12. Stinson SF, Schuller HM, Reznik G. *Atlas of tumor pathology of the Fischer rat*. Boca Raton, Florida: CRC Press, 1990.
13. Petz B. *Osnove statističke metode*. Zagreb, 1970: 121–69.
14. Meerof JC, Schreiber DS, Trier JS et al. Abnormal gastric motor function in viral gastroenteritis. *Ann Intern Med* 1980; **92**: 370–3.
15. Meddern JG, Horowitz M, Jamieson GG et al. Abnormalities of esophageal and gastric emptying in progressive systemic sclerosis. *Gastroenterology* 1984; **87**: 922–6.
16. Reddy AB, Wright RA, Wheeler GE et al. Non-obstructive gastroparesis in amyloidosis improved with metoclopramide. *Arch Intern Med* 1983; **143**: 247–8.
17. Reynolds JL. Prokinetic agents: A key in the future of gastroenterology. *Gastroenterol Clin North Am* 1989; **18**: 437–57.
18. Mistiaen W, Van Hee R, Block P et al. Gastric emptying for solids in patients with duodenal ulcer before and after highly selective vagotomy. *Dig Dis Sci* 1990; **35**: 310–6.
19. Hunt JN, Mac Donald I. The effect of intra-gastric instillation of meal on gastric function in man. *J Physiol* 1951; **113**: 185–8.
20. Kelly KA. Gastric emptying of liquid and solids: roles of proximal and distal stomach. *Am J Physiol* 1989: **239**: (Gastrointest Liver Physiol 2): G71–G76.

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Chemotherapy of small cell lung cancer

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Despite the fact that small cell lung cancer (SCLC) is a very chemosensitive disease, the long-term results from the present treatment are very disappointing with 5 year survival of less than 5%. The present article is an overview of the chemotherapy used today and future treatment perspectives.
Most centers today use a combination of epipodophyllotoxin derivates (Etoposid, (VP-16) or Vumon (VM-26) and a platin derivate (Cisplatin or Carboplatin) as a "standard" treatment for SCLC. Less toxic treatment for the elderly patients are described, especially the role of oral single agent treatment.
"High dose" treatment with or without bone marrow support has not yet resulted in prolonged survival. Future treatment strategies are discussed.

Key words: lung neoplasms – drug therapy; carcinoma, small cell; brain metastases

Introduction

Lung cancer is one of the most important public health problems in the world. The incidence of this malignant disease continues to increase in the developed world, particulaly among women. By the year 2000 the estimated number of new cases worldwide is expected to exceed 2 million.[1] Approximately 25 % of all lung cancer cases are of the small cell variety (SCLC). Despite few or no symptoms about 60 % of the patients have documented distant metastatic disease at presentation.[2]

In contrast to the other major types of lung cancer, SCLC is highly sensitive to both chemotherapy and radiation therapy. However, patients with extensive stage disease are rarely cured, even with aggressive treatment. On the other hand patients with limited stage disease sometimes experience long-term progression free survival with chemotherapy with or without thoracic radiotherapy and, occasionally, cure. Furthermore, chemotherapy is effective in ameliorating the symptoms of the superior vena cava syndrome, bronchial obstruction, pleural effusion and even brain metastases. Virtually, all patients with SCLC should therefore receive chemotherapy as part of their initial treatment.

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"Standard" chemotherapy

A number of drugs have been identified with single agent activity in SCLC.[3] The relative effectiveness of the individual drug is difficult to compare because only few of them are studied in previously untreated patients, but mostly in heavily pretreated patients. However, most of the drugs have reported response rates of 30–60 % as single agent treatment (Table 1). Early randomized trials demonstrated that **combination chemotherapy** was superior to single agent treatment.[4,5] In the late 1970s and early 1980s cyclo-phosphamide-based combination chemotherapy regimens represented the most commonly used induction therapy. A typical example is the CAV regimen: cyclophosphamide/doxorubicin (adriamycin^{R})/vincristine which has demonstrated overall response rates of 65-90 % in limited stage disease and complete response rates of 20–40 % with a small number of 5 years survivors.[2,6]

Table 1. Active single agents in small cell lung cancer.

Drug	Approximate response rate (%)
Etoposide	75
Teniposide	75
Ifosfamide	60
Cisplatin	50
Carboplatin	40
Cyclophosphamide	40
Vincristine	35
Methotrexate	35
Doxorubicin	30
Hexamethylmelamine	30
Vinblastine	30
Vindesine	30
Lomustine	15

During the early to mid 1980s many clinical trials focused on the integration of etoposide into existing chemotherapy regimens. Although none of these trials yielded a major improvement in survival most were associated with a modest improvement in median survival which in some instances was statistically significant.[7, 8]

The combination of etoposide (E) and cis-platin (P) is of special interest because it appears to have the best therapeutic index of any regimens, and in a number of trials this combination (EP) has been used as the initial chemotherapy for patients with SCLC. Overall results in previous untreated patients show that the complete response rate average more than 50 % with a median duration of survival in these studies that compared favorably with results achieved with traditional induction regimens such as CAV or CAE (cyclophosphamide, doxorubicin, etoposide).[6–10]

While most of the treatment regimens today include cisplatin and etoposide, more recently cisplatin has been replaced by carboplatin in combination with oral etoposide in the treatment of poor prognosis patients with SCLC[11] and those studies suggested that the combination of carboplatin with oral etoposide is a highly effective regimen for the treatment of SCLC patients with results equal to and comparable with more intensive schedules.[11, 12] However, it is too early yet to evaluate the long term results (> 3 years) on that regiment. The median survival from the study by Carney[11] is 43 weeks (range 4–128). In one randomized study cis-platin was compared to carboplatin, both in combination with etoposide, and no difference was obtained with regard to response and survival.[12] The ease of administration of the combination of carboplatin and etoposide with acceptable toxicity would suggest that this combination could be the treatment of choice at least for a subset of patients with SCLC, especially those patients who cannot tollerate more intensively given treatment.

The strategy **of alternating "non-cross resistant" chemotherapy** was prompted by theoretical considerations put forth in a mathematical model developed by Goldie and Goldman.[13]

A study by Evans et al in 1987[14] demonstrating a better survival with a regimen of CAV in alternation with EP compared to CAV alone raised the clinical interest for this question in patients with SCLC. However, the possibility could not be eliminated, that the superiority of the alternating treatment was due to a better efficacy of the EP treatment than the CAV treatment. Two subsequent randomzied studies by Roth et al[9] and Fakuoka et al[6] compared CAV, EP and CAV alternating with EP, and no difference in survival was seen among the three treatment groups in either of the studies. The value of the sequential administration of two cycles of etoposide and cisplatin after completion of six cycles of CAV was evaluated in a large study of limited disease patients by Einhorn et al,[15] and the median survival was prolonged by seven months with etoposide and cisplatin.

However, the majority of studies using alternating non-cross resistant combination chemotherapy have not shown a major benefit for this approach.[16] Although alternating regimens produce only minimal survival advantages at best, they do reduce toxicity that depends on the cumulative dose of a single drug such as doxorubicin induced cardiomyopathy and cisplatin induced neuropathy. The problem is, however, that from a experimental therapeutic point of view the so called "non-cross resistant" treatment with CAV and EP are today not considered as a true non-cross resistant combination chemotherapy.[17]

The Copenhagen experience[18]

In Copenhagen clinical studies focusing on the treatment of patients with SCLC have been performed by the Copenhagen Lung Cancer Group since 1973. In the period 1985-1990 484 previously untreated patients ≤ 70 years old were included in study designed with the following aims: 1. to compare two induction regimens containing teniposide (VM 26), vincristine (VCR) and either cis-platin (P1) or carboplatin (JM-8) followed by an alternating chemotherapy and 2. to compare these regimens with alternating regimen alone.

Arm 1: D_1-D_1-D_1 evaluate – A-B-C-D_1-A-B-C-D_1 – evaluate

Arm 2: D_2-D_2-D_2- evaluate – A-B-C-D_2-A-B-C-D_2 – evaluate

Arm 3: A-B-C – evaluate – A-B-C-A-B-C-A-B – evaluate

A: Doxorubicine, VCR

C: Pl, hexamethylmelamine, vindesine

D_1: Pl, VM 26, VCR

D_2: JM-8, VM 26, VCR

There was no survival difference in patients treated with the two platinum containing induction arms, while the survival was superior in the two induction arms compared to the alternating control arm (Table 2).

Table 2. Median survival (M.s.) and 2-years survival.

	LD		ED		All	
	M.s. weeks	2 years	M.s. weeks	2 years	M.s. weeks	2 years
Reg. I	58	20 %	36	10 %	48	18 %
Reg. II	61	18 %	38	13 %	49	15 %
Reg. III	48	15 %	30	5 %	42	10 %

Treatment of elderly patients with SCLC

Approximately 25–30 % of newly diagnosed patients with SCLC are older than 65, and the number of elderly patients with SCLC will continue to increase over the next 20 years. It is therefore important to give greater consideration to the management of elderly SCLC patients. Single-agent chemotherapy have demonstrated to be very useful in the elderly patients. Etoposide or its analogue teniposide (VM-26) alone has yielded response rates of 65 to 80 percent in elderly patients, including complete responses in 20 to 25 percent of patients, only moderate toxicity and median survival of 9 to 11 months in controlled[19] and uncontrolled trials.[20] Although better results might have been obtained with combinations of drugs with or without radiotherapy no randomized trials have addressed these questions in this subgroup of patients. However, more recently it is reported that the combination of orally given etoposide in combination with carboplatin is a well tollerated combination also for elderly patients.[21]

Etoposide has clearly demonstrated schedule dependence. A study of Slevin et al[22] has shown that prolonged administration of etoposide produces greater responses than the same total dose given in a shorter time frame. Furthermore the study has demonstrated that the overall response rate and survival were significantly greater for patients who received 5 days of i.v. therapy than for those who received a single day of treatment. Randomized trial comparing intermittent and continuous etoposide in elderly patients with previously untreated SCLC are presently ongoing in Copenhagen.

Many factors may influence the approach to the administration of chemotherapy to the elderly patients. Co-morbid illnesses and/or performance status rather than the age are the principle factors which will dictate the therapeutic approach and for many of these patients the aim of treatment is to balance the probability of cure or palliation against the risk of toxicity and quality of life. The presence or absence of co-morbid disease leading to impairment of cardiac, pulmonary or renal function should be considered as well as other medication, which may lead to potential drug interactions with the chemotherapy. Furthermore, elderly patients have often poor compliance and errors in self-medication.

At present, single agent chemotherapy with oral etoposide seems to be an appropriate option for elderly patients with SCLC in whom the likelyhood of severe toxicity from combination therapy is high. The treatment is well tollerated and has shown to give a high response rate (75–80 %), and long term survivors (> 2 years) are reported even in this group of patients.[19] The most optimal schedule is not established and future studies should also include a comparisson of single agent treatment with "mild" combination treatment.

Dose intensity without bone marrow support

Drug delivery can be intensified by increasing the doses or by reducing the intervals between treatments. Intensification strategies include high-dose induction chemotherapy, late intensification chemotherapy with or without bone marrow support and weekly chemotherapy have been studies.

During the 70s and early 80s the clinical investigations hypothesized that a dose response relationship existed in the treatment of SCLC and "more chemotherapy was better", and early trials appeared to support these results.[23, 24] However, randomized trials comparing "high dose" regimens to "stand-

ard" doses failed to demonstrate significant differences in survival.[25–28] Retrospectively, however, it can be discussed whether the "high-dose" treatment really could be considered as such from an up-to-date point of view.

In a study by Ihde and co-workers[29] they failed to demonstrate a survival benefit in patients with extensive stage SCLC randomized to high dose therapy compared to standard dose therapy. They randomized 90 patients to standard dose PE vs. high dose PE. Patients randomized to the standard dose arm received 80 mg/m^2 of cisplatin days 1,3 plus 80 mg/m^2 etoposide days 1–3 for cycles 1 and 2. Patients randomized to the high dose arm received 27 mg/m of cisplatin days 1–5 and 80 mg/m^2 of etoposide days 1–5 for cycles 1 and 2. All patients received standard dose PE cycle 3 and 4. In cycles 5 through 8 completely responding patients continued standard dose PE, all other patients received either cyclophosphamide, doxorubicin and vincristine or if possible a combination drug program based on in-vitro drug testing of tumor cell lines established from individual patients. Despite 68 % higher doses and a 46 % higher dose-rate intensity actually given to patients randomized to high-dose PE compared to those randomized to receive standard dose PE, complete response rates (23 % vs. 22 %) and median survival durations (10.7 months and 11.4 months) respectively, were not statistically significant. Furthermore, dose escalation of chemotherapy was associated with enhanced toxicity.

Another approach to increase the total dose delivery was to evaluate the use of prolonged administration of chemotherapy, the so called **"maintenance therapy"**. Randomized clinical trials evaluating the maintenance chemotherapy for 5 to 7 months following 6 months of induction chemotherapy demonstrated that, although, the duration of initial treatment remission could be prolonged, survival was not significantly improved by this approach, and the treatment was associated with increased toxicities due to the protracted exposure to chemotherapy.[30–34]

Yet, another method for increasing the intensity of chemotherapy in SCLC is to intensify the schedule. Studies evaluating cisplatin, vincristine, doxorubicin and etoposide (CODE) have shown high response rates (> 90 %) and encouraging two year survival rates in patients with extensive stage disease. Once again, however, these results have not been confirmed in a randomized study evaluating four drug, high dose weekly chemotherapy against "standard" alternating CAV/PE.[35]

In contrast to "late intensification" Arriagada et al[36] reported recently a study of **"initial intensification"** randomized 105 patients to receive a first course of either "high dose" cyclophosphamide (300 mg/m^2) days 2–5 plus cisplatin, 100 mg/m^2 day 2 or "lower dose" of cyclophosphamide (225 mg/m^2) days 2–5 plus 80 mg/m^2 cisplatin on day 2. All patients received the lower doses of cyclophosphamide and cisplatin, plus doxorubicin and etoposide for course 2 through 6. Thoracic radiation was given concurrently in both groups starting with the second cycle of chemotherapy. Although there was no significant difference in complete response rate, the two year survival for the 55 patients who received the higher doses of chemotherapy was 43 % compared with 26 % for the 50 patients who were randomized to receive the lower doses of cyclophosphamide and cisplatin for cycle 1 ($p = 0.02$). One possible reason for their positive results was that the delivery of higher initial doses of drugs early prevented the emergence of chemoresistant tumor clones. They suggest that the advantage of only a 20 % to 25 % increase in the doses of cyclophosphamide and cisplatin may have been that the resultant toxicity was not severe, and did not necessitate delay of subsequent cycles of standard doses of chemotherapy as may have been the case in other trials which evaluated the use of much higher doses of drugs in cycle 1.

A meta-analysis of dose-intensity in SCLC involving 60 published studies failed to demonstrate a correlation between dose intensity of CAV (cyclophosphamide, adriamycin, vincristine) or cisplatin/etoposide and response rate or survival for limited or extensive stage disease. Furthermore, no consistent correlation in relative dose intensity of any individual drugs and outcome was observed.[37]

Weekly chemotherapy have not in phase III-studies for patients with SCLC demonstrated any advantage compared to standard treatment given at intervals of three weeks.[28, 35] Comparisson of dose intensity given in weekly programs compared to standard programs have shown that weekly delivery of myelosuppressive chemotherapy does not allow recovery of granulocytes. However, it is still too early to say whether this approach is significant beneficial for patients with SCLC.

Dose intensity with bone marrow support

High dose chemotherapy with autologous bone marrow transplantation ABMT have been studied by

several groups. The largest studies by Souhami et al[38] and Smith et al[39] reported median relapse free survival and overall survival similar to those associated with standard chemotherapy approaches. In a randomized study of intensive chemotherapy and ABMT by Humblet et al[40] they found the complete response (CP) rate increasing from 39 % to 79 % with the intensive post induction chemotherapy. The relapse free survival was significantly increased in the group as a whole and in a subset of patients with limited stage disease.

A recent study by Elias et al[41] has again evaluated the effects of intensive chemotherapy with bone marrow support in patients with SCLC who were in complete or partial response following conventional chemotherapy. In this phase II study, however, patient selection and consolidative chemotherapy were chosen to address some of the prior issues raised with earlier trials. Nineteen patients with limited stage SCLC who had achieved a partial or complete response to first live conventional dose chemotherapy were treated with high dose cyclophosphamide, cisplatin and carmustine with autologous bone marrow support and thoracic and cranial radiotherapy. After high dose chemotherapy, 15 of 19 were in complete response with a one and two year survival rate of 73 % and 53 %, respectively.

The role of colony stimulating factors in small cell lung cancer

The colony stimulating factors (CSFs) are glycoprotein hormones that stimulate proliferation and differentiation of hematopoetic progenitor cells. Possible uses for these agents in the treatment of small cell lung cancer are to allow possible dose escalation of myelosupressive chemotherapy agents, to protect patients prophylactically from febrile neutropenia prior to standard chemotherapy and to speed neutrophil recovery following chemotherapy.

The effect of prophylactic granulocyte – colony stimulating factors (G-CSF) has been studied by Crawford et al.[42] This randomized placebo controlled study of patients receiving chemotherapy for SCLC demonstrated that prophylactic G-CSF can significantly reduce neutropenia and infective complications following standard-dose chemotherapy. Patients received standard dose cyclophosphamide, doxorubicin and etoposide with placebo or G-CSF 230 microgram/m^2 on days 4–17. One or more febrile neutropenic episodes occurred in 77 % of the placebo group but in only 40 % of the G-CSF group. The duration of neutropenia (neutrophil count < 0.5 × 10^9/l) was 6 days with placebo and only 1 day with G-CSF. The number and duration of hospital admissions were less in the G-CSF group. However, regarding tumor respons and survival there was no difference in either arm. The side effect mild to moderate bone pain was documented in 20 % of patients given G-CSF. Another prospective randomized trial was conducted in patients with SCLC receiving PE alternating with ifosfamide and doxorubicin to determine whether G-CSF could increase the received dose intensity of weekly chemotherapy. G-CSF decreased dose reductions due to neutropenia, but did not result in increased dose intensity due to non-hematologic toxicities.[43] Other studies have suggested that the incidence of neutropenic fever with standard dose chemotherapy is low (about 18 %) and that routine use of G-CSF in this setting is expensive and not associated with a cost savings or therapeutic benefit.[44] In a recently published study by Bunn et al patients with limited stege SCLC receiving concurrent chemotherapy and radiation therapy, patients randomized to receive granulocyte-macrophage colony stimulating factor (GM-CSF) had more infections, more days febrile and a significant increase in thrombocytopenia compared to those randomized to no GM-CSF and there was no benefit in response rates or survival time by using GM-CSF.[45]

Duration of chemotherapy and treatment of progressive tumors

In the beginning of the chemotherapy era it was though that more and longer chemotherapy was better, and treatment durations of 12–18 months was not unusual.[2] However, as mentioned earlier the principle of prolonged administration of chemotherapy in patients who responded to treatment did not improve survival.[30, 33, 34, 36] The most usual treatment duration today is about 6 months, but no randomized studies have yet established the most optimal treatment duration. Small-cell carcinoma that progresses during or after initial chemotherapy is usually refractory to further treatment and is always incurable; however, the likelihood of disease regression and palliation with subsequent chemotherapy in patients who have previously responded is greater if tumor regrowth is preceded by at least a few months of no treatment.[10, 47, 48] Chemotherapy

should therefore be discontinued after four to six months in patients who respond and then resumed at relapse if clinically appropriate. Thus, the success of second line chemotherapy is dependent on multiple factors including:

– the interval between cessation of primary therapy and the detection of recurrence
– the nature of the response to primary therapy and
– the composition of the primary chemotherapy.

Long-term survival

SCLC is an extremely responsive tumor. The introduction of combination chemotherapy as the principle form for treatment of SCLC led to an increase in median survival and suggestion that a significant proportion of patients might be cured. Unfortunately, the results from long-term survival studies indicate that only a small proportion of patients with SCLC are cured by current treatment. Souhami and Law reported on 3681 cases of SCLC treated in major centres in UK and found that only 3 % were alive at seven years (3,6 % LD, 1 % ED).[49] The results from the clinical trials in the Copenhagen Lung Cancer Study Group including 1714 patients were comparable with the results from the UK. The rate of 5-years survivors was 3,5 %. Among the 828 patients with limited disease 40 patients (4.8 %) became long-term survivors and 20 of 886 patients (2.3 %) of the ED patients. The 10-years survival rate was 1,8 %.[50] These results document that patients with small cell lung cancer continue to relapse up to and occasionally after 5 years.

Beyond 6 years other smoking-related diseases become the major cause of death. Particularly chronic bronchitis, vascular disease and smoking related cancer. These survival data although demonstrating the bad long term prognosis of SCLC do not indicate that treatment is not worthwhile. Some patients, most of them initially presented with limited disease, are cured. However, for the vast majority of patients treatment is palliative and for most of the patients chemotherapy undoubtedly provides effective palliation of symptoms with prolongation of short time survival.

New drugs

Over the past five years a number of new agents with activity against lung cancer have been identified. The relative resistance of SCLC to second line therapy has raised a considerable dilema in the development of strategies to identify new drugs to treat the disease. When new agents are tested in previously treated patients, response rates are lower than they might be in untreated patients, and it is possible that potentially active agents might be missed. Ideally new agents should be tested in previously untreated patients.

An alternative approach has been to incorporate new agent as part of combination regimen or to offer new agents to those patients who have not received therapy for 3 or more months.

Taxanes

The taxanes, representated by the prototypic agent paclitaxel (Taxol) and the semisynthetic analogue docetacxel (Taxotere) are the first class of anti-microtubule agents developed since the vinca alkaloids.

Paclitaxel: has been evaluated in two phase II-studies involving previously untreated patients with extensive-stage SCLC.[51, 52] In one study preliminare published by Eastern Cooperative Oncology Group (ECOG) 32 evaluable patients were treated with Taxol 250 mg/m^2 intravenously over 24h every 3 weeks. There were no patients with CR, while PR was found in 11 patients (34 %). However, further 3 patients had a greater than 50 % shrinkage of their disease, but did not have the 4 week follow up which is a requirement of PR. In another study 37 evaluable patients were treated. There were no CR's, but 15 patients had PR (41 %). There are several ongoing phase II studies with paclitaxel. In two recently published preliminary results from treatment with paclitaxel in combination with cis-platin/carboplatin and etoposide high response rates were reported.[53, 54] However, it is too short observation for long term results.

Docetaxel: In an EORTC-study, Smyth et al[55] performed a phase II-trial of docetaxel 100 mg/m^2 i.v. as a 1 h-infusion every 3 weeks. Among 27 patients (23 patients had prior treatment) 5 of 18 (28 %) had PR.

The camptothecins

The topoisomerate I targeting agents represent one of the most promising classes of antineoplastic agents under development.

CPT-11 (irinotecan) is a camptothecin derivate with greated aqueons solubility than comptothecin.

In phase I studies the principal dose-limiting effect on all schedules has been myelosuppression, but non-hematologic side effects like diarrhea have avoided dose escalation. Masuda et al[56] studied CPT-11 in 15 previously treated evaluable patients with SCLC and 47 % had a PR. Fujiwara et al[57] evaluated CPT-11 plus cis-platin in previously untreated patients with SCLC. Among 18 patients with LD evaluable for response there were 4 patients with CR (22 %) and 10 PR's (50 %). Among 14 patients with ED there were 3 patients with CR's (21 %) and 8 patients with PR (57 %).

Topotecan: is a water soluble comptothecin analogue with topoisomerase I-targeting activity. The drug's dose-limiting toxicity in phase I-studies was neutropenia and in some cases also trombocytopenia. In an ECOG-study[58] 41 patients with previosly untreated extensive disease SCLC were treated with topotecan 2.0 mg/m^2/day i.v. 5 days every 3 weeks. PR was seen in 39 % and in a study of Ardizzoni et al[59] 29 previously untreated patients were treated with 1.5 mg/m^2/day × 5 every 3 weeks and 10 % had CR and 25 % PR.

Gemcitabine

Gemcitabine is a new nucleoside analogue antimetabolite. In phase I-trials the dose-limiting toxicity was myelosuppression, mainly trombocytopenia and anemia. In a NCI/Canada study[60] gemcitabine was evaluated in previously untreated patients (23 evaluable) and there was one CR (4 %) and six patients had PR (26 %).

However, all the phase II-studies with the above mentioned new drug have relatively small numbers of patients and future approach should be to evaluate these new drugs in combination with the other active drugs for the treatment of SCLC.

Combination of thoracic radiotherapy and chemotherapy

The role of mediastinal irradiation in the treatmenf of patients with SCLC have been discussed for many years. Meta-analyses indicate that the addition of radiotherapy to combination chemotherapy has improved survival significantly for the patients with **limited** small cell lung cancer.[61] Hovewer, the randomized trials that formed the bases for these analyses were from early this decade and the previous one. Most of the chemotherapy regimens were cyclohosphamide/doxorubicin based and none of them had up front cis-platin based chemotherapy programs. Thus, the chemotherapy used in the trials are today considered as sub-optimal. The combined treatment modality has resulted in excess toxocity, which is likely to be related to chemotherapy and radiotherapy factors and/or combined modality interactions. The meta-analyses could not establish that either sequence, concurrent or sequential treatment was optimal.

The combination chemotherapy including cis-platin (PI) and etoposide (E) is today the cornerstone of the systemic treatment of patients with SCLC. Turisi has recently reviewed the radiotherapy factors and discussed the state of art with the combination of thoracal irradiation and PE-based chemotherapy in relation to dose of irraditation, volume, fraction and timing.[62] Most centers today are using mediastinal irradiation combined with PE-based chemotherapy regimen as the cornerstone of therapy for patients with limited SCLC. However, both local and systemic failures avoid the therapeutic success.

While the **local** failures might be reduced by more optimal given radiotherapy (better targeting, increasing intensity or total dose, hyperfractionation etc.) the toxocity, especially esophagittis is still a significant problem, but the **systemic** failures as well is a documentation of the need for a better systemic treatment.

Treatment of brain metastases

While the brain was thought to be a sanctuary site in the chemotherapy of SCLC for many years, this concept has been changed. Several studies have demonstrated a high response rate on the initial brain metastases when treated with chemotherapy alone, and when evaluated by subsequent. CT-scans the response rates in the brain is similar to the response rates extracranially.[63] Thus, the treatment strategy today for patients who present with brain metastases in the initial phase of the disease course, is systemic treatment with the same chemotherapy as used for extracarnial disease.

However, the treatment of brain metastases diagnosed **during** chemotherapy is not quite clear. At that stage the tumor might not be sensitive to the given chemotherapy and the treatment strategy must depend on several factors: 1. Are the extracranial

disease under control 2. Can the symptoms be controlled by steroids alone? and 3. What is the patients performance status and prognosis?

If the extracranial disease is under control on chemotherapy and/or radiotherapy cranial irradiation seems reasonable. However, if the patient develop brain metastases and have progressive disease outside the brain only symptomatic treatment with steroids seems reasonable.

Prophylactic cranial irradiation

Brain metastases is a serious clinical problem in patients with SCLC. The brain is a frequent site of metastasis and is clinical evident in about 10 % of patients at tim of primary diagnosis and demonstrated in about 50 % of the patients at time of autopsy.[64]

The possibility of using prophylactic cranial irradiation (PCI) in the management of SCLC patients was suggested already in 1973,[65] based on an early prediction of an increase in the incidence of brain metastases with increased survival. However, still in 1995 this question is not completely solved. The topic has recently been reviewed in details elsewhere.[66]

Until now there has not been demonstrated any significant impact of survival – not either for patients who receive CR on systemic treatment – by using PCI.

The problem with the published studies has been the small number of patients with CR available for the PCI-studies and the lack of randomization. Currently, there are some ongoing multicenter trials, which hopefully will include large enough number of patients to obtain sufficient statistical power to detect a potential survival benefit by using PCI. Presently, it is general agreement that PCI is not justified in patients who are not in CR. The answer whether PCI should be given recommended routinely to patients in CR or not has to await the ongoing trials.

Future strategy in the treatment of SCLC

During the past 10–15 years the treatment of SCLC has improved and the existing chemotherapy with or without thoracic radiotherapy are capable of effecting marked prolongation of survival, especially for patients presenting with limited disease with a median survival close to 20 months, 2 years about 40% and occasional cures. However, further research is needed to improve especially the systemic treatment. However, conventional chemotherapy with well known cytotoxic drugs in different combinations have not made a breakthrough in the treatment of patients with SCLC. Therefore, future investigations have to focus on several new areas including. 1. new drugs prefereably with novel mechanisms of action. 2. Modulations of drug resistance. 3.

Biological therapy, 4. Gene therapy and 5. Prevention of secondary malignancies (chemoprevention).

New drugs are discussed above. Of special interest would be to test the new drugs in combination with the well known drugs with verified effect in SCLC. There are ongoing studies for patients with extensive SCLC using sequential treatment of Topoisomerate I and II inhibitors.[67]

Despite the fact that most of the SCLC tumors are chemosensitive the major obstacle is the drug resistance. There are several mechanisms by which SCLC tumors become resistent of the cytotoxic agents. The presence of p-glycoprotein does not appear to be common in SCLC.[68, 69] Nevertheless, p-glycoprotein inhibitors should be included in the future investigational strategy of therapy as well as strategies designed to alter the topoisomerase level, which play an important role in the DNA replication and repair. Recently, bcl-2 transcripts and protein have been found to be expressed in 5/6 SCLC cell lines,[70] and transfection of bcl-2 into a SCLC cell line has shown to increase chemoresistance.[71] These mechanisms are further studied and might be included in the future treatment strategy.

It has been known for many years that SCLC is associated with production of several peptide hormones, which function as autorine growth factors such as gastrin releasing peptide (GRP), insulin-like growht factor (IGF-1), transforming growth factors (TGF-beta) and several others.[72] Monoclonal antibody to GRP has in a preliminary study shown to give complete response in a patient with SCLC,[73] and early clinical studies with other peptide antigens, i.e. somatostatin analogue are ongoing.

Mutatiton of the gene p-53 have been found in virtually and small cell lung cancer cell lines and in most of the tumors from the patients, and more than half of SCLC cell lines fail to express retinoblastoma gene protein product.[72] Correction of these

abnormalities through gene therapy might play a role in the future strategy.

As previously mentioned a high percentage of the long-term survivors from SCLC develop a secondary malignancy, most often a tobacco-related cancer.[50] Therefore, chemoprevention studies are warranted in the long-term survivors of SCLC and ongoing studies with retinoid acids for patients with lung cancer seem promising.[74]

References

1. Stanley K, Stjernsward J. Lung cancer – a worldwide problem. 1989; *Chest* **96:** 1S–5S.

2. Hansen HH. Management of small cell cancer of the lung. *Lancet* 1992; **339:** 846–9.

3. Grant S, Gralla R, Kris M et al. Single agent chemotherapy trials in small cell lung cancer, 1970 to 1990: The case for studies in previously treated patients. *J Clin Oncol* 1992; **10:** 484–98.

4. Edmondson J, Lagakos S, Selawry O et al. Cyclophosphamide and CCNU in the treatment of inoperable small cell carcinoma and adenocarcinoma of the lung. *Cancer Treat Rep* 1976; **60:** 925–32.

5. Lowenbraun S, Bartolucci A, Smalley R et al. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. *Cancer* 1979; **44:** 406–13.

6. Fukuoka M, Furuse K, Saijo N et al. Randomized trial of cyclophosphamide, doxorubicin and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung lancer. *J Natl Cancer Inst* 1991; **83:** 855–61.

7. Hirsch FR, Hansen HH, Hansen M et al. The superiority of combination chemotherapy including etoposide based on in vivo cell cycle analysis in the treatmen of extensive small-cell lung cancer: A randomized trial of 288 consecutive patients. *J Clin Oncol* 1987; **5**: 585-91.

8. Johnson DH, Hainsworth JD, Hande KR et al. Current status of etoposide in the management of small cell lung cancer. *Cancer* 1991; **67**: 231–44.

9. Roth BJ, Johnson DH, Einhorn LH et al. Randomized study of cyclophosphamide, doxorubicin and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer. A phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992; **10**: 282–91.

10. Batist G, Carney DN, Cowan KH et al. Etoposide (VP-16) and cisplatin in previously treated small-cell lung cancer: clinical trial and in vitro correlates. *J Clin Oncol* 1986; **4**: 982–6.

11. Carney DN. Carboplatin/etoposide combination chemotherapy in the treatment of poor prognosis patients with small cell lung cancer. *Lung Cancer* 1995; **12**, suppl, **3**: 77–83.

12. Skarlos DV, Samantas E, Kosmidis P et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irraditation in small celll lung cancer: a Hellenic cooperative oncology group study. *Ann Oncol* 1994; **5**: 601–7.

13. Goldie JH, Goldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treatment Rep* 1982; **66**: 439–49.

14. Evans WK, Feld R, Murray N et al. Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer. *Ann Int Med* 1987; **107**: 451–8.

15. Einhorn LH, Crawford J, Birch R et al. Cis-platin plus etoposide consolidation following cyclophosphamide, doxorubicin and vincristine in limited small cell lung cancer. *J Clin Oncol* 1988; **6**: 451–6.

16. Dombernowsky P. Primary treatment of small cell lung cancer. In: Hirsch FR ed. *Lung Cancer: Status and future perspectives*. Bristol-Myers Squibb, 1993: 83–100.

17. Jensen PB. Personal communications.

18. Hirsch FR, Dombernowsky P, Hansen HH. Treatment of small cell lung cancer: The Copenhagen Experience. *Anticancer Res* 1994; **14**: 317–20.

19. Bork E, Ersbøll J, Dombernowsky P et al. Teniposide and etoposide in previously untreated small-cell lung cancer: a randomized study. *J Clin Oncol* 1991; **9**: 1627–31.

20. Carney DN, Grogan L, Smit EF et al. Single-agent oral etoposide for elderly small cell lung cancer patients. *Semin Oncol* 1990; **17**, suppl, **2**: 49–53.

21. Carney DN. Carboplatin/etoposide combination chemotherapy in the treatment of poor prognosis patients with small cell lung cancer. *Lung Cancer* 1995; **12**, suppl, **3**: 77–83.

22. Slevin M, Clark PI, Joel SP et al. A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. *J Clin Oncol* 1989; **7** 1333.

23. Cohen M, Creaven P, Fossieck BJ et al. Intensive chemotherapy of small cell bronchogenic carcinoma. *Cancer Treat Rep* 1977; **61**: 349–54.

24. Abeloff M, Ettinger D, Order S et al. Intensive induction chemotherapy in 54 patients with small cell carcinoma of the lung. *Cancer Treat Rep* 1981; **65**: 639–46.

25. Figueredo T, Hryniuk W, Strautmanis I et al. Co-trimoxazole prophylaxis during high-dose chemotherapy of small-cell lung cancer. *J Clin Oncol* 1985; **3**: 54–64.

26. Ihde D, Mulshine J, Kramer B et al. Randomized trial of high vs. standard dose etoposide (VP 16) and cisplatin in extensive stage small cell lung cancer (SCLC). *Proc Amer Soc Clin Oncol* 1991; **10**: 240.

27. Ihde D, Mulchine J, Kramer B et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lunc cancer. *J Clin Oncol* 1994; **12**: 2022–34.

28. Sculier J, Paesmans M, Bureau G et al. Multiple-drug weekly chemotherapy versus standard combination regimen in small-cell lung cancer. A phase II randomized study conducted by the European Lung Cancer Wrokshop Party. *J Clin Oncol* 1993; **11**: 1858–65.

29. Ihde D, Mulshine J, Kramer B et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994; **12**: 2022–34.

30. Ettinger DS, Finkelstein DM, Abeloff MD et al. A randomized comparison of standard chemotherapy versus alternating chemotherapy and maintenance versus no maintenance therapy for extensive-stage small-ceel lung cancer: A phase III study of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1990; **8**: 230–240.

31. Giaccone G, Dalesio O, McVie G et al. Maintenance chemotherapy in small-cell lung cancer: long term results of a randomized trial. *J Clin Oncol* 1993; **11**: 1230–40.

32. Party LCW. Controlled trial of twelve versus six courses of chemotherapy in the treatment of small-cell lung cancer: Report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancers* 1989, **59**: 584–90.

33. Spiro S, Souhami R, Geddes D et al. Duration of chemotherapy in small cell lung cancer: A Cancer Resarch Campaign Trial. *Br J Cancer* 1989; **59**: 578–83.

34. Splinter T. EORTC 08825. Induction vs induction plus maintenance chemotherapy (CT) in small cell lung cancer (SCLC). Definitive evaluation. Proc ASCO 7: 202, 1988.

35. Miles D, Souhami R, Spiro S et al. A randomized trial comparing »standard« 3 weekly with chemotherapy (C/T) in patients (PTS) with small cell lung cancer (SCLC). *Proc ASCO* 1992; **11**: 289.

36. Arriagada R, le Chevalier T, Pignon J-P et al. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. *N Engl J Med* 1993; **329**: 1848–52.

37. Klasa R, Murray N and Coldman A. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. *J Clin Oncol* 1991; **9**: 499–508.

38. Souhami R, Hajichristou H, Miles D et al. Intensive chemotherapy with autologous bone marrow transplantation for small-cell lung cancer. *Cancer Chemother Pharmacol* 1989; **24**: 321–5.

39. Smith I, Evans B, Harland S et al. High-dose cyclophosphamide with autologous bone marrow rescue after conventional chemotherapy in treatment of small-cell lung carcinoma. *Cancer Chemother Pharmacol* 1985; **14**: 120–4.

40. Humblet Y, Symann M, Bosly A et al. Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: A randomized study. *J Clin Oncol* 1987; **5**: 1864–73.

41. Elias A, Ayash L, Frei III E et al. Intensive combined modality therapy form limited-stage small-cell lung cancer. *J Natl Cancer Inst* 1993; **85**: 559–66.

42. Crawford J, Ozer H, Stoller R et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients will small-cell lung cancer. *N Engl J Med* 1991; **325**: 164–170.

43. Miles D, Fogarty O, Ash C et al. Received dose-intensity. A randomized trial of weekly chemotherapy with and without granulocyte colony-stimulating factor in small-cell lung cancer. *J Clin Oncol* 1994; **12**: 77–82.

44. Nichols C, Fox Em Roth Be et al. Incidence of neutropenic fever in patients treated with standard-dose combination chemotherapy for small-cell lung cancer and the cost impact of treatment with granulocyte colony-stimulating factor. *J Clin Oncol* 1994; **12**: 1245–50.

45. Bunn P, Crowley J, Kelly K et al. Chemoradiotherapy with or without granulocyte-macrophage colony stimulating factor in the treatment of limited stage small- cell lung cancer: A prospective phase III randomized study of the southwest oncology group. *J Clin Oncol* 1995; **13**: 1632--41.

46. Controlled trial of twelve versus six courses of chemotherapy in the treatment of small-cell lung cancer: report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancer* 1989; **59**: 584–90.

47. Giaccone G, Donadio M, Bonardi G et al. Teniposide in the treatment of small-cell lung cancer: the influence of prior chemotherapy. *J Clin Oncol* 1988; **6**: 1264–70.

48. Johnson DH, Greco FA, Strupp J et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. *J Clin Oncol* 1990; **8**: 1613–7.

49. Souhami RL, Law K. Longevity in small-cell lung cancer:: A report to the Lung Cancer Subcommitteee of the United Kingdom Coordinating Committee for Cancer Research. *Br J Cancer* 1990; **61**: 584–9.

50. Lassen U, Østerlind K, Hansen M et al. Long-term survival in small-cell lung cancer: Posteatment characheristics in patients surviving 5 to 18 + years. An analysis of 1714 consecutive patients. *J Clin Oncol* 1995; **13**: 1215–20.

51. Ettinger DS, Finkelstein DM, Sarma R et al. Phase II study of taxol in patients (pts) with extensive-stage smal-cell lung cancer (SCLC): an Eastern Cooperative Oncology Group Study. *Proc Am Soc Clin Oncol* 1993; **12**: 329.

52. Kirschling RJ, Jung SH, Jett JR for the North Central Cancer Treatment Group. A phase II trial of taxol and G-CSF in previously untreated patients with exentive-stage small cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1994; **13**: 326.

53. Levitan N, McKenney J, Tahsildar H et al. Results of a phase I dose escalation trial of paclitaxel, etoposide and cisplatin followed by lilgramstim in the treatment of patients with extensive stage small-cell lung cancer. *Proc Bristol-Myers Squibb Symposium.* Am Soc Clin Oncol, 1995: 99.

54. Hainsworth JD, McKay CE, Miller PS et al. Treatment of small-cell lung cancer (SCLC) with paclitaxel (one hour infusion), carboplatin, and low dose daily etoposide. *Proc Bristol-Myers Squibb Symposium,* Am Soc Clin Oncol, 1995: 100.

55. Smyth JF, Bowman A, Smith I et al. Taxotere is active in small-cell lung cancer (SCLC). A phase II trial of the EORTC Early Clinical Trials Group (ECTG). *Eur J Cancer* 1993; **29A,** suppl, **6:** 154.

56. Masuda N, Fukuoka, Kusunoki Y et al. A new derivate of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992; **10**: 1225–9.

57. Fujiwara Y, Yamakido M, Fukuoka M et al. Phase II study of irinotecan (CPT-11) and cisplatin (CDDP) in patients with small-cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1994; **13**: 330.

58. Schiller JH, Kim K, Johnson D for the Eastern Cooperative Oncology Group. Phase II study of topotecan in extensive stage small cell lung cancer. *Proc Soc Clin Oncol* 1994; **13**: 330.

59. Ardizzoni A, Hansen H, Dombernowsky P et al. Phase II study of topotecan in pretreated small cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1994; **13**: 336.

60. Cormier Y, Eisenhauer Ea, Muldal A et al. Gemcitabine is an active new agent in previously untreated extensive small cell lung cancer (SCLC). *Ann Oncol* 1994; **5**: 283–5.

61. Pignon J-P, Arriagada R, Ihde D et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992; **327**: 1618–24.

62. Turisi AT. Combined platinum etoposide with radiation therapy in limited stage small cell lung cancer: an effective treatment strategy. *Lung Cancer* 1995; **12**: suppl, **3**: S41–S51.

63. Kristensen CA, Kristjansen PEG, Hansen HH. Systemic chemotherapy of brain metastases from small cell lung cancer – A review. *J Clin Oncol* 1992; **10**: 1498–502.

64. Hirsch FR, Paulson OB, Hansen HH and Olesen Larsen S. Intracranial metastases in small cell carcinoma of the lung. *Cancer* 1983; **51**: 933–7.

65. Hansen HH. Should initial treatment of small cell lung-carcinoma include systemic chemotherapy and brain irradiation. *Cancer Chem Rep* 1973; **4**: 239–41.

66. Kristjansen PEG, Hansen HH. Prophylactic cranial irradiation in small cell lung cancer – an update. *Lung Cancer* 1995; **12**: suppl **3**: S23–S40.

67. Johnson DH. Future dirctions in the management of small cell lung cancer. *Lung Cancer* 1995; **12,** suppl **3**: S71–S75.

68. Lai S-L, Goldstein L, Gottesman MM et al. MDR1 gene expression in lung cancer. *J Natl Cancer Inst* 1989; **81**: 1144–50.

69. Poupon MF, Arvelo F, Goguel AF et al. Response of small-cell lung cancer xenografs to chemotherapy: multidrug resistance and direct clinical corrrelates. *J Natl Cancer Inst* 1993; **85**: 2023–9.

70. Ikegaki N, Latsuata, M, Minna J and Tsujimoto Y. Expression of bcl-2 in small cell lung carcinoma cells. *Cancer Res* 1994; **54**: 6–8.

71. Ohmori T, Podack ER, Nishio K et al. Apoptosis of lung cancer cells caused by some anti-cancer agents (MMC, CPT-11, ADM), inhibited by bd-2. *Biochem Biophys Res Commun* 1993; **192**: 30–6.

72. Richardson GE, Johnson BE. The biology of lung cancer. *Semin Oncol* 1993: **20**: 105–27.

73. Kelly MJ, Avis RI, Linnoila RI et al. Complete response in a patient with small cell lung cancer treated on a phase II trial using a murine monoclonal antibody (2A11) directed against gastrin releasing peptide (GRP). *Proc Am Soc Clin Oncol* 1993; **12**: 339.

74. Hong WK, Benner SE and Lippman SM. Retinoid chemoprevention of lung cancer. *Lung Cancer,* 1994; **11:** suppl **2**: 92–3.

Radiol Oncol 1996; 30: 205-9.

Prognostic value of staging laparotomy in supradiaphragmatic clinical stage I and II Hodgkin's disease

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In the period 1974–1989, 219 patients with supradiaphragmatic clinical stage I and II Hodgkin's disease were treated at the Institute of Oncology in Ljubljana; of these 95 (43 %) patients underwent staging laparotomy. Of laparotomized patients, those with pathological stage III–IV, and of non-laparotomized, those with unfavorable prognostic factors (B-symptoms, bulky mediastinum) received chemotherapy: the remaining patients were treated by irradiation. No statistically significant difference in the survival and disease-free survival between laparotomized and nonlaparotomized patients could be found.

Key words: Hodgkin's disease; staging laparotomy; prognostic value

Introduction

Staging laparotomy (SL) is the most accurate albeit agressive diagnostic method for the verification of subdiaphragmatic spread of Hodgkin's disease (HD). There is a considerable controversy of opinions as to when and whether this method is indicated at all.

The present retrospective study is aimed to assess whether SL had any impact on survival (S), disease-free survival (DFS) and treatment modality used in patients with supradiaphragmatic clinical stage (CS) I–II HD.

Patients and methods

Our retrospective study was carried out on a series of 219 adult patients with supradiaphragmatic HD CS I–II, who underwent their primary treatment at the Institute of Oncology in Ljubljana in the period from January 1974 to December 1989. Their age ranged between 15 and 82 years (mean 36 yrs); there were 110 males and 109 females. In all the patients the diagnosis was confirmed histologically.[1]

Preoperative evaluation comprised a complete history, physical examination, routine laboratory tests, chest X-ray, bone marrow biopsy, and in the majority of patients also pedal lymphography, Ga-scintiscan of the whole body and computer tomography and/or ultrasonography of the abdomen. Stage was determined according to Ann Arbor classification.[2] Bulky mediastinal disease was defined as the largest transverzal diameter exceeding one third of the transthoracic diameter at the level of the 5th and 6th thoracic vertebral body.

Candidates for SL were nor selected at random. SL consisted of splenectomy, wedge and needle biopsy of both liver lobes, biopsy of multiple lymph nodes, biopsy of all lymph nodes that appeared to be involved with disease or involvement was suspected on lymphangiogram, bone marrow sampling and appendectomy. An oophoropexy was performed in premenopausal women. Metalic clips were placed at biopsy sites.

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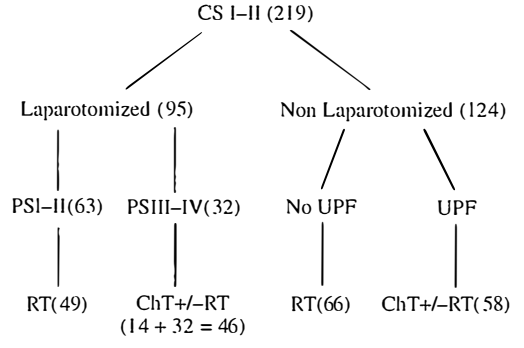
The following treatment approach was selected (Figure 1): Laparotomized patients with pathological stage (PS) I–II were treated by radiotherapy (RT), patients with PS III–IV by chemotherapy (ChT) +/–RT. In non-laparotomized patients the treatment approach was selected according to the following prognostic factors: patients with B-symptoms and/or bulky mediastinum received ChT+/–RT while the remining ones were treated by RT alone. Subtotal nodal irradiation (STNI) was almost always (81/115) the RT field chosen for patients treated only by RT. ChT used was one of MOPP-like or MOPP/ABV-like schemes. In ChT+/–RT group of patients almost all (98/104) were treated by ChT and RT.



CS = clinical stage PS = pathological stage
RT = radiotherapy ChT = chemotherapy
UPF = unfavorable prognostic factors

Figure 1. Hodgkin's disease with clinical stage I–II (n = 219): Treatment approach.

Follow up ranged from 4 to 205 months, median 64 months. Survival was defined as the lapse of time from the onset of treatment to death, or to the date of last follow-up examination. All deaths regardless the cause have been included. Disease-free survival was defined as the lapse of time from the onset of treatment to the date of the first recurrence. Complete response was defined as disappearance of all symptoms and measurable changes; partial response was defined as disappearance of measurable changes by > 50 %; progression as an increase in measurable changes by > 25 % or appearance of new sites; unchanged conditions denoted responses that could neither be defined as a partial response nor a progress.

Statistical analysis was done by means of BMDP statistic program.[3] Survival (S) and disease-free survival (DFS), as well as differences in the survival of laparotomized and nonlaparotomized patients were shown and analysed using the Kaplan-Meier method and log-rank test.[4]

Results

SL was performed in 95 (43 %) of 219 patients with CS I–II, while the remaining 124 (57 %) did not undergo laparotomy.

The laparotomized and non-laparotomized groups were homogeneous with respect to the clinical properties (Table 1), including some well established prognostic factors; the only difference noted was related to age: among those older than 60 years there were 6 laparotomized and 21 non-laparotomized patients, of these 10 were older than 70 years.

Table 1. Hodgkin's disease with clinical stage I–II (n = 219): Clinical features.

Clinical features	Non laparotomized (n = 124) n	Laparotomized (n = 95) n	p
Sex			
males	59	51	NS
females	65	44	NS
Age (yrs)			
range	15,4–82,8	15,3–63,4	
medium	39,9	32,4	0.0004
Histology			
LP/NS	86	55	NS
MC/LD	30	35	NS
unclassified/cytology	8	5	NS
B symptoms	14	9	NS
Stage			
I	39	36	NS
II	85	59	NS
Mediastinum size			
bulky	17	13	NS
undefined	16	10	NS

LP/NS = Lymphocyte predominant/Nodular sclerosis
MC/LD = Mixed cellularity/Lymphocyte depleted

The survival and disease-free survival of laparotomized and non-laparotomized patients were compared irrespective of the treatment method used; no statistically significant difference could be established (Figures 2 and 3).

Further on, we analysed S and DFS of laparotomized and non-laparotomized patients treated by radiotherapy alone. Both groups were found to be

homogeneous regarding prognostic factors and did not differ from each other as to the S and DFS (Table 2). The same applies to ChT+/–RT treated patients (Table 2).

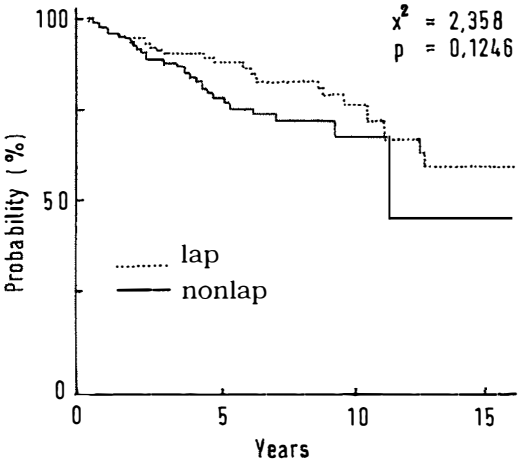


Figure 2. Hodgkin's disease with clinical stage I–II: Survival – laparotomized (59) : non laparotomized (124).

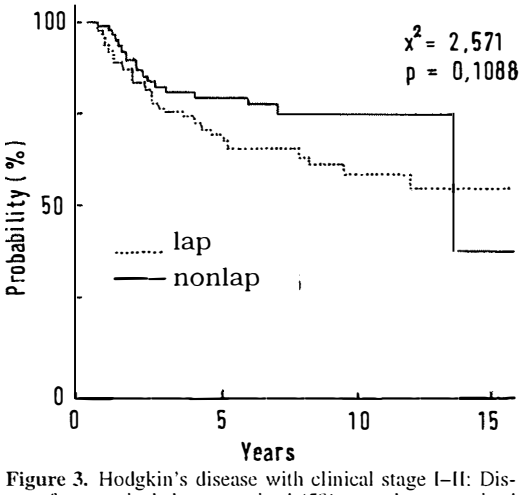


Figure 3. Hodgkin's disease with clinical stage I–II: Disease free survival: laparotomized (59) : non laparotomized (124).

Table 2. Probability of 10 yrs survival (S) and disease free survival (DFS) by treatment approach – laparotomized : non laparotomized.

	RT			ChT+/–RT		
	Lap.(49)	Nonlap.(66)	p	Lap.(46)	Nonlap.(58)	p
DFS	55 %	75 %	NS	64 %	74 %	NS
S	88 %	78 %	NS	68 %	57 %	NS

RT = radiotherapy
ChT = chemotherapy

Discussion

SL was used with the aim to identify those patients in whom radiation treatment would be effective enough to avoid chemotherapy. The laparotomized patients were treated according to the outcome of SL, while non-laparotomized ones received treatment with respect to the prognostic factors. It should be expected that the laparotomized patients have a better DFS and S in respect to non-laparotomized patients because of the exact staging. The results of our study, however, failed to confirm these expectations: (1). The laparotomized patients generally started with their first treatment a month later,[5] which is consistent with other reports.[6] (2). The number of patients receiving ChT in both groups was approximately the same (Figure 1). (3). It is essential, however, that no statistically significant difference in survival and disease-free survival could be established between the laparotomized and non-laparotomized patients (Figure 2 and 3). Review of the available literature has shown that other authors in their prevailingly retrospective and non-randomized studies also failed to prove any statistically significant differences in the survival[7–11] and DFS of both groups.[7, 9, 10] There are only two exceptions: while the first report claims DFS of laparotomized patients to be longer[8], the second one finds it to be shorter.[11] (4). No stastically significant difference in S and DFS could be established even between very comparable groups of patients in our study. These were patients without unfavorable prognostic factors treated only by RT: nonlaparotomized (n = 66) and laparotomized, PS I–II (n = 49) (Figure 1, Table 2). Second to our opinion, no statistically significant difference in S and DFS between these two groups could be established because both groups were almost always treated by STNI which involves also lymph nodes of the upper abdomen and spleen, which are the most common localisations of HD in the abdomen in supradiaphragmatic CS I–II HD patients.[5] Therefor we could conclude that if STNI is used there is no need for SL in patients with CS I–II without unfavorable prognostic factors?

The drawbacks of our study are obvious: (1). The decision for SL in CS I–II was not randomized; (2). Due to the inconsistency of the attending physicians 22 % (14/63) patients with PS I–II received ChT for having one of the unfavourable prognostic factors and thus unfortunately paid a double price by having undergone both SL and ChT (Figure 1).

But in spite of that and regardless the acceptable morbidity and non-existent mortality[5], the obtained results are not in favor of the continuation of SL practice at our institute, since our laparotomized patients do not seem to have drawn any benefit from it in comparison with non-laparotomized patients.

In view of the mentioned facts, indications for SL become questionable. We tried to find a solution to this problem in the literature, but it turned out that the question was too complex to be answered by simple "yes" or "no", and requires consideration of all pros and cons.

Arguments in favor of SL

(1) Despite new and more accurate diagnostic investigations, SL still remains the most precise method for diagnosis of subdiaphragmatic HD. Only splenectomy with histological examination enables exact evaluation of spleen involvement. Despite normal clinical findings, at least one forth of HD patients presents with spleen involvement, while only a half of those with clinically suspicious involvement actually have HD in the spleen. Using standard investigations, it is difficult to detect lymphoma in the upper abdominal lymph nodes which cannot be imaged by lymphography. SL is able to explain suspicious lymphography findings. Although HD involvement in the liver is rare, exact diagnosis is possible only by laparotomy-based biopsy.

(2) Splenectomy decreases the risk of irradiation damage to the kidney and lung base on the left as well to the heart.

(3) Oophoropexy helps to preserve fertility in women requiring irradiation to the pelvis.

(4) SL enables the selection of treatment according to the outcome, so that many patients can be spared unnecessary ChT or on the other hand ChT is not omitted in those patients who need it.

Arguments against SL

(1) SL-related morbidity and mortality; although the former is acceptable, and the latter rare in centers with adequate experience.

(2) Life-long risk of sepsis due to splenectomy.[12-17]

(3) A higher incidence of acute myeloblastic leukemia after splenectomy in patients receiving MOPP ChT.[18, 19]

(4) At least one-month delay in treatment beginning.[5, 6]

(5) In the case of recurrence after RT alone, the patient can still be cured with ChT +/– RT.[7, 20]

(6) Knowledge of prognostic factors can help us to identify at least 20 % of patients with CS I–II who require either ChT or a combined therapy.[7, 21]

(7) Knowledge of clinical properties can be used to assess the risk of HD spread in the abdomen.[22-26]

Conclusion

From all the above mentioned it is clear that SL is a diagnostic and not a therapeutic procedure. All authors are consistent in their belief that it is indicated only when the method of treatment depends on SL outcome,[18, 22-25, 27] which means that candidates for RT, i.e. therapy with less short-term and long-term side-effects than ChT, are selected on the basis of SL results. Certainly it is not justified in patients with > 50 % recurrence rate after RT alone.[27] It is also not sensible when ChT is planned regardless the SL outcome,[18, 24, 25, 27, 28] which is the case in patients with a huge mediastinal tumor mass, numerous E sites, and CS III_2A and IIIB or IV. Further, SL is not indicated in patients with CS I–II and a low risk of positive laparotomy since in such cases RT proves to be sufficient.[22, 24-26] In the present paper only some general guidelines have been given. It cannot be prescribed whether in patients belonging to either of the two groups SL should be used or not, and which treatment modality should be selected. There are great variances between different centers as to the availability and quality of diagnostic procedures, as well as to the quality of SL and competence of their diagnostic & therapeutic teams. Therefore, in every individual center indications for SL can be determined and treatment approach selected only after all the above mentioned conditions have been carefully evaluated, and all arguments for and against SL considered, taking into account the risk vs. benefit for the patient.

References

1. Lukes RJ, Craver LF, Hall TC, et al. Report of the Nomenklature Committee. *Cancer Res* 1966; **26**: 1331–6.

2. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a Committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; 7: 1630–6.

3. Dixon WJ, Brown MB, Engelman L, Jennrich RI, eds. *BMDP statistical software manual*. Vol 1, 2. Berkeley: University of California Press, 1990.

4. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977; **35**: 1–39.

5. Vovk M, Šumi-Križnik T, Jenko-Fidler M et al. Staging laparotomy for Hodgkin's disease in adults: one center experience. *Radiol Oncol* 1995; **29**: 223–8.

6. Carde P, Burgers JMV, Henry-Amar M, et al. Clinical stages I and II Hodgkin's disease: a specific tailored therapy according to prognostic factors. *J Clin Oncol* 1988; **6**: 239–52.

7. Haybittle JL, Easterling MJ, Bennett MH, et al. Review of British National Lymphoma Investigation studies of Hodgkin's disease and development of prognostic index. *Lancet* 1985; **i**: 967–72.

8. Bergsagel DE, Alison RE, Bean HA, et al. Results of treating Hodgkin's disease without a policy of laparotomy staging. *Cancer Treat Rep* 1982; **66**: 717.

9. Cox JD, Stoffel TJ. Clinical versus pathologic stage I and II Hodgkin's disease. *Oncology* 1980; **37**: 325–8.

10. Gomez GA, Reese PA, Nava H, et al. Staging laparotomy and splenectomy in early Hodgkin's disease. *Am J Med* 1984; **77**: 205–10.

11. Foss Abrahamsen A, Host H, Jorgensen OG. Is staging laparotomy of therapeutic value in patients with supradiaphragmatic Hodgkin's disease, clinical stage IA–IIA? *Scand J Haematol* 1980; **25**: 439–44.

12. Green D, Ghoorah J, Douglass HO, et al. Staging laparotomy with splenectomy in children and adolescents with Hodgkin's disease. *Cancer Treat Rev* 1983; **10**: 23–38.

13. Shochat SJ, Donaldson SS, Hartman GE, Link MP. Staging laparotomy in childhood Hodgkin's disease: the Stanford experience. *Med Pediat Oncol* 1989; **17**: 321–2.

14. Taylor MA, Kaplan HS, Nelsen TS. Staging laparotomy with splenectomy for Hodgkin's disease: the Stanford experience. *World J Surg* 1985; **9**: 449–60.

15. Baccarani M, Fiacchini M, Galieni P, et al. Meningitis and septicaemia in adults splenectomized for Hodgkin's disease. *Scand J Haematol* 1986; **36**: 492–8.

16. Coker DD, Morris DM, Coleman JJ, et al. Infectioin among 210 patients with surgically staged Hodgkin's disease. *Am J Med* 1983; **75**: 97–109.

17. Desser RK, Ultmann JE. Risk of severe infection in patients with Hodgkin's disease of lymphoma after diagnostic laparotomy and splenectomy. *Ann Intern Med* 1972; **77**: 143–6.

18. Rosenberg SA. Exploratory laparotomy and splenectomy for Hodgkin's disease: a commentary. *J Clin Oncol* 1988; **6**: 574–5.

19. Van Leeuwen FE, Somers R, Hart AM. Splenectomy in Hodgkin's disease and second leukemias. *Lancet* 1987; **2**: 210–11.

20. Levy J. Current practice in the staging of Hodgkin's disease. *Br J Hosp Med* 1989; **41**: 497.

21. Brada M. Early stage Hodgkin's disease in adults: which is the correct treatment? *Postgrad Med J* 1989; **65**: 824–9.

22. Brada M, Easton DF, Horowich A, Peckham MJ. Clinical presentation as a predictor of laparotomy findings in supradiaphragmatic stage I and II Hodgkin's disease. *Radiother Oncol* 1986; **5**: 13–22

23. Aragon de la Cruz G, Cardenes H, Otero J, et al. Individual risk of abdominal disease in patients with stages I and II supradiophragmatic Hodgkin's disease: A rule index based on 341 laparotomized patients. *Cancer* 1989; **63**: 1799–1803.

24. Leibenhaut MH, Hoppe RT, Efron B, Halpern J, Nelsen T, Rosenberg SA. Prognostic indicators of laparotomy findings in clinical stage I–II supradiaphragmatic Hodgkin's disease. *J Clin Oncol* 1989; **7**: 81–9.

25. Mauch P, Larson D, Osteen R et al. Prognostic factors for positive surgical staging in patients with Hodgkin's disease. *J Clin Oncol* 1990; **8**: 257–65.

26. Vovk M, Šumi-Križnik T, Jenko-Fidler M et al. Clinical features as a predictor of laparotomy findings in supradiaphragmatic stage I and II Hodgkin's disease. *Radiol Oncol* 1995; **29**: 318–25.

27. Rosenberg SA. Laparotomy and splenectomy in Hodgkin's disease: a reapprisal after twenty years. *Scand J Haematol* 1985; **34**: 289–92.

28. Rosenberg SA, Kaplan HS. The evolution and summary results of the Stanford randomized clinical trials of the management of Hodkin's disease: 1962–1984. *Int J Radiat Oncol Biol Phys* 1985; **11**: 5–22.

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Advantages and disadvantages of hormone replacement therapy

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In the developed countries, more than 30 % of female population is in the postmenopusal period of their life. Approximately one third of these present with severe clinical menopausal symptoms, such as hot flushes, sleeplessness, night sweats, and depression. Many women search medical help. By means of hormone replacement therapy (HRT), these problems can be either completely eliminated or alleviated in 90 % of women. The suspected association between HRT and risk of carcinoma should not be ignored, however. While estrogens in combination with progestogens exert a protective effec against ovarian and endometrial carcinomas, a possible correlation between HRT and breast cancer has not been fully explained yet. Nevertheless, some published reports have indicated a slightly increased risk of breast cancer after a prolonged use of HRT.

Key words: estrogen; replacement therapy

Is menopause a pathological or physiological condition? In endocrinology, the cessation of ovarian function is the only situtation where replacement of lacking hormones is not a self-evident act.

W. Craesman

Menopause

By definition, menopause is the last menarche in woman's life, which means the end of her fertile period. In the developed countries it occurs at about 50 years of age. Since a healthy woman is expected to live for another 30 years, the postmenopausal period is relatively long.[1] Considering the fact that life expectancy of female population has been increasing steadily in this century, certain changes in morbidity and mortality can be expected in this population group.

The cessation of menstruation occurs due to ovarian disjunction. The duration of their activity is determined by genetic factors as well as by the number of primordial follicles. In the fertile period the ovaries comprise approximately 7 million follicles. Their number starts to decrease before birth and continues to do so even more rapidly after it. The process ends with atrophy of the ovaries which cease to produce estradiol, the most potent estrogen; only a minimal quantity of androstendione is being release instead. In the peripheral tissues, this can be converted into estrone through aromatization process, while a small quantity is converted into estradiol. With respect to the premenopausal period, in postmenopause the rate between estradiol and estrone changes in favour of estrone which is a weak estrogen. The diminished secretion of estradiol and progesterone lead to changes in hypothalamic and hypophyseal function. Uncontrollable release of high GnRH values stimulates the frontal part of hypophysis to FSH and LH secretion.

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Postmenopausal symptoms occur due to hormonal changes. Approximately one third of women will be free of any complaints, 35 % have minor symptoms that can be easily endured while in 30 % of women the severity of complaints requires medical attention.

Generally, acute symptoms occur a few months prior to the onset of menopause. These include vasomotor symptoms, sleeping disorders and psychological problems. The most frequent complaints occurring a result of vasomotor instability are hot flushes, night sweating, palpitations and headaches. Pathophysiology of vasomotor symptoms has not been fully explained yet. Most probably they should be ascribed to hypothalamic termoregulatory mechanism disorders. The vasomotor symptoms persist for more than 5 years in 25 % of women, while in a small group they can even last for the rest of life.

Various epidemiological studies have shown that women between 45 – 50 years of age are more prone to depression than males. It has also been proved that depression symptoms are encountered less frequently in females who are maintained on estrogen replacement therapy after ovariectomy.[2] Other authors support the theory that depression associated with menopause occurs because of hot flushes and other difficulties.

The symptoms that occur later includ changes in the urogenital tract. Amog these, dry vagina, dyspareunia and atrophic vaginitis are most disturbing. Local atrophy is one of the causes of urethral syndrome, which manifests itself with dysuria and frequent urination without evidence of urinary tract infection.

Chronic changes become evident a few years after the menopause. They include osteoporosis and cardiovascular disorders. Osteoporosis is characterized by a gradual decrease in bone density and altered microarchitecture of bone tissue. As a result, the bones become fragile and compression fractures of the vertebral bodies, as well as fractures of the neck, femur and wrist are rather common.

Cardiovascular diseases are the leading cause of death in postmenopausal female population. After the menopause, the levels of cholesterol in blood tend to increase. Low HDL and high LDL and VLDL values are associated with an increased risk of cardiovascular disorders which are described as atherogenic lipid profile.[3]

All the described changes can be either diminished or prevented by the use of hormone replacement therapy (HRT). When choosing candidates for hormone replacement therapy all the advantages of such treatment should be weighted against its possible drawbacks. Thus, HRT is considered suitable in women with evident symptoms of estrogen shortage, as well as in those with risk factors for osteoporosis and in those with familial history of caridovascular disorders. HRT is introduced immediately after the cessation of ovarian function or even in premenopausal period – on the occurrence of problems. The medications used should contain minimal doses of estrogen. Conjugated equinous estrogen or estrogen sulphate can prevent the onset of osteoporosis already at a dose of 0.625 mg. Estrogen is combined with progesterone for 10–14 days per month cycle.[4] Women, who still have the uterus, should receive combined estrogen-progesterone preparations, while those without it, can be given estrogen alone.[5] Prior to the introduction of HRT, potential recipients should undergo a thorough gynecological check as well as clinical examination of the breast and mammography.

Advantages of HRT

The replacement of sexual hormones in menopause has several advantgates. It can significantly reduce the vasomotor symptoms and psychogenic problems. The urogenital symptoms gradually disappear. The risk of cardiovascular diseases is decreased by 30–70 % while an already existing coronary disease is associated with a longer survival. The positive effect is increased by years of HRT use.[6] Exogenous estrogen inhibits bone resorption and reduction of bone density, this effect being most beneficial in the first 5 menopausal years when the loss of bone mass is most rapid. It has been proved that 5 years of continuous estrogen use can protect women against osteoporosis related bone fractures.[7] The results of Harvard Nurses Health Study have shown that women with surgery entailed menopause who were receiving HRT had significantly less cardiovascular disorders than those without postoperative HRT.[8]

HRT and carcinomas

While estradiol and estrone induce the epithelial proliferation, progesterone and the end product of estrogen metabolism reduce the proliferative effect

of estradiol and estrone. Progesterone protects the organism against hyperstimulation by decreasing the level of nuclear estrogenic receptors, as well as by inhibiting the conversion of androsterone into estrone and thus reducing the number of mitoses. Moreover, it potentiates the activity of 17-ß estradiol-dehydrogenase whic changes estradiol into the less active estrone.[1]

Breast cancer

In the developed countries, breast cancer in postmenopausal period is the most frequent cancer in females. Its incidence increases by advancing age. Therefore, possible influence of estrogen on the onset of breast cancer deserves our full attention. Nevertheless, despite numerous studies, the association between HRT and breast cancer risk has not been thoroughly clarified yet. There is a great number of epidemiological studies concerned with this pressing issue. However, more than 20 case-control studies and 4 cohort studies report inconsistent results with either increased or decreased relative risk, or no effect at all.[9] Comparison of the results is difficult and unreliable due to the fact that estrogen alone was used as HRT in a majority of large series studies, while in some others HRT consisted of a combination of estrogen and progesterone. Also, the number of cases in individual studies was different, and so was also the duration of treatment. Inconsistency of the results obtained is therefore more than obvious.

Some of the published reports claim that the risk of breast cancer development increases by the duration of HRT use, and that the relative risk (RR) increases to 1.5 after 20 years of therapy. The results of a Swedish cohort study refer to 23000 women followed up for 5–7 years. RR was found to have elevated to 1.1. After more than 9 years of HRT use RR increased to 1.7.[10]

So far, we can conclude that the epidemiological data obtained till now, fail to point out a clear correlation between HRT and the onset of breast cancer.[11]

The question remains, whether HRT is indicated in women with familial history of breast cancer. A presumably higher risk should be associated with the occurrence of breast cancer in the premenopausal period. After the menopause, the risk for all women of the same age group remains the same. It is believed that the risk of breast cancer in women with familial history is not associated with the use of HRT.[7] Therefore, in the postmenopausal period there is no specific group of women in whom the use of HRT would be contraindicated.

Endometrial carcinoma

In the middle of the 70's, there were several studies published which reported an association between the use of estrogen and an increased relative risk of endometrial carcinoma. After 5 years of therapy with estrogen alone, the RR amounted to 4.1, while after 10 years of use it increased to 11.6. Those data appeared rather alarming, and as a result, they started to combine estrogen with progesterone. It was found that the addition of progesterone in the duration of 12–14 days per month can completely inhibited the development of cystic and adenomatous hyperplasia, and RR for endometrial carcinoma decreased to 0.2–0.4.[11, 12] These results were derived from a large number of clinical and epidemiological studies.

Ovarian cancer

Few case-control studies were published on possible correlation between HRT and ovarian carcinoma. In a majority of these the corrrelation could not be confirmed, while some authors report on a minimally increased risk associated with long-term use of HRT. Furhter studies are required to provide an answer to this question.[13]

Gastrointestinal cancer

According to some epidemiological studies, some reproductive factors may play a role in the etiology of colorectal carcinoma. Estrogen and progesterone receptors were found in normal as well as carcinomatous epithelial cells of the colon.

There were 15 studies published on the correlation between HRT and colorectal cancer. Based on the data obtained, it can be concluded that HRT does not represent a risk factor for the development of colorectal cancer in females. Some authors have even manged to prove a protective effect of HRT.[14]

Estrogen receptors can also be found in a certain proportion of gastric cancer. Nevertheless, there is no evidence that sexual hormones would play any

role in gastric carcinogenesis. There is no information available on a possible correlation between HRT and gastric cancer.

Conclusion

The use of HRT in postmenopause decreases the morbidity and mortality of caridovascular diseases. It alleviates the menopausal symptoms and prevents the onset of osteoporosis.

In hysterectomized women estrogen therapy without the addition of progesterone is sufficient, while in theose with the uterus preserved, estrogen should be given in combination with progesterone.

In conclusion, we believe that the favorable effect of estrogen on the morbidity and mortality of cardiovascular diesases outweighs the potential risks. Presently, we lack sufficient data which would enable us to identify the group of patients in whom the use of HRT would entail a potential risk.[15]

HRT should not be regarded as an elixir of eternal youth and the solution of all menopause-related problems. It is not well tolerated by every woman and it is not completely free of any danger. Many women cannot benefit from it owing to the fear of adverse side effects.

While the doctor is the one who should inform the woman on the effects, advantages and potential risks of HRT, the woman herself should decide whether to use the suggested therapy or not.

References

1. Holst Ravn S, Rosenberg J, Bostofte E. Postmenopausal hormone replacement therapy – clinical implications. *Eur J Obstet Gynecol Reprod Biol* 1994; **53:** 81–93.
2. Sherwin BB. Sex steroids have diverse effects on brain structure and function. In: Berg, Hammar M eds. *The modern management of the menopause.* New York: The Partenon Publishing Group, 1994: 269–78.
3. Vyas S, Gangar K. Postmenopausal oestrogens and arteries. *Br J Obstet Gynecol* 1995; **102:** 942–6.
4. Hammond CB. Estrogen replacement therapy: What the future holds. *Am J Obstet Gynecol* 1989; **12:** 1864–8.
5. Andrews WC: Keynote adress: North American menopause society annual meeting 1994. *Menopause* 1995; **2:** 59–65.
6. Ettinger B, Friedman GD, Bush T, Quesenberry CP. Reduced mortality associated with long-term postmenopausal therapy. *Obstet Gynecol* 1996; **87:** 6–12.
7. Sands R, Boshoff C, Jones A, Studd J. Current opinion: Hormone replacement therapy after a diagnosis of breast cancer. *Menopause* 1995; **2:** 73–80.
8. Stampfer MJ, Colditz GA, Willet WC et al. Postmenopausal estrogen therapy and cardiovascular disease: 10 year follow-up from the Nurses Health Study. *N Engl J Med* 1991; **325**: 756–62.
9. Colditz GA, Egan KM, Stampfer MJ. Hormone replacement therapy and risk of breast cancer: results of epidemiological studies. *Am J Obstet Gynecol* 1993; **168**: 1473–80.
10. Bergkvist L, Adami HO, Persson I, Bergstrom R, Krusemo U. Prognosis after breast cancer diagnosis in women exposed to estogen and estogen-progestagen replacement therapy. *Am J Epidemiol* 1989; **130**: 221–8.
11. Breckwoldt, Keck C, Karck U. Benefits and risks of hormone replacement therapy. *J Steroid Biochem Molec Biol* 1995; **53**: 205–8.
12. Wile AG, DiSaia PJ. Hormones and breast cancer. *Am J Surg* 1989; **157**: 438–42.
13. Van Leeuwen FE, Rookus MA. The role of exogenous hormones in the epidemiology of breast, ovarian and endometrial cancer. *Eur J Clin Oncol* 1989; **25**: 1961–72.
14. MacLennan SC, MacLennan AH, Ryan P. Colorectal cancer and estrogen replacement therapy: a meta-analisis of epidemiological studies. *Med J Australia* 1995; **162**: 591–3.
15. Lobo RA, Speroff L. International consesus conference on postmenopausal hormone therapy and the cardiovascular system. *Fertil Steril* 1994; **61**: 592–5.

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Differential diagnosis between bone metastases and osteomalacia

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In oncology the diagnosis of skeletal metastases is a frequent one, in fact so frequent that other diagnoses such as metabolic bone diseases affecting patients with cancer may be overlooked. In our report two cases of osteomalacia referred to an oncologist are presented; in both of them the diagnosis of diffuse bone metastases of unknown origin was suspected. The differential diagnosis is discussed and the importance of bone marrow biopsy using Yamshidi needle for diagnosis of metabolic bone disease is emphasized.

Key words: bone neplasm-secondary, osteomalacia, diagnosis, differential

Introduction

Bone metastases represent 60-65 % of malignant lesions in the bones. They are often the first manifestation of malignant disease and sometimes the primary site of malignancy remains unknown. The spine and pelvis are most often affected, lesions distal to elbows and knees are rare. Malignancies most often associated with skeletal metastases are lung, breast, prostate, renal and thyroid cancer.[1]

The diagnosis is usually established with the help of history (pain), clinical examination (painful succussion, altered mobility, deformities due to pathologic fractures), laboratory tests (elevated serum alkaline phosphatase, sometimes serum calcium), X-ray of the skeleton (osteolytic, osteoplastic, osteolytic-osteoplastic lesions, pathologic fractures), skeletal scintigrafy and sometimes CT and MR.

Osteomalacia is a disease due to pathologic loss of mineralized bone.[2] Because of a low serum calcium concentration a substantial part of the bone matrix is not normally mineralized. The density of the bone is thus diminished, which leads to bending of bones and pathologic fractures.

Clinical conditions associated with osteomalacia are:

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1. Deficiency of vitamin D (dietary absence of vitamin D or inadequate exposure to sunlight)
2. Diminished absorption of vitamin D (diseases of the bile ducts, diseases of proximal part of the small bowel, exocrine pancreatic insufficiency, gastrectomy)
3. Disorders of vitamin D metabolism (liver diseases, drugs that activate hepatic oxidative enzymes, resistance to vitamin D)
4. Kidney disorders (loss of phosphates)
5. Chronic use of large amount of antacids containing Mg and Al, which form with phosphates insoluble complexes

Osteomalacia usually presents clinically as bone, joint and muscle pain and fatigue.

Beside the medical history and clinical examination the most important diagnostic procedures for osteomalacia are laboratory findings (low values of serum calcium and phosphates, elevated serum PTH and later alkaline phosphatase) and aspecific and specific x-ray changes of bones.

Case histories

Case 1

A 47 year old woman was admitted to our Institute with a diagnosis of bone metastases of unknown origin.

She was a smoker for several years and 16 years ago a diagnosis of Bürger's disease was established.

She had diabetes mellitus regulated with diet and oral therapy, and angina pectoris.

Two years previously she noticed pain in her legs when walking which became so severe that for half a year she could only move around in a wheelchair.

On clinical examination, she was found to have pale skin, ataxia, dextroconvex scoliosis of thoracic spine, painful spine on succussion, muscular weakness of all muscles of the lower extremities.

The laboratory tests revealed a normocytic normochromic anemia Hb 81 g/l (normal 120-180 g/l), elevated chlorides 110 mmol/l (normal 95-105 mmol/l), elevated alkaline phosphatase to 4.32 μkat/l (normal 0.50-1.50), lowered serum phosphate 0.7 mmol/l (normal 0.8-1.4) and serum calcium to 1.7 mmol/l (normal 2.10-2.60). All other laboratory parameters (biochemical, protein electrophoresis) were within normal limits.

On skeletal X-ray, the spine showed structural atrophy (osteopenia). In the pelvis and ribs numerous fractures in the area of Looser zones were seen.

We performed a bone marrow biopsy of spina iliaca posterior superior with a Yamshidi needle. Histologically the bone marrow aspirate was within normal limits while bone tissue showed osteomalacia (Figure 1).

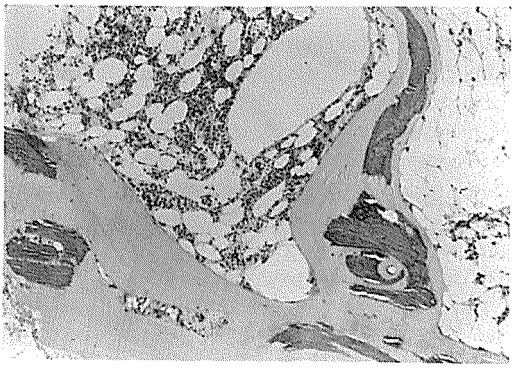

Figure 1. Trabecular bone of patient with osteomalacia. Wide osteoid seams cover trabecular surfaces without increased numbers of osteoclasts.

We concluded that the changes in the bone were due to osteomalacia and not to bone metastases. The patient was referred to an endocrinologist for further investigations and treatment. At follow up, after three years, her symptoms lessened and otherwise she was doing well.

Case 2

A 72-year old woman was referred to our Institute with a diagnosis of diffuse skeletal metastases. A partial resection of her stomach (Billroth II) was performed 37 years ago for unknown reason. She was treated 13 years ago with radioactive iodine because of goiter. At recent follow-up examination, she had no problems related to thyroid.

Her main complaint was pain in her hips, spine, legs and thorax for two years which worsened with weather changes.

Clinical examination showed 1x1cm elastic lump in the right breast; the mobility in the left hip was painful and limited, she was limping.

Pathologic laboratory findings were as follows: elevated serum chlorides (107 mmol/l), elevated alkaline phosphatase (4.42 μkat/l), lowered serum calcium (2.0 mmol/l).

Mammography and ultrasound guided fine needle aspiration biopsy of the lump in her left breast were negative for carcinoma, but showed benign dysplasia.

On bone scintigraphy accumulation of the isotope was seen in the ribs, sacrum, sacroiliacal joints, head of the left femur, os pubis and proximal epiphysis of left tibia (Figure 2).

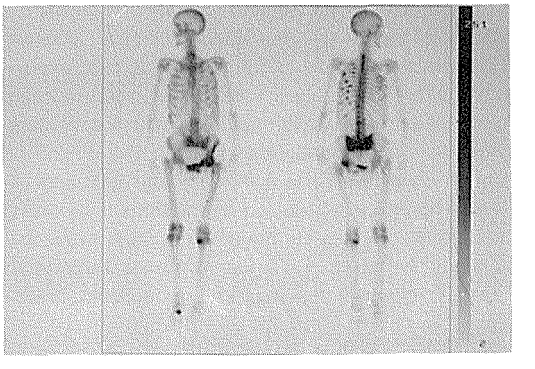

Figure 2. Increased uptake in the ribs, sacrum, sacroiliacal joints, head of the left femur, os pubis, knees, small joints of the right foot and along both femurs – fractures? The scintigram is not typical for osseus metastases.

On bone X-rays, multiple old fractures of bilateral ribs were seen with abundant callus formation (Figure 3). In the spine, structural atrophy was seen with osteochondrosis. In the pelvis old fractures with callus formation were seen

We performed a bone marrow biopsy with a Yamshidi needle at the typical site. Aspiration of bone marrow revealed normal bone marrow with 2 % of

plasma cells and histology osteomalacia. The patient was referred to an endocrinologist for therapy (vitamin D, Ca) and is doing well after one year of follow up.

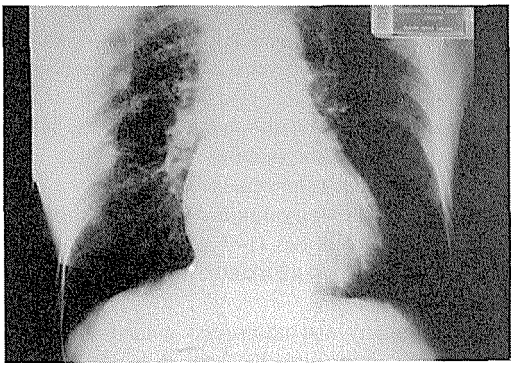

Figure 3. Multiple fractures of ribs mainly seen on the right side with abundant callus formation.

Discussion

Bone pain, associated with multiple bone lesions on X-ray is most often caused by metastases. In most of such cases, the treatment can only be palliative (surgery and/or radiotherapy and/or hormone or chemotherapy) and sometimes only symptomatic. Patients in whom the first manifestation of disease are bone lesions are examined for occult malignancy and if a diagnosis is not established, a bone biopsy is performed. For patients with established malignant disease and bone lesions, the diagnosis of bone metastases is usually easy and treatment is given. The aim of our case presentations is to stress some points when some doubt about such a diagnosis should be raised and some other rare differential diagnostic possibilities such as osteomalacia, entertained.

How can medical history, clinical examination and laboratory and radiological findings lead us to a diagnosis other than bone metastases in such cases?

Medical history

The quality of bone pain is essentially the same in osteomalacia and bone metastases. The pain in osteomalacia is localized most often in the pelvis and hips[2] while in bone metastases the patients usually localize pain at the affected site. The duration of pain is very important. In osteomalacia it may be present for several years.

Data regarding possible abnormalities in vitamin D intake or absorption (Billroth II operation in our second case) should lead us to more detailed investigations regarding the bone changes.

Clinical examination

There are no essential differences in clinical evaluation of patients suffering from bone metastases, myeloma or metabolic bone disease, if we do not find obvious signs of the primary malignancy.

Laboratory tests

Typical findings for osteomalacia are decreased values of serum calcium and phosphate and elevated alkaline phosphatase and PTH[2,3] which was also the case in both of our patients.

In metastatic bone disease the alkaline phosphatase is also usually elevated but hypocalcemia is rarely seen and is sometimes associated with osteoblastic metastases,[4] the serum calcium might be elevated, more often in association with malignancies of lung, breast, head and neck.[1]

Serum chloride was also increased in both of our patients probably due to secondary hyperparathyroidism.[5]

Bone scintigraphy

Bone scintigraphy (with Tc^{99m} diphosphonate) is mostly used to detect primary and secondary bone tumors, metabolic bone disease and inflammatory bone disease.

In metastatic bone disease the typical finding are multiple bone lesions of enhanced activity with asymmetric arrangement, more common in the axial part of the skeleton. The metastases may give an impression of photopenic effect.[6]

The lesions of osteomalacia on bone scans are very similar to metastases although they are usually more symmetric.[7]

Bone scan in osteomalacia demonstrates increased uptake of tracer in pseudofractures usually in the ribs when mild disease is present. In severe cases characteristic metabolic feature may be seen; increased tracer uptake in axial skeleton, in long bones, in periarticular areas, prominent calvaria and mandibule, absent kidney images, beading of costochondral junction. The same pictures may be found in other metabolic diseases and in metastases. While the bone scan is nonspecific, there are often seen recognizable patterns of abnormality and may strongly suggest (not confirm) a specific diagnosis.[8]

The scintigraphy is non-specific. A comparison with skeletal x-ray is necessary.[9]

As a detecting method for pseudofractures bone scintigraphy is more sensitive than x-ray.[7,8,10]

Skeletal X-rays

A definite x-ray diagnosis of osteomalacia is not easy. The bone density is usually diffusely diminished.

Radiographic findings include a decrease in bone density, loss of secondary trabeculae with prominence of the remaining primary trabeculae, blurred, indistinct cortical margins, and characteristics pseudofractures or Looser zones (unmineralized osteoid seams) which are typically symmetrical in distribution, and most frequently seen in the axillary margin of the scapula, femoral neck, pubic and ischial rami, and ribs oriented at 90° to the cortical margin.[11,12,13] Specific signs of hyperparathyridism as subperiostal erosions, especially of the phalanges, long bones and distal ends of the clavicles are in the severe cases often present.[14]

Bone biopsy

Bone biopsy with Yamshidi needle (from spina iliaca posterior superior under local anesthesia) is adequate for metabolic and infiltrative bone marrow disease and thus decreases the need and importance of some complex biochemical and radiological procedures. The frozen section can be used for fluorescent microscopy, enzyme and imunohistochemical procedures. The method can be performed in any histologic laboratory with a cryostat and the diagnosis can be established quickly.[15] Bone biopsy performed in this manner cannot confirm the bone metastases (unless they are localized right at the site of biopsy) but can disclose a number of metabolic and infiltrative bone diseases - in our cases osteomalacia. Bone biopsy may be combined with tetracycline labeling.[5]

Conclusion

Osteomalacia is a rare disease, and may on occasion be confused with metastatic bone disease. However, there are some clues that might lead us to the right direction, or at least shed some doubt into the diagnosis of bone metastases. From our cases such clues are: long history of pain and hypocalcemia with hypophosphatemia and elevated serum alkaline phosphatase. In the first case there were quite typical radiological findings, in the second case it was only after biopsy that a diagnosis was made. Bone biopsy seems a simple and reliable method to diagnose osteomalacia.

References

1. Rosier RN, Boros L, Konski A. Bone tumors. In: Rubin P ed. *Clinical oncology*. Philadelphia: W.B. Saunders Company, 1993: 509–30.
2. Krane MS, Holick MF. Metabolic bone disease. In: Isselbacher KJ, Adams RD, Braunwald E, Petersdorf RG, Wilson JD, Martin JB, Fauci AS, eds. *Harrisons principles of internal medicine*. New York: McGraw-Hill, 1991: 1921–33.
3. Rosenthal NR. Metabolic bone disease. In: Dugdale DC, Eisenberg MS, eds. *Medical diagnostics*. Philadelphia: W.B. Saunders Company, 1992: 456–60.
4. Buskin P. Hypocalcemia associated with metastatic bone disease. *Arch Intern med* 1973: **132:** 539–47.
5. Wallach J. *Interpretation of diagnostic tests*. Boston: Little, Brown and Company, 1996: 47–279.
6. Mc Afee JG. Radionuclide imaging in metabolic and systemic skeletal diseases. Seminars in Nuclear Medicine 1987; **17:** 334–9.
7. Singh BN, Spies SM, Mehta SP, et al. Unusual bone scan presentation in osteomalacia: Symmetrical uptake-A suggestive sign. *Clin Nucl Med* 1978; **3:** 292–5.
8. Fogelman I, McKillop JH, Greig WR, et al. Pseudofracture of the ribs detected by bone scanning. *J Nucl Med* 1977; **18:** 1236.
9. Velchik MG, Makler PT, Alvi A. ●steomalacia. An Inposter of osseus metastasis. *Clin Nucl Med* 1985; **10:** 783–5.
10. Macfarflane JK, Lutkin JE, Burwood A. The demonstration by scintigraphy of fractures in osteomalacia. *Br J Radiol* 1977; **50:** 369.
11. Edeiken J. Metabolic and dystrophic bone disease. In: Edeiken J, ed. *Roentgen diagnosis of disease of bone*. Baltimore: Williams & Wilkins, 1981: 829–1046.
12. Rosenthall L, Lisbona R: Metabolic bone disease. In: Rosenthall L, Lisbona R, eds. *Skeletal imaging*. Norwalk: Appleton- Century- Crofts, 1984: 225–42.
13. Pitt MJ: Rickets and osteomalacia. In: Resnick D, Niwayama G, eds. *Diagnosis of bone and joint disorders with emphasis on articular abnormalities*. Philadelphia: W B Saunders, 1981: 1683–1713.
14. Alper SL, Lodish HF.Disorders of the kidney and urinary tract. In: Isselbacher KJ, Adams RD, Braunwald E, Petersdorf RG, Wilson JD, Martin JB, Fauci AS, eds. *Harrisons principles of internal medicine*. New York: McGraw-Hill, 1991: 1131–218.
15. Stevens A, Palmer J. Frozen sections of bona biopsies in metabolic and other bone diseases. Histopatology 1985; **9:** 315–4.

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Dose delivery uncertainty in photon beam radiotherapy

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Even slight variations in total dose delivered to the patient in external beam photon radiotherapy can significantly alter the probability of tumour control and normal tissue complications. For this reason, the International Commision on Radiation Units and Measurements (ICRU) has recommended a goal of a ±5% precision in the dose delivered to the target volume. In this paper, we present the results of an uncertainty analysis which tracked the uncertainty in dose delivery through the entire radiotherapy process: calibration of the secondary standard, calibration of a field instrument, output determination of the treatment unit, measurement of beam parameters, calculation of an isodose distribution, calculation of the required machine setting, and the delivery of the radiation dose to the patient on the treatment machine. Our study finds cumulative beam intensity uncertainties of ±3.8 % (one standard deviation) and cumulative beam positional uncertainties of ±5.5 mm (one standard deviation). The effect of these uncertainties on the dose to the patient is illustrated on a typical case.

Key words: neoplasms-radiotherapy; radiotherapy dosage; photons

Introduction

Regardless of how sophisticated radiotherapy becomes, there will always be some uncertainty associated with the delivery of dose to the patient. The radiation dose delivered is influenced by the following elements: (1) calibration of the institution's secondary standard chamber at a national calibration laboratory; (2) calibration of a field instrument from the secondary standard chamber; (3) use of the field instrument in output determination for treatment units in the clinic; (4) measurement of beam parameters used in the calculation of the dose distribution and machine setting; (5) calculation of a dose distribution based on measured parameters and accounting for patient contour and tissue heterogeneities; (6) calculation of the machine setting for the daily fraction; and finally (7) patient set-up on treatment machine and possible patient or organ motion during treatment. It is important to determine the magnitude of the various contributions to the overall uncertainty; corrective efforts can then be applied efficiently to improve the accuracy of dose delivery and minimize the uncertainty.

Clinical studies[1, 2, 3] have shown that relatively small changes in the dose delivered to the patient in photon beam radiotherapy lead to appreciable changes in the probabilities both for tumour control and normal tissue complications. Although the dose-response curve varies with the type of disease treated, the ICRU[4] has recommended that institutions strive to deliver the dose to the target volume with an overall accuracy of ±5 % of the prescribed dose. This recommendation provided the motivation for a detailed uncertainty analysis undertaken at the Montreal General Hospital on photon beams produced by a Clinac-18 linear accelerator (10 MV beam) and a Theratron T-780 cobalt unit. In this paper we discuss the linear accelerator data; similar results and conclusions were obtained for the cobalt unit.

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Materials and methods

The uncertainty associated with each of the seven steps above was analyzed carefully and then combined to compute the overall uncertainty. We assume the uncertainties for the different steps to be uncorrelated which implies that the overall uncertainty is obtained by a quadrature summation of the individual uncertainties. This simple approach seems acceptable since there is considerable uncertainty on the uncertainty estimates themselves.

Except for step (1) which is in the hands of a national calibration laboratory and step (7) for which we referred to published studies, the uncertainty for each of the other steps listed above may be ascertained by examining the spread in results of repeated measurements of the quantity in question. The number of repetitions in our experiments was 30, with the uncertainty expressed as the standard deviation of the 30 measurements. A 0.6 cm^3 Farmer chamber (NE 2581) and a digital electrometer (Keithley 35617) were used in all experiments, except in the water tank scans where a 0.1 cm^3 water-proof ionization chamber was employed (Therados RK 83-05).

In order to obtain a realistic measure of the uncertainty for a given quantity, it is not sufficient to simply perform the set-up once and repeat the measurement thirty times, because the spread in measurement results is caused mainly by slight differences in set-up rather than by statistical variations in the measured parameter. Thus the set-up must be redone for each measurement. As an example, consider measuring the uncertainty on the wedge factor. Determination of the wedge factor involves taking the ratio of readings for a 10 × 10 cm^2 field at the depth of dose maximum (d_{max}) in phantom for the wedged field and the open field. For each measurement of the wedge factor, one must reset the field size, gantry angle, collimator angle, realign the chamber, and re-insert the wedge in the tray if one is to acquire a realistic uncertainty, representative of different measuring conditions.

Results

The secondary standard

The uncertainty on the cobalt-60 calibration factor for the secondary standard chamber provided by our national calibration laboratory[5] is 0.5 %. This is defensible since the precision of primary standards of cobalt-60 radiation, established through comparisons of numerous primary standards around the world,[6, 7] is within 0.3 % and the act of calibration introduces additional, non-negligible uncertainties.

Calibration of the field instrument

The calibration of the field instrument from the secondary standard chamber is performed in air by subjecting the two chambers to identical exposures in a cobalt-60 beam, and solving for the calibration factor, N_X^{field}, of the field instrument:

$$N_X^{field} = \frac{N_X^{sec} M^{sec}}{M^{field} P_{ion}^{field}} \quad , \qquad (1)$$

where N_X^{sec} is the calibration factor of the secondary standard chamber, M^{sec} and M^{field} are the meter readings of the secondary standard and field chamber, respectively, and P_{ion}^{field} accounts for recombination loss in the field instrument.

The uncertainty on the calibration factor of the field instrument can be deduced from the uncertainties on each of the variables in Eq. (1) using the usual quadrature summation. Experiments have shown that with normal care the uncertainty on readings taken in the calibration set-up with our chamber is about 0.07 %, reflecting the uncertainty on M^{sec} and M^{field}. If this estimate seems unusually low compared to typical clinical measurements, it is because in the calibration set-up the chamber is clamped to a rigid rod extending from the accessory tray which permits a highly-reproducible positioning. The uncertainty on P_{ion} for our chamber is less than 0.02 % and, as stated above, the uncertainty on the calibration of the reference chamber is 0.5 %. Combining these uncertainties with the uncertainties on the meter readings for each chamber gives a total uncertainty for the cobalt-60 calibration factor of our field chamber of 0.5 %, essentially attributed to the calibration factor of the secondary standard chamber.

Further analysis of the field instrument might include experiments to examine chamber response for dependence on polarity, angle of rotation and angulation, stem exposed to the beam, charge recombination, charge leakage, cable irradiation, and total dose. Extensive experimentation conducted prior to our uncertainty analysis confirmed that none of these effects is significant under typical conditions of use.

Output determination

The AAPM TG-21 dosimetry protocol[8] used in North America introduces a number of dose transfer coefficients and chamber-dependent correction factors by which the meter reading M obtained at a given depth in phantom must be multiplied to obtain the dose to medium at the same point:

$$D_{med} = MN_{gas}\left(\bar{\bar{L}}/\rho\right)_{air}^{med} P_{wall} P_{repl} P_{ion} \quad , \qquad (2)$$

where $\left(\bar{\bar{L}}/\rho\right)_{air}^{med}$ is the ratio of the restricted stopping powers for the medium material and air, P_{wall} is a correction factor dependent on the thickness and geometry of the chamber wall, P_{repl} is a gradient correction necessary for measurements not performed at d_{max} in phantom, and P_{ion} accounts for recombination loss. All of these factors are evaluated at the beam energy for which one is measuring D_{med}. The chamber-gas calibration factor, N_{gas}, is given by:

$$N_{gas} = N_X^{field} \frac{kW_{air}A_{wall}A_{ion}}{\left(\bar{\bar{L}}/\rho\right)_{air}^{wall}\left(\bar{\mu}_{ab}/\rho\right)_{wall}^{air}} \quad , \qquad (3)$$

where N_X^{field} was described in Eq. (1), k is a conversion factor from roentgen to C/kg (2.58×10^{-4} C/(kg•R)), W_{air} is the mean energy required to create an ion pair in air (33.97 eV/ion pair), A_{wall} is a correction factor dependent on the thickness and geometry of the chamber wall, A_{ion} accounts for recombination loss, $\left(\bar{\bar{L}}/\rho\right)_{air}^{wall}$ is the ratio of the restricted stopping powers for the chamber wall material and air, and $\left(\bar{\mu}_{ab}/\rho\right)_{wall}^{air}$ is the ratio of mass-energy absorption coefficients for air and the chamber wall material. All quantities in N_{gas} are evaluated at cobalt-60 photon energy.

Estimates of the uncertainties on the dose transfer coefficients are given in the literature[9,10] as follows: stopping power ratios are known to 0.6 %, while the mass-energy absorption coefficients and W_{air} are known to 0.2 %. The uncertainty on P_{repl} is estimated[11] at 0.2 %. From the TG-21 protocol,[8] we estimate the uncertainty on A_{wall} and P_{wall} to be 0.2 %. Uncertainties on A_{ion} and P_{ion} are negligible. From these values we calculate the uncertainty on N_{gas} for a typical field chamber to be about 1.0 %. Repeated measurements with a new set-up performed each time, have shown that the uncertainty on the meter reading, M, is 0.26 % for the 10 MV beam. Thus, combining the uncertainties on all factors in Eq. (2) gives an uncertainty of 1.2 % on the measurement of D_{med} at a given depth in phantom for our 10 MV beam.

The output of a treatment unit is generally defined as the dose rate to medium at d_{max} in phantom, for a 10×10 cm^2 field in units of cGy/min for a cobalt machine or cGy/MU for a linear accelerator. For output determination our institution employs a water phantom with an ionization chamber placed at 5 cm depth. The dose at d_{max} is then found by dividing the measured dose at 5 cm depth by the percent depth dose for a depth of 5 cm. With repeated measurements, we have established the uncertainty on percent depth dose measurements in a water tank to be around 0.5 %. This, combined with the 1.2 % uncertainty of the dose measurement at 5 cm depth, results in an output uncertainty of 1.3 %. Furthermore, the agreed upon tolerance of the output calibration is ±12 % which means that, frequently, the calibration can be off by over 1 %. This added uncertainty results in a cumulative uncertainty of approximately 1.8 % on the output of the 10 MV beam. In certain circumstances the output uncertainty may be even higher: for instance, with the use of highly-elongated fields because of the collimator-exchange effect or with very low monitor unit settings because of the monitor end-effect.

Input for the treatment planning system

For each field size in the range of fields sizes clinically employed, a treatment planning system typically requires percent depth doses and dose profiles at a number of depths in phantom as input for its dose calculation algorithm. The results of repeated water-tank scans (with a new set-up performed for each scan) revealed that the uncertainty on percent depth doses on the beam central axis and dose profiles well within the radiation field limits is of the order of 0.5 %. The uncertainty for dose profiles is considerably higher (~10 %) in the penumbra region because of the steep dose gradient in this region. For the percent depth doses, the uncertainty is negligible near d_{max} (since normalization is performed at this point) and slowly increases to reach about 0.8 % at a depth of 30 cm in the water phantom.

Dose distribution calculation

Uncertainties introduced in computerized treatment planning are the result of uncertainties in the beam data entered into the computer, imperfections in the calculation algorithm, and inaccuracies in the pa-

tient data which consists of body, organ, and target contours, as well as tissue heterogeneities. These factors can be expected to generate incongruities between calculated dose distributions and measured ones, with the act of measurement occasioning additional uncertainies. According to the ICRU:[12] "A computer-produced dose distribution can be considered to be accurate enough if it differs from relative dose measurements by less than 2 % (or 0.2 cm in position of isodose lines in special circumstances involving very steep dose gradients) in points of relevance for the treatment". However, a very comprehensive U.S. study[13] comparing six systems (using four different computational algorithms) found about a 3 % agreement (or 0.3 cm in position of corresponding isodose lines in regions of high dose gradient) for a wide range of test conditions. A Scandinavian study[14] tested the accuracy of six other systems in typical clinical situations and their results concurred with those of the U.S. study.

Calculation of machine setting

To calculate the machine setting from the physician's prescription, relative dose factors and wedge factors are needed in addition to the basic output calibration data. Reproducibility tests, once again, allowed us to conclude that the uncertainty on the relative dose factor is 0.3 % and the uncertainty on the wedge factor is 0.4 %.

Patient treatment

Concerning patient set-up, an extensive study by Rabinowitz,[15] as well as several studies of lesser scope,[16, 17, 18] were undertaken to assess the magnitude of positional uncertainties. These studies have found that the variability in patient position from one treatment fraction to another is about 3 mm, practically irrespective of site. Since these variations are random, their cumulative effect over the full course of treatment will be to increase the effective penumbra of the beam. Internal organ motion during irradiation is an additional positional uncertainty. A study of brain motion[19] has measured translations of 0.5 mm, which are negligible, while an estimate for the abdomen[20] is 4 mm. For thoracic irradiations, breathing and swallowing increase positional uncertainties still further.

The transfer of the patient from the simulator to the treatment couch also produces an uncertainty which the studies have found to be about 4 mm. Contrary to the inter-fraction positional uncertainties, this uncertainty occurs only once and thus has a systematic effect over the whole treatment course.

Discussion

The uncertainties in dose delivery described above naturally fall into two categories: beam intensity uncertainties and positional uncertainties. *Beam intensity uncertainties* encompass uncertainties attributed to the calibration of the field chamber, the output determination of the treatment unit, shortcomings of the treatment planning system, the quantities required in the calculation of the machine setting (relative dose factor and wedge factor), and variation in position of the patient along the beam axis. *Positional uncertainties* include variations in position of the patient across the beam and deficiencies of the treatment planning system in regions of high dose gradient, i.e., the beam penumbra.

To provide an example of the effect of the uncertainties on the dose delivered to a patient we have selected a typical three-field pelvic case with a prescription of 45 Gy to isocentre. For this case, beam intensity uncertainties yield a total of 3.8 % (one standard deviation). Positional uncertainties yield a total 5.5 mm (one standard deviation).

These uncertainties can be illustrated according to an approach suggested by Goitein.[21] Three dose maps are produced for the patient. A first map gives the nominal dose distribution; this is the dose distribution which we intend to deliver. A second map gives the largest possible dose that each point can receive; it is calculated with the beam weighting increased by 3.8 % and the field sizes increased by 5.5 mm on each of the four sides of the treatment fields. A third map gives the smallest possible dose that each point can receive; it is calculated with the beam weighting decreased by 3.8 % and the field sizes decreased by 5.5 mm on each of the four sides of the fields.

The three maps for our typical case are shown in Figure 1 where normalization is performed to give the dose in Gray. Points well within the field limits are affected only by the uncertainty on the beam intensity; for example, the isocentre dose, in comparison to the nominal dose of 45 Gy, may vary from 43.2 Gy to 46.8 Gy, or by ±13.8 % of the nominal dose. Points near a field limit suffer the effects of both the beam intensity uncertainties and the positional uncertainties. For instance, the nomi-

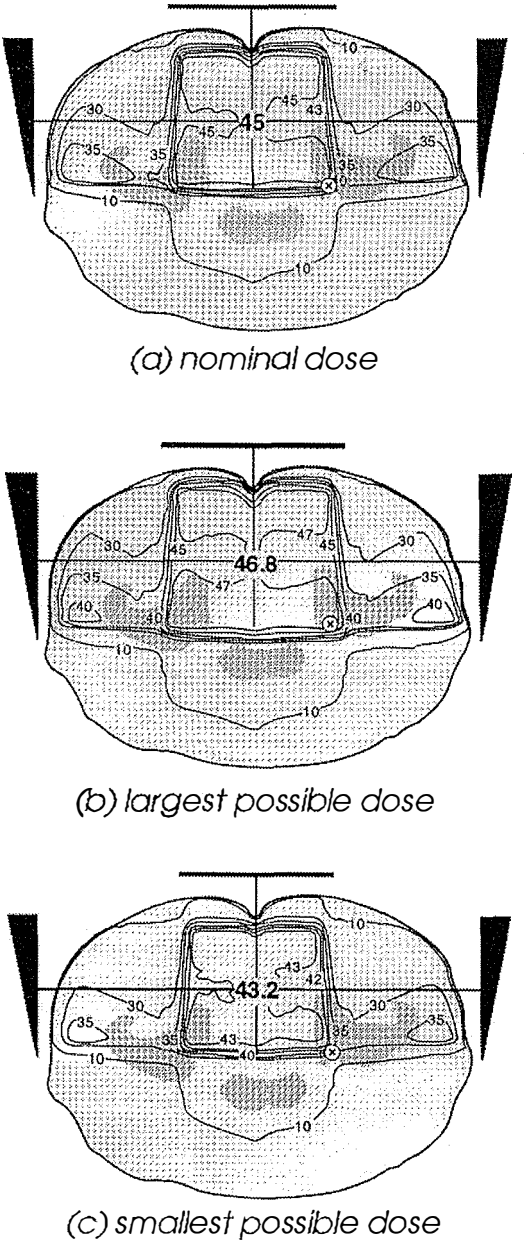

Figure 1. Effect of uncertainties in the radiotherapy process on the patient dose. For a typical example of pelvic irradiation with a three-field technique we show: (a) the nominal distribution, (b) the largest possible dose each point may receive, (c) the smallest possible dose each point may receive. Normalization is adjusted to give the dose in Gy. The isocentre dose may vary from 43.2 Gy to 46.8 Gy compared to the nominal 45 Gy, while the dose to a typical point in the penumbra region denoted by ⊗ may vary from 35 Gy to 47 Gy compared to the nominal 43 Gy.

nal dose delivered to the point denoted by ⊗ in Figure 1 is 43 Gy; because of the uncertainties the actual dose delivered to this point may vary from 35 Gy (−19 %) to 47 Gy (+9 %).

Conclusions

For the beam intensity uncertainties, our estimated total of 3.8 % (one standard deviation) is in conformity with the ICRU recommendation of ±5 % (if the ICRU recommendation is to be taken as one standard deviation). For the positional uncertainties, the 1 cm margin that physicians routinely add to all sides of the target volume would seem sufficient to account for the positional uncertainties of ±5.5 mm (one standard deviation) found in our study.

The uncertainties illustrated by the typical case shown above are representative of those associated with routine radiotherapy in the majority of modern centres; no special precautions are required to achieve this level of precision. Despite the partially subjective character of uncertainty estimates, other studies have come to very similar results.[20, 22, 23, 24] If the precision of dose delivery in radiotherapy is to be improved, treatment planning systems must become more sophisticated and better patient positioning devices must be developed. These two steps have been shown to be the major contributors to the overall uncertainty.

Since substantial variability also exists in medical diagnosis and dose prescription, further improvements in the accuracy and precision of radiotherapy will have to come both from the physical side and from the medical side. Yet the physical side plays a crucial role, for it is only when a high degree of accuracy and precision exists in the delivery of dose that clinical conclusions regarding the relative merit of different fractionation schemes, total doses, and normal tissue tolerance can be drawn.

References

1. Brahme A. Dosimetric requirements in radiation therapy. *Acta Rad Onc* 1984; **23:** 379–91.

2. Herring DF, Compton DMJ. The degree of precision required in the radiation dose delivered in cancer therapy. *Proceedings of the Third International Conference on Computers in Radiotherapy, Special Report No. 5* 1971.

3. Shukovsky LJ. Dose, time, volume relationships in squamous cell carcinoma of the supraglottic larynx. *Am J Roentgenol* 1970; **108:** 27–9.

4. International Commission on Radiation Units and Measurements. *Determination of absorbed dose in a patient irradiated by beams of x or gamma rays in radiotherapy procedures (ICRU Report No. 24).* 1976.

5. National Research Council of Canada: Institute for National Measurement Standards. *Calibration of the NPL secondary standard dosemeter, model 2560, serial number 071, with the Nuclear Enterprises probe, model 2561, serial number 080: A document prepared for the Montreal General Hospital, report pirs-0484.* January 30, 1995.

6. Niatel M-T, Loftus TP, Oetzmann W. Comparison of exposure standards for Co-60 gamma rays. *Metrologia* 1975; **11:** 17–25.

7. Comparison of uncertainty estimates. *Comité consultatif pour les étalons de mesure des radiations ionisants (Section 1). CCREMRI (1) R(1)-9 BIPM.* 1985.

8. AAPM Task Group 21. A protocol for the determination of absorbed dose from high energy photon and electron beams. *Med Phys* 1983; **10:** 741–71.

9. Boutillon M, Perroche-Roux AM. Re-evaluation of the W for electrons in dry air. *Phys Med Biol* 1987; **32:** 213–9.

10. Andreo P. Uncertainties in dosimetric data and beam calibration. *Int J Radiat Oncol Biol Phys* 1990; **19:** 1233–47.

11. Attix F. A proposal for the calibration of plane-parallel ion chambers by accredited dosimetry calibration laboratories. *Med Phys* 1990; **17:** 931–3.

12. International Commission on Radiation Units and Measurements. *Use of computers in external beam radiotherapy: procedures with high-energy photons and electrons (ICRU Report No. 42).* 1987.

13. Masterson ME, Barest G, Chui C-S, Doppke KP, Epperson RD, Harms WB, Krippner KE, Mohan R, Slessinger ED, Sontag MR, Urie MM, Wallace RE, Wong JW. Inter-insitutional experience in verification of external beam photon dose calculations. *Int J Radiat Oncol Biol Phys* 1991; **21:** 37–58.

14. Kosunen A, Järvinen H, Vatnitskij S, Ermakov I, Chervjakov A, Kulmala J, Pitkänen M, Väyrynen T, Väänänen A. Intercomparison of radiotherapy treatment planning systems for external photon and electron beam dose calculations. *Radiother Oncol* 1993; **29:** 327–35.

15. Rabinowitz I, Broomberg J, Goitein M, McCarthy K, Leong J. Accuracy of radiation field alignment in clinical practice. *Int J Radiat Oncol Biol Phys* 1985; **11:**,1857–67.

16. Hunt MA, Kutcher GJ, Burman C, Fass D, Harrison L, Leibel S, Fuks Z. The effect of set-up uncertainties on the treatment of nasopharynx cancer. *Int J Radiat Oncol Biol Phys* 1993; **27:** 437–47.

17. Huizenga H, Levendag PC, De Porre PMZR, Visser AG. Accuracy of radiation field alignment in head and neck cancer: a prospective study. *Radiother Oncol* 1988; **11:** 181–7.

18. Hukku S, Das KJM, Nangia S, Kumar A, Ayyagari S. The use of portal images to study the accuracy of radiation field alignment and patient positioning in head and neck cancer. *Proceedings of the XIth International Conference on the Use of Computers in Radiation Therapy.* 1994; 268–9.

19. Enzmann DR, Pelc NJ. Brain motion: measurement with phase-contrast MR imaging. *Radiology* 1992; **185:** 653–60.

20. Svensson GK. Quality assurance in radiation therapy: physics efforts. *Int J Radiat Oncol Biol Phys* 1984; **10:** Suppl 1, 23–9.

21. Goitein M. Limitations of two-dimensional treatment planning programs. *Med Phys* 1982; **9:** 580–6.

22. Leunens G, Verstraete J, Dutreix A, van der Schueren E. Assessment of the inhomogeneity at target level by in vivo dosimetry: can the recommended 5 % accuracy in the dose delivered to the target volume be fulfilled in daily practice? *Radiother Oncol* 1992; **25:** 242–50.

23. Leunens G, Van Dam J, Dutreix A, van der Schueren E. Quality assurance in radiotherapy by in vivo dosimetry. 2. determination of the target absorbed dose. *Radiother Oncol* 1990; **19:** 73–87.

24. Svensson H. Quality assurance in radiation therapy: physical aspects. *Int J Radiat Oncol Biol Phys* 1984; **10:** Suppl 1, 59–65.

Radiol Oncol 1996; 30: 224-5.

News of the EAR

Report on the Meeting of the EAR Executive Bureau held in Leuven on 16/17 March 1996

I. Relations EAR – E.U.

I.1. PHARE Programme

Poland has proposed a programme devoted to the improvement of radiation protection. The programme could be taken into consideration within the framework of the harmonization of the E.U. legislation.

The EAR project plans to set up a workshop between leading Eastern and Western European radiologists and E.U. partners for a better knowledge of the PHARE. Programme and the economic problems of investment in Imaging in Western European countries. The E.U. is asked to support the workshop. Furthermore, the EAR suggests creating a watchdog group in Imaging in Eastern European countries.

I.2. TASTE Project

TASTE is an accompagnying measure to assure decision makers in the assessment of teleneuromedicine services. The Executive Bureau has approved that the EAR be on the Advisory Board of the TASTE Project.

II. EAR committees

II.1. Committee for Subspecialities

An addendum to the EAR Guidelines for Training in Radiology General has been worked out. It lists recommendations for training programmes for the years 2, 3, 4 and in some instances 5. Each society represented in the Committee will suggest a detailed training programme in the respective subspeciality. At least two years of training in a subspeciality will be mandatory in order to reach the level of a subspecialist. The fifth year of training in general radiology, if it is devoted to one subspeciality, should be considered one year credit for the subspecialisation training.

The Committee decided that interventional radiology should be a programme of its own.

II.2. Education committee – Eucore

I. ISHERWOOD ended his term of office as Dean of EUCORe in March 1996. During his deanship he has mainly set the guidelines for training in radiology general which are presently at the level of the UEMS for harmonization. These guidelines have been sent to all the EAR member Societies. Continuing Medical Education (CME) will be the main task to be achieved by the Education Committee in the future.

II.3. Professional Organization Committee (P.O.C.)

The new board took up duty in October 1995 for a period of 4 years. Dr. G. HURLEY serves as Chairman, Prof. P. SCHNYDER as Vice Chairman and Dr. P. PETREL as Secretary to the Committee.

II.4. Committee of Computer Science Applications in Radiology

An ECR-EAR server will be created in Vienna. The address of the server on WWW is Euro-Rad-Org. The server could collect data bases and educational or scientific material on radiology. The editorial committee of the data base will arise from the editorial committee of "European Radiology".

II.5. Congress Committee ECR'97

Two meetings prior to ECR will be held on Breast US and interventional MRI. The poster space will be increased. Two film reading sessions will be provided. Twelve research grants will be awarded.

III. EAR educational programmes

– In the framework of the Halley Project a single refresher course took place in Hungary (May 1996) with all the speakers of the four previous courses.

– The Tutorial Campus 1996 in Graz will be carried out for Hungarian radiologists.

– The EAR Exchange Programme Visiting Junior Radiologists to Eastern Europe is set up with visits to Hungary, Poland, Romania, Russia and Slovakia.

– Five different ESDIR seminars will take place in 1996.

– A meeting took place during the RSNA 1995 between representatives of ECR and RSNA. It was decided that in the future such meetings, including the Asian Oceanic Society and ISR, should take place during the RSNA. The objectives of the meetings should be to help the organisers of local, regional or international congresses with their radiology educational programmes.

IV. Amendments to the ear charter and internal regulations

Amendments were taken into consideration prior to their submission to the General Assembly in March 1997.

V. Working group on cost effectiveness

The national member Societies have received an informative letter asking them to nominate a national expert to the Working Group which will be led by Prof. L. DALLA PALMA.

Next meeting of the Executive Bureau: Vienna 28 September 1996

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

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Head and neck radiology

BRACCO's Pan-European teaching seminar, Pecs Kolping Haz, Hungary, 29–30 March 1996

Three well-known professors of radiology, Julian Kabala, John Bradshaw and Roger Bodley from the U.K. came to Pecs for two days in order to give a series of lectures within the program of BRACCO's Pan-European teaching seminars.

On the first day, as a warm-up, they tested our knowledge on the anatomy of the head and neck, and the most common diseases of these sites. The lectures also touched upon the head and neck anatomy as imaged by CT and MR scans as well as on the vascular disorders of the brain (i.e. bleeding, infarction).

On the next day, we upgraded our knowledge on injuries, as well as on malignant and infectious diseases of the head and neck. There was a possibility od discussion between the lecturer and audience during the seminar.

After the lectures, the participants were divided into small groups of 8–9 people in order to discuss CT and MR scans with the lecturers, thus being able to learn from the basics how to recognize the abnormalities.

Twenty-seven medical doctors took part in this course, among them a lot of young physicians from the Department of Radiology, University Medical School of Pecs. There were also participants from radiology departments of various other hospitals (Baranya County Hospital, Children's Hospital, Hospital of Baja, etc.), and a few neurosurgeons were present as well.

The whole meeting was sponsored by Bracco company.

In summary, thas was an interesting and useful course, which not only offered us the opportunity to upgrade our professional knowledge but also to brush up our English.

Dr. Vercse Andrea
Department of Radiology

Radiol Oncol 1996; 30: 226-7.

Report on the 5th Radiological Refresher Course of the Halley Project

Budapest, Tihany (Hungary), 6–9 May 1996

Sponsor: Bracco International

This year within the frame of the Halley Project the 5th radiological refresher course was organized for radiologists of the former socialist countries. The aim of such courses is to develop a European standard in approaching and solving everyday problems of radiological diagnosis and interventional procedures. The leader of the program Professor L. Dalla Palma invited 33 lecturers, specialists of the radiology of the chest, musculosceleton, abdomen and urinary tract. In this short report I try to summarize the most interesting pieces of information by grouping them according to the subject.

Chest:

The status of the bronchioli can be well assessed by doing high resulution CT, can be more sensitive than spirometry. Smokers and ex-smokers show increased air trapping. CT is an excellent way for diagnosing bronchiectasis. CT is extremely good in picking up tumours which may be out of reach of the bronchoscope. It may even obviate need for bronchoscopy. The radiologist can help the pulmonary surgeon by marking the tumour that is to be excised. Before the wedge resection the radiologist performs a CT guided puncture and fills the tumour with a mixture of nonionic contrast agent and methylene blue. As he pulls the needle out he also marks the way to the visceral pleura. When the surgeon is doing the thoracoscopy he easily finds the blue spot on the lung surface and cuts the marked area away. Before pulling the excised tumour out through the thoracotomic channel, the tumour tissue is put into a plastic bag in order to prevent tumour cell inoculation.

In case of chest emergencies the chest x-ray of a patient lying on the back can show basal hyperlucency, well visible lateral sinuses and cardiac apex as signs of pneumothorax. Pleural empyemas can be treated by draining them. Rinsing with fibrinolytics is very useful as it can prevent formation of smaller, isolated abscesses.

Musculosceletal system:

Using a digital image processing system exposure differences as 20x over- or underexposure can be easily corrected. This means there are practically no bad exposures.

In case of vertebral bone metastases efficient pain relief can be provided by injecting cement into the vertebral bodies. The cement will fill the small fractures.

Diseases of the small intestine:

Even 25 or 30 years after radiotherapy, isolated segments of the small intestine can develop strictures or wall thickening. Long term use of NSAID-s can lead to the formation of ring like strictures on the small intestine.

Urographic contrast media:

After the administration of any urographic contrast agent vacuolisation can be observed in the proximal renal tubules. Experiments are going on to develop tungsten containing contrast media. Gadolinium-DPTA used for MR imaging is also good as contrast agent for intraarterial digital subtraction angiography or CT.

Diagnosis of renovasular hypertension:

Patients are given captopril that causes efferent vasodilatation and the drop of the filtration pressure. Under such conditions, if there is a narrowing on the renal artery, the excretion of the given kidney will be slower and this is well detectable with isotope renography. If captopril scintigraphy is positive, some kind of angiography, e.g. traditional angiography is not the method to choose because it only shows the first 3 cm section of the renal artery.

Urinary tract infections in children:

Kidnevs are examined primarily with ultrasound and isotopes. I.v. urography is only used to sort out difficult anatomical abnormalities. On ultrasound a dilated collecting system indicates reflux if the bladder is full, whereas a dilated collecting system with empty bladder is the sign of obstruction. Scintigraphy gives well reproducible results, is easy and functional, shows renal scars and the child can be lying on the back during the examination.

Interventional uroradiology:

The rendez-vous procedure can help to get through strictures of the ureter. Two catheters are used simultaneously and fluid that separates the ureteral walls is injected in a gentle way.

Apart from the above mentioned there were lectures on the painful knee and foot, oropharyngeal dysphagia and defecography, tumours of the liver, pancreas and prostate gland and finally on management issues in radiology. Just two important points concerning the latter:

1. Selection of co-workers is crucial in preventing problems.
2. Rejected ideas must be treated with courtesy.

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Department of Radiology
University Medical School of Pécs, Hungary

Book review

Radiation Toxicology – Bone Marrow and Leukaemia

Edited by Jolyon H. Hendry and Brian I. Lord. Elsevier Science Taylor & Francis, Great Britain, 1995. Pages: 360, Illustrations, Tables, Hard cover. ISBN (cloth) 07484 0338 8.

The book has 11 chapters and includes epidemiological studies of exposed populations, treatment methods for accidentally exposed individual or patients treated with irradiation at different dose levels and different radiation qualities.

The first chapter is a summary of all the aspects discussed in the book, the second chapter links the summary with the later chapters by sketching the proces involved in blood production. The contents of the book are logically build, the narrativeis generally pleasant and easily readable. The first 2 chapters make an interesting introduction and give the different professional profiles a helpful lead for focusing on the items interesting to them. This is a handbook for teaching scientist as well as for students. The students will find historical and basic information on radiation physics, bone marrow function, but also on new developments in genetics, pathogenesis and treatment of leukaemia. For the teaching scientist it will provide interesting facts from related specialities with valuable references in his field of interest. The radiation oncologist as well as the medical oncologist will find most helpful chapters on the effect of radiation on the bone marrow and experimental as well as clinical approach to treatment of radiation induced injury to hematopoesis.

It is a probably an impossible task to produce a perfectly balanced text covering such a broad field – from radiation physics through cancerogenesis, clinical hematology to genetic problems. The authors have, neverthless achieved an attractive book, loaded with information and certainly useful for a variety of specialists.

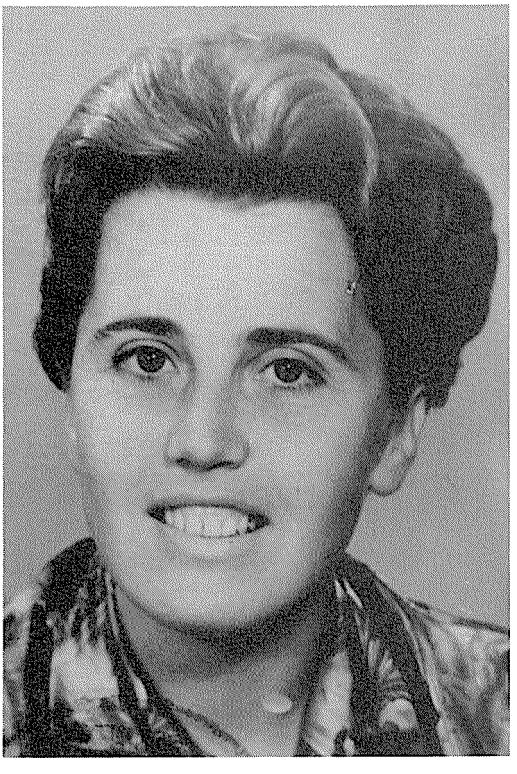
Among minor shortcomming stand out the numerous abbrevations certainly not familiar to all readers, an addendum with a list of abbreviations would be welcome. There is a certain scarcity of up to date references. All in all, the work may be warmly recommended, it should be a welcome addition to every medical library and should find its way to a wide circle of concerned professionals.

Berta Jereb; M. D.

In memoriam

Dr. Tatjana Šumi-Križnik

In May 1995 we parted from Dr. Tatjana Šumi-Križnik, the first medical oncologist and an unforgettable colleague.



She graduated from the Faculty of Medicine, University of Ljubljana, in 1955, started to work at the Institute of Oncology, and passed her board exam in anesthesiology in 1962.

Nearly at the same time, she was faced with the reality of her illness. Being a wife and a mother of two sons she did not give in, but rather engaged all her forces in the study of internal medicine, led by her interest in the research of lymphomas – a systemic cancer disease.

In 1969 she passed her board exam in medical oncology. With great enthusiasm she headed the group for diagnosis, treatment and research of lymphomas. She was among the first who started with a team approach to diagnosis and treatment at the Institute of Oncology in Ljubljana, and also succeeded in animating her co-workers for such work. She always strove for quality and advances in the diagnosis and treatment of cancer. Considering favourable treatment results obtained in patients with Hodgkin's disease, she systematically followed the guidelines in accordance with her own experience as well as that of other renown institutions in the developed world. With great knowledge and a sound professional distance towards introducing new cytotoxic drugs in the beginning of the 70's, she was the first to perform multidrug chemotherapy for lymphomas and advanced breast cancer, which is evident from her bibliography.

She contributed to regular and active co-operation at oncological and hematological meetings and congresses in the country and abroad. Despite her personal problems associated with her disease, she was a permanent source of energy and inspiration to her co-workers engaged in the field of lymphomas, proving all the time her organizational abilities and enthusiasm for continuous study and scientific research: The favourable results of these endeavours are reflected in good survival outcome of lymphoma patients.

She will always be remembered for her consistency and accuracy at work, and the fact that the patient's benefit was always in the first plane of all her activities. In the beginning of the 70's, she was the first to point out the paramount role of medical oncologists in comprehensive cancer care, which has also become generally recognized world-wide.

Unfortunately, her grave disease forced her to retire as early as in 1980. Nonetheless, as a result of her systematic teaching of young doctors and nurses, she left behind a well organized team and department for lymphomas. Unfortunately, her wish for a faster development of clinical oncology has remained unfulfilled due to insufficient personnel. Those of us, who had the opportunity to work with her, will do our best to follow in her footsteps, thus proving that her outstanding efforts were not in vain.

Maria Fidler-Jenko

Notices

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

Prostate cancer

November 4–6, 1996.

The advanced course will take place in Milan, Italy.

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

Oncology

November 8–10, 1996.

The »ASCO Fall Education Conference« will be offered in Phoenix, AZ, USA.

Contact ASCO Headquarters, 435 North Michigan Av., Suite 1717, Chicago, USA; or call + 1 312 644 0828; or fax + 1 312 644 8557.

Oncology

November 18–22, 1996.

The »13th Asia Pacific Cancer Conference« will be offered in Penang, Malaysia.

Contact Secretary – General, 13th Asia Pacific Cancer Conference, National Cancer Society of Malaysia (Penang Branch) A2.27 Komtar, 100 000 Penang, Malaysia, or call + 604 614 140, or fax + 604 618 691.

Head ad neck tumours

November 25–27, 1996.

The advanced course on oral cavity and oropharynx tumours will take place in Milan, Italy.

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

Cancer clinical trials

December 5–8, 1996.

The training course will be offered in Ioanina, Greece.

Contact European School of Oncology, c/o Egnatia Epirus Foundation, 9 Hatziyiani St., 115 28 Athens, Greece; or call +30 1 724 3144; Fax: +30 1 724 3145.

As a service to our readers, notices of meetings or courses will be inserted free of charge. Please sent information to the Editorial office, Radiology and Oncology, Vrazov trg 4, 1105 Ljubljana, Slovenia.

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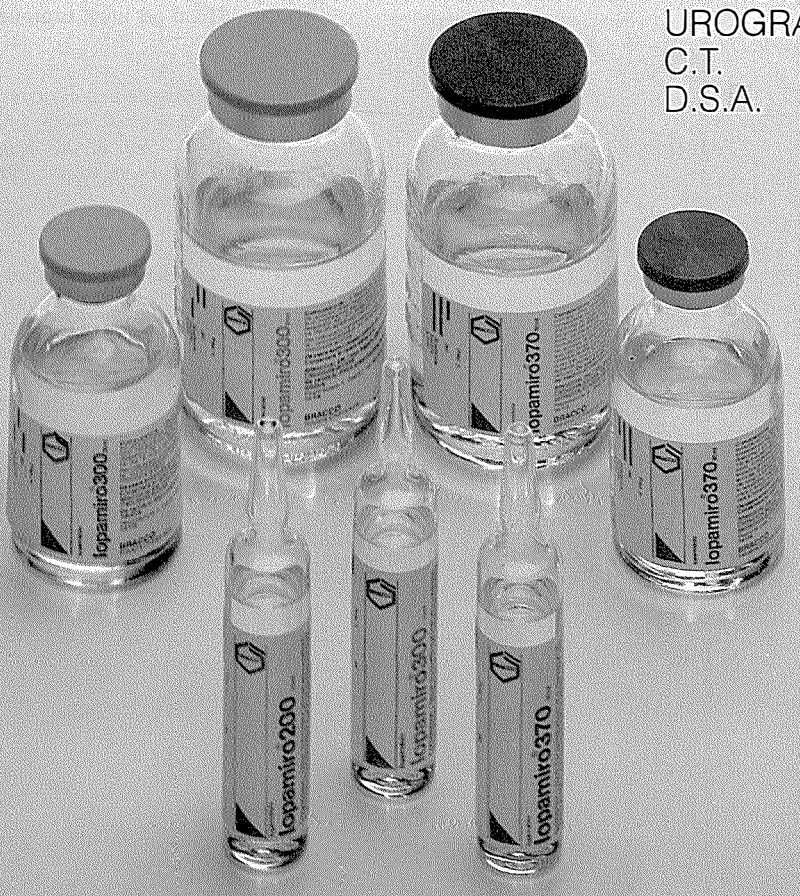

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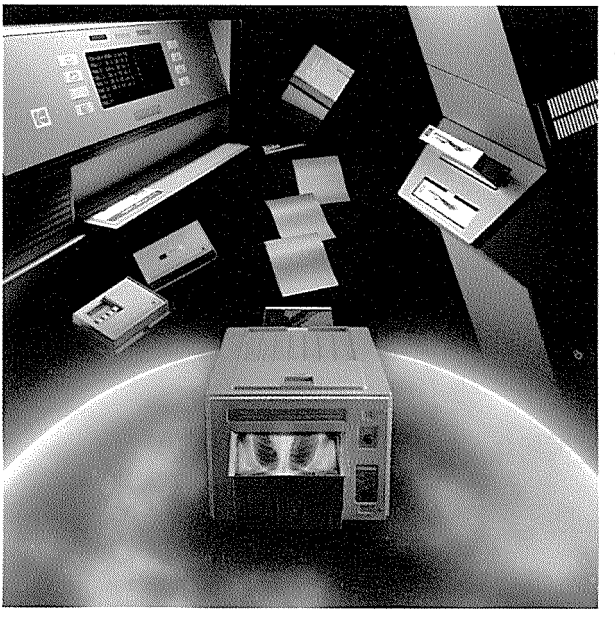

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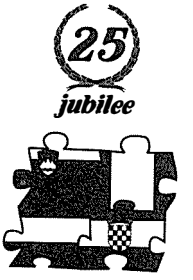

XXV Annual Jubilee Meeting of the Radiologists from the Alpe Adria Region

LJUBLJANA, November 22–23, 1996

GENERAL INFORMATION

SECRETARIAL OFFICE:

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Assist. prof. dr. Živa ZUPANČIČ

MEETING LOCATION:

University Medical Center Ljubljana
Lecture room 1

PROJECTION:

Simultaneous double projection
Slides with 5×5 cm frames

OFFICIAL LANGUAGE:

English

PRAVOPIS MEDICINSKIH IZRAZOV

M. KALIŠNIK IN SODELAVCI

V pripravi je druga, dopolnjena in popravljena izdaja dolgo pričakovanega priročnika, ki ga bodo s pridom uporabljali vsi, ki želijo vedeti, kako se v slovenskih besedilih pravilno pišejo, izgovarjajo in pregibajo medicinski termini.

Knjiga vsebuje okrog 30.000 geselskih iztočnic in okrog 40.000 stalnih zvez, skupaj torej okrog 70.000 medicinskih izrazov. Izbor je bil skrbno pretehtan, tako da so vključeni strokovni izrazi, ki jih uporabljajo naši medicinski strokovnjaki za sporazumevanje med seboj in s kolegi na tujem, pa tudi z nestrokovnjaki, zlasti še s pacienti. Izbrani so pri nas uporabljani izrazi, ki so aktualni, nedvoumni, reprezentativni in praktično pomembni ter jih študenti medicine spoznajo med dodiplomskim študijem. Termini so slovenski, poslovenjeno zapisani latinski ali latinizirani grški, izvirno zapisani latinski ali latinizirani grški ali grški. Izjemoma so vključeni tudi termini v drugih, živih jezikih, ki jim praviloma sledijo ustrezni in priporočeni slovenski izrazi.

Pri pripravi te knjige so sodelovali biomedicinski strokovnjaki, večinoma učitelji medicinske fakultete, in jezikoslovci. Uporabljeno je bilo gradivo, ki so ga leta zbirali in obdelovali pisci in svetovalci za Medicinski terminološki slovar, ki se pripravlja in bo izraze tudi razložil.

Delo je bilo večletno in so ga moralno in gmotno podpirale številne ustanove, društva in firme. Zato je možno ponuditi knjigo v prednaročilu po subvencionirani ceni 4.000 SIT; ponudba velja do 30. septembra 1996. Cena priročnika po tem roku bo 5.000 SIT.

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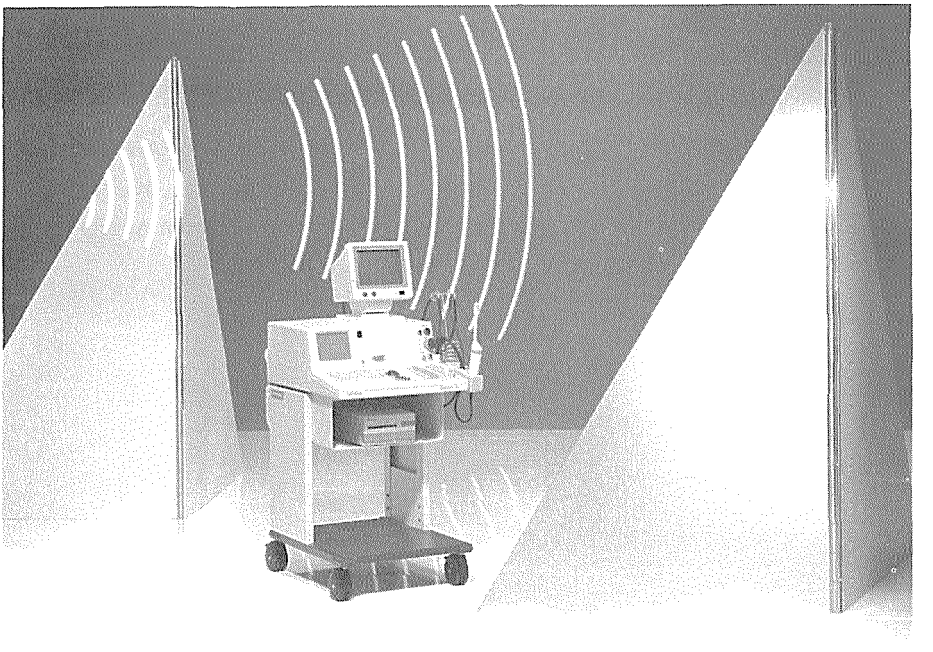

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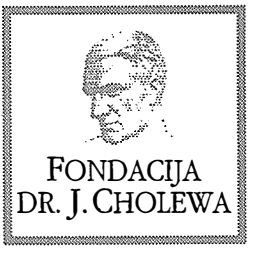

Activity of "Dr. J. Cholewa Foundation" for cancer research and education – report for the first and second quarter of 1996

"Dr. J. Cholewa Foundation" for cancer research and education continues its activity in the first half of 1996 as it was outlined at the meetings of the executive and scientific councils of the Foundation at the end of 1995.

The two researchers that were bestowed research grants in 1995 successfully concluded their basic oncological research studies in reputed cancer research institutions in The United States of America and France.

As mentioned in the previous issue of "Radiology and Oncology", the Foundation invited all the interested individuals to submit their applications for the research grants for scientific work in oncology. Public announcement was made in a major national daily newspaper, and research grants were awarded to four of the applicants, three from Ljubljana and one from Maribor.

The Foundation supported the organisation of a symposium titled "Diagnostic Algoritms in Malignant Disease" that took place in Laško in May, 1996.

At the meeting between the representatives of "Dr. J. Cholewa Foundation" for cancer research and education and "Slovenian Scientific Foundation" (Slovenska Znanstvena Fondacija) the ways of possible future collaboration were explored.

"Dr. J. Cholewa Foundation" for cancer research and education will participate in the sponsorship of the "International Conference on Epithelial Lesions of the Larynx", to be held on October 28–30th, 1996, in Ljubljana, Slovenia.

Collaboration with European School of Oncology from Milan will be extended. Specific points and goals of this collaboration will be discussed with high level officials of the European School of Oncology in the near future.

A decision was taken that the general assembly of "Dr. J. Cholewa Foundation" for cancer research and education will take place in the middle of June, 1996. It is expected the names of new members of the executive council of the Foundation will be proposed on this occasion.

From the past and present activity of the Foundation it is clear that it continues to follow its goals.

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

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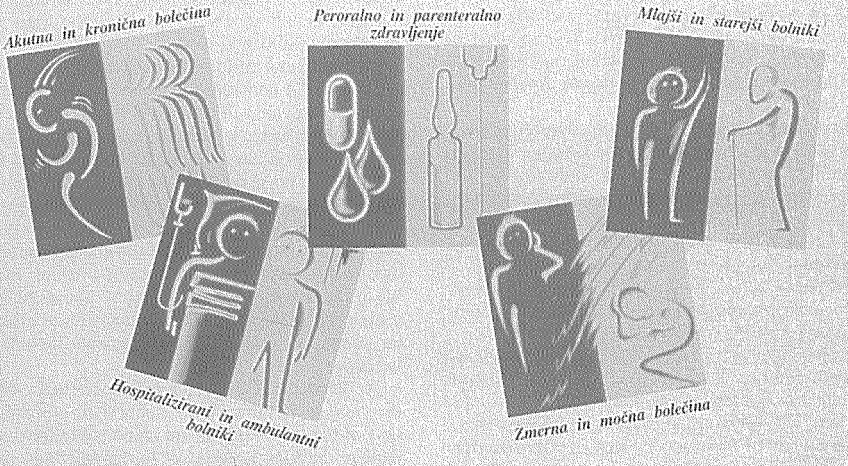

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Submission of manuscript: Manuscripts written in English should be submitted in triplicate (the original and two copies), including the illustrations to the Editorial Office: *Radiology and Oncology*, Institute of Oncology, Vrazov trg 4, SI-1105 Ljubljana, Slovenia; (Phone: + 386 61 1320068, Fax: +386 61 13 14 180, e-mail: oshrestha@mail.onko-i.si). Authors are asked to submit their manuscripts also on a 3.5" 1.44 Mb formatted diskette. The type of computer and word-processing package should be specified (Word for Windows is preferred).

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General instructions: Radiology and Oncology will consider manuscripts prepared according to the Vancouver Agreement (*N Engl J Med* 1991; **324:** 424-8, *BMJ* 1991; **302:** 6772.). Type the manuscript double spaced on one side with a 4 cm margin at the top and left hand side of the sheet. Write the paper in grammatically and stylistically correct language. Avoid abbreviations unless previously explained. The technical data should confirm to the SI system. The manuscript, including the references may not exceed 15 typewritten pages, and the number of figures and tables is limited to 4. If appropriate, organise the text so that it includes: Introduction, Material and methods, Results and Discussion. Exceptionally, the results and discussion can be combined in a single section. Start each section on a new page and number these consecutively with Arabic numerals.

Title page should include a concise and descriptive title for the paper; the full name(s) of the author(s); the institutional affiliation of each author; the name and address of the corresponding author (including telephone, fax and e-mail) and abbreviated title. This should be followed by the abstract page, summarising in less than 200 words the reasons for the study, experimental approach, the major findings (with specific data if possible), and the principal conclusions, and providing 3-6 key words for indexing purposes. The text of the report should then proceed as follows:

Introduction should describe the background of the investigation, citing only the essential references and stating the aim of the study.

Material and methods should provide enough information to enable experiments to be repeated. New methods should be described in detail. Research on human and animal subjects should indicate that ethical approval of the study was obtained.

Results should be presented clearly and concisely without repeating the data in the tables and figures. Emphasis should be on clear and precise presentation of results and their significance in relation to the aim of the investigation.

Discussion should explain the results, and not simply repeat them, interpret their significance and draw conclusions. It should review the results of the study in the light of previously published work.

Illustrations and tables: All illustrations and tables must be numbered and referred to in the text, with appropriate location indicated in the text margin. Illustrations must be labelled on the back with the author's name, figure number and orientation, and should be accompanied by a descriptive legend on a separate page. Line drawings should be supplied in a form suitable for high-quality reproduction. Photographs should be glossy prints of high quality with as much contrast as the subject allows. They should be cropped as close as possible to the area of interest. In photographs mask the identities of the patients. Tables should be typed with double spacing with descriptive title and, if appropriate, units of numerical measurements included in column heading.

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

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

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

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