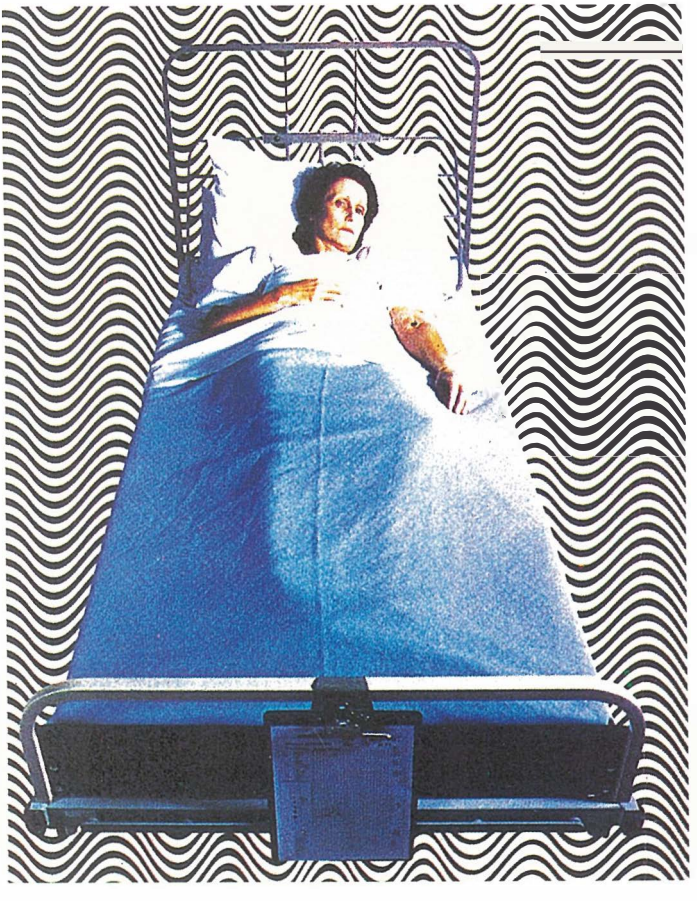
RADIOLOGY AND ONCOLOGY

1995
Vol. 29 No. 3
Ljubljana

ISSN 1318-2099
UDC 616-006

POOPERATIVNA SLABOST IN BRUHANJE

NELAGODJE IN STISKA
OGROŽATA USPEH OPERATIVNEGA POSEGA



PREPREČEVANJE
Ena sama intravenska injekcija po 4 mg pri uvajanju v anestezijo

ZDRAVLJENJE
Ena sama intravenska injekcija po 4 mg

Zofran
ondansetron

Glaxo

Podrobnejše informacije dobite pri: Glaxo Export Limited
Podružnica Ljubljana, Cesta v Mestni log 55,
61115 Ljubljana, p.p. 17, Slovenija
Telefon: (386 61) 123 10 70, 123 20 97, 123 23 19
Telefax: (386 61) 123 25 97

RADIOLOGY AND ONCOLOGY

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

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

Affiliated with
Societas Radiologorum Hungarorum
Friuli-Venezia Giulia regional groups of S.I.R.M.
(Italian Society of Medical Radiology)

Correspondence address
Radiology and Oncology
Institute of Oncology
Vrazov trg 4
61000 Ljubljana
Slovenia
Phone: + 386 61 1320 068
Fax: + 386 61 1314 180

Reader for English
Olga Shrestha

Design
Monika Fink-Serša

Key words und UDC
Eva Klemenčič

Secretaries
Milica Harisch
Betka Savski

Printed by
Tiskarna Tone Tomšič, Ljubljana, Slovenia

Published quarterly

Bank account number 50101 678 48454
Foreign currency account number
50100-620-133-27620-5130l6
Nova Ljubljanska banka d.d. – Ljubljana

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

According to the opinion of the Government of the Republic of Slovenia, Public Relation and Media Office, the journal RADIOLOGY AND ONCOLOGY is a publication of informative value, and as such subject to taxation by 5 % sales tax.

Indexed and abstracted by
BIOMEDICINA SLOVENICA
CHEMICAL ABSTRACTS
EXCERPTA MEDICA/ELECTRONIC PUBLISHING DIVISION

CONTENTS

INTERVENTIONAL RADIOLOGY

Laser angioplasty and thrombolytic treatment for femoral artery occlusion
Otto W, Rowiński O, Małkowski P, Paczkowski P, Pruszyński B, Karwowski A **185**

ULTRASOUND AND COMPUTERISED TOMOGRAPHY

Value of ultrasound in the diagnosis of acute appendicitis
Drinković I, Brkljačić B, Odak D, Hebrang A **190**

Color-Doppler in the diagnosis and postoperative follow-up of varicoceles
Drinković I, Brkljačić B, Stepanić V, Hebrang A **194**

Venous thrombosis of the portal system. Etiology, diagnosis and treatment – analysis of 225 cases
Małkowski P, Michałowicz B, Pawlak J, Otto W, Leowska E, Rowiński O, Paluszkiewicz R, Paczkowski PM, Zieniewicz K **198**

Direct sagittal computed tomography in diagnosis and treatment of internal derangements of the temporomandibular joint
Roić G, Klarić Jurković T, Pandurić J, Čop S **203**

EXPERIMENTAL ONCOLOGY

Changes in some collon mucosal cells after irradiation
Zorc-Pleskovič R **207**

Glutathione concentration and glutathione S-transferase activity in gynecological normal and tumor tissues: A preliminary report
Osmak M, Babić D, Abramić M, Miličić D, Bizjak L, Beketić-Orešković L, Čepulić E, Orešković S, Jukić S, Eljuga D **211**

CLINICAL ONCOLOGY

High rate of complication in patients with carcinoma of the cervix surgicaly treated after radical radiotherapy
Fras AP **218**

Staging laparotomy for Hodgkin's disease in adults: One center experience
Vovk M, Šumi-Križnik T, Jenko-Fidler M, Petrič-Grabnar G, Kremžar M, Novak J, Senčar M, Zakotnik B, Vodnik-Cerar A, Jakšić B **223**

Electrochemotherapy with bleomycin. The first clinical experience on malignant melanoma patients
Rudolf Z, Štabuc B, Čemažar M, Miklavčič D, Vodovnik L, Serša G **229**

Cytostatic chemotherapy for small cell lung cancer in patients of age 75 years or older
Berzinec F, Kroslak M, Petricek S, Arpasova M, Kuzmova H **236**

RADIOPHYSICS

Analytical representations of clinical electron beam central axis depth doses
Wierzbicki W, Podgorsak EB **240**

COMMUNICATIONS

European Code Against Cancer
Boyle P, Primic-Žakelj M **248**

REPORT

Report from the ESO training course on tumor biology
Čemažar M **250**

NOTICES **253**

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

Fundacija doc. dr. J. Cholewa, Ljubljana; Inštitut za diagnostično in intervencijsko radiologijo, KC Ljubljana; Klinika za otorinolaringologijo in maksilofacialno kirurgijo, KC Ljubljana; Klinički zavod za dijagnostičku interventnu radiologiju, KBC Rebro, Zagreb; Onkološki inštitut, Ljubljana

Radiol Oncol 1995; 29: 185–9.

Laser angioplasty and thrombolytic treatment for femoral artery occlusion

Włodzimierz Otto,[1] Olgierd Rowiński,[2] Piotr Małkowski,[1] Paweł Paczkowski,[1] Bogdan Pruszyński,[2], Andrzej Karwowski[1]

[1] Clinic of General Surgery & Liver Diseases, [2] II Department of Rentgenodiagnosis, Medical Academy of Warsaw, Warsaw, Poland

Among 27 patients with femoral artery occlusion that were treated by transluminal Nd:YAG laser angioplasty, in 16 patients the procedure was combined with intraarterial infusion of rTPA (Actilyse – Boehringer Ing).
In 5 out of 11 patients from the initial group recanalization was not successful. In 16 patients from rTPA group satisfactory immediate results were achieved in all cases. In long time observations ranging from 9 to 24 months all patients remained free from symptoms, although in 4 out of them angiography and Doppler ultrasound examination reveal no flow in femoral artery. In the remaining 12 patients (75 %), the previously occluded artery is patent.
No complications of laser angioplasty nor intraarterial infusion of rTPA were noted in this series.

Key words: arterial occlusive diseases-therapy; femoral artery; thrombolytic therapy; angioplasty, laser

Introduction

Laser angioplasty is the new method of treatment in some cases of arteriosclerotic occlusion of peripheral arteries, resulted in ischemia of lower extremities.[1–4] Among different laser applicators, the Neodymium: Yttrium – Aluminium – Garnet laser (Nd:YAG) appeared to be the most suitable instrument for such procedure.[5–7] Compared to other lasers, the Nd:YAG is much more powerful and allows to perform angioplasty with sapphire or ceramic tips at the end of laser fiber. This contact method of laser recanalization is performed in different centers and generaly accepted, as presented in many publications.[8–10]

Many observations also indicate that mechanical or thermal methods of the artery recanalization should be combined with thrombolytic treatment. The recombinant tissue-type plasminogen activator (rTPA) seems to be the best agent in these cases, much more safe and effective that urokinase or streptokinase.[11–14]

We would like to present our own experience in the treatment of femoral artery occlusion with the method of laser angioplasty, combined in 16 cases with intrarterial infusion of rTPA.

Correspondence to: Wlodzimierz Otto, MD, Clinic of General Surgery & Liver Diseases, Medical Academy of Warsaw, Babacha la, 02-097 Warsaw, Poland

UDC: 616.137.87-005.6-08

Materials und methods

In the Clinic of General Surgery & Liver Dise-

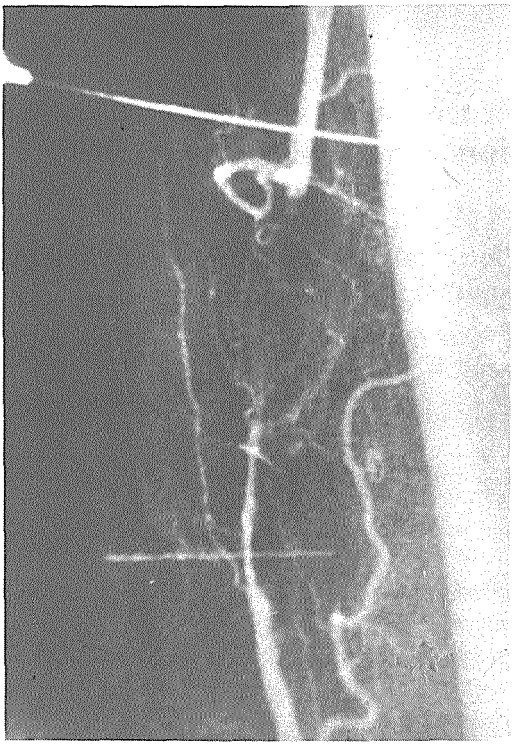


Figure 1. Initial arteriography just before recanalization.

ases and the II Department of Rentgenodiagnosis, Medical Academy of Warsaw, the procedures have been performed since 1991. We use SLT (Surgical Laser Technology), Nd:YAG laser and contact method of vaporization.

The laser fiber is introduced to the lumen of artery in antegrade fashion by Seldinger technique, and angiography is performed to localize precisely the proximal wedge of occlusion. Then the sapphire tip is positioned close to it under fluoroscopy. Recanalization is proceeded in step by step fashion with 8 to 12 watts, at 1 seccond of power output. The position of the laser fiber tip and the state of recanalization is continously observed under fluoroscopy during the time of procedure. Arteriography is made as well, by means of infusion of small amount of contrast medium after each step of recanalization (Figure 1).

When the recanalization of artery is successfully achieved, the laser fiber is passed through the place of occlusion for several times to enlarge lumen of recanalized artery and make the canal more smooth. Despite of successful laser recanalization, the procedures were completed with baloon angioplasty in all cases (Figure 2, Figure 3).

The procedure was carried out in 27 patients, 20 males and 7 females. The average age was 58. In all cases the diagnosis was established by arteriography and ultrasound Doppler examination which indicated femoral artery occlusion, ranging from 2 to 16 cm in length. All patients suffered from ischemia of lower extremity for several weeks and were in II – III stage of ischemia, according to Fontain scale. All of them were excluded from operative treatment due to respiratory and circulatory insufficiency, or did not want to be operated upon. A day prior to the procedure, all patients received 3 tablets of aspirin. On the day of procedure, in the initial group of 11 patients we used heparin, administered as bolus injection in dose of 5000 u., followed after recanalization by intra-

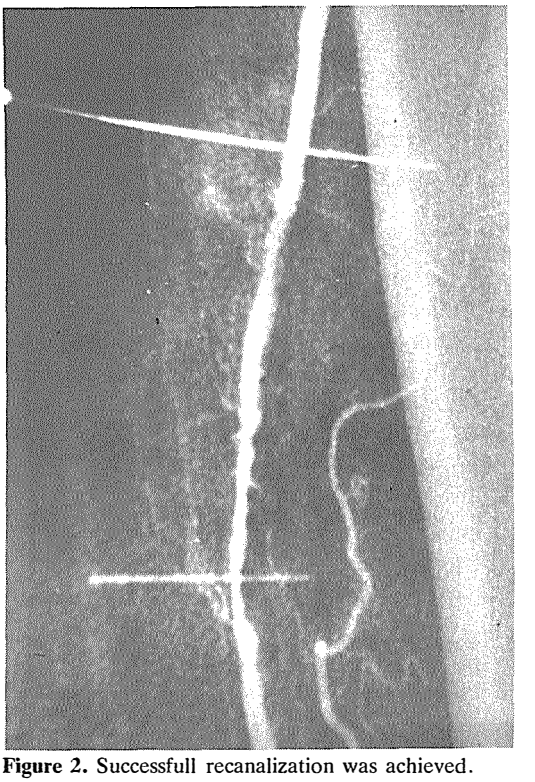


Figure 2. Successfull recanalization was achieved.

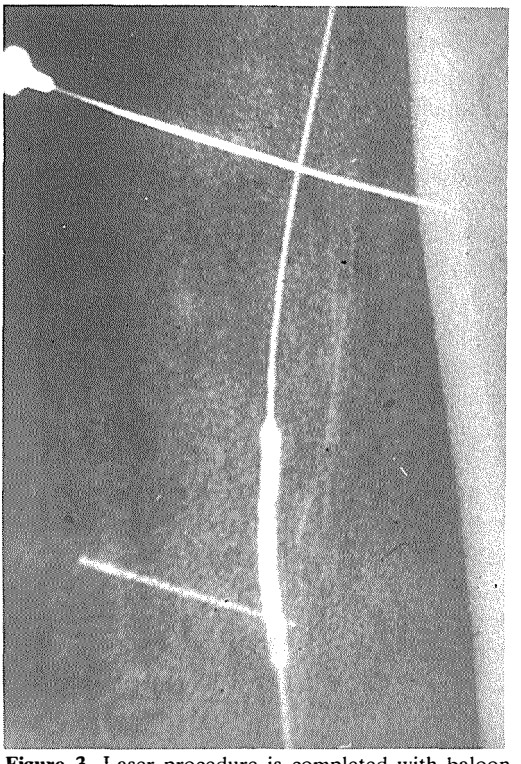


Figure 3. Laser procedure is completed with baloon angioplasty.

venous infusion of heparin in dose of 1 000 u./hour during 2–3 days.

In the next group of 16 patients laser angioplasty was followed by infusion of rTPA (Actilyse – Boehringer Ing.) in dose of 2 mg / hour administered intraarterial during 10 hours.

All patients were treated subsequently with dicumarol and the flow through the femoral artery was controlled by clinical and Doppler ultrasound examination.

Results

In the initial group of 11 patients, treated with laser angioplasty and heparin, in 5 patients the procedure failed. In 3 of them perforation of the artery occured, resulting in immediate leg amputation in 2 patients. In 2 others laser recanalization was not successful, followed the amputation of extremity soon. Two patients died.

In 6 patients successful recanalization of the artery was achieved and they were discharged from hospital free from symptoms.

In the group of 16 patients, treated with laser-baloon angioplasty and the infusion of rTPA, complications have not been noted. Full recanalization of artery and the release of symptoms was achieved in all cases, as confirmed by arteriography done at the end of procedure in each patient (Figure 4, Figure 5).

All patients who underwent successfuly recanalization, remained free from symptoms from 9 to 24 months, averagely 9 months. As confirmed by Doppler ultrasound examination, the

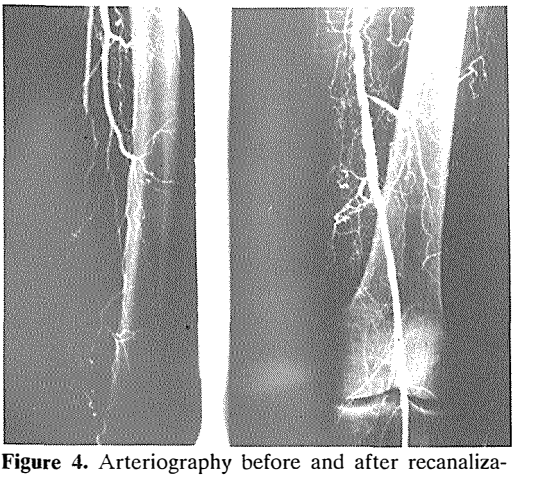


Figure 4. Arteriography before and after recanalization in patient with femoral occlusion.

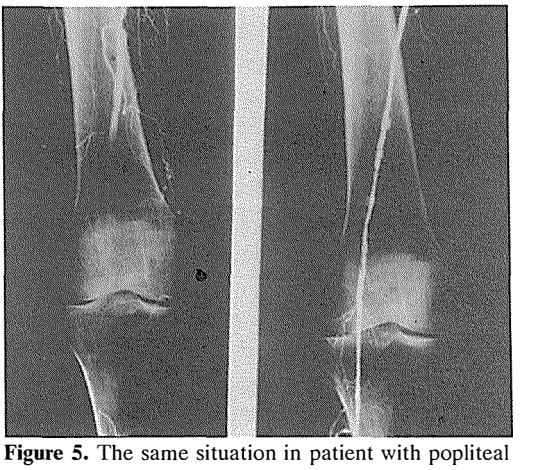


Figure 5. The same situation in patient with popliteal occlusion.

artery is patent in 70%, with normosystolic flow through the recanalized lumen. In 30%, Doppler usg indicates structure or partial reocclusion of artery, however, there are no syptoms of ischemia observed, at the distal part of the extremity in these patients.

Discussion

Transluminal laser-baloon angioplasty is a relatively new method of treatment, however, in few centers around the world hundreds of such procedures have been done successfuly. The observations indicate that the laser recanalization, especially when combined with thrombolytic treatment, may be as effective as surgery in some cases of artery occlussion due to arteriosclerosis.[1–3, 5, 7–9]

Our observations seem to confirm the others experience. Effective recanalization of the artery was achieved by contact Nd:YAG laser waporization in most of our patients. The best results were observed in the middle-aged patients, in whom the length of occlusion did not exceed 7–8 cm and was localized in canal of Hunter. The longer occlusions and occlusions localized in popliteal artery, especially in old patients were much more complicated.[15, 16]

The procedure of laser angioplasty is generaly free from pain, except the infusion of contrast medium. During procedure maximum attention must be given to the position of the laser tip inside the artery. All the time when the laser beem is applied, the tip should remain in touch with atheromatous plaques. The applieance of laser energy without close contact to the occluding changes increases thermal damage but dimishes the efficacy of vaporization and may cause perforation of the artery. Thus the laser fiber should be pushed very gently along the artery, always against the delicate resistance at the end of the fiber.

On the other hand, one should be very careful and not push the fiber too hard. It is relatively stiff and may produce mechanical perforation of the wall of artery. Pain that is felt by patients is usually the only one but the most important signal of perforation. This serious complication occured in 3 out of 11 patients from the first group, to whom laser angioplasty was applied initialy. Undoubtedly, uncomplicated recanalization that was achieved in the second group of 16 patients treated with additional infusion of rTPA should be related to increasing experience and more knowledge in the laser use. Also the patients were chosen to the procedure much more carefully, as well.

The perforation of artery is the most serious problem. Thermal and mechanical damager during the procedure are the most common reasons for this complication. The damage might be the result of faults in the laser tip construction resulting in non-axial distribution of emitted energy. More often it is caused by technical faults in the procedure itself. Nevertheless, it is not neccessary to terminate the procedure when perforation of the arterial wall occurs. According to ghe majority of observations the final outcome depends on successfull recanalization of the artery and restoring of normal blood flow distally to the occlusion. Therefore the procedure should be continued, unless recanalization could not be achieved.[1–4, 6]

The recanalized part of artery presents itself as an irregular canal. In some places strictures and persistent occlusions may be seen. They cannot be vaporized with the laser without the risk of artery perforation, so the procedure must be completed by baloon dilatation. This remains the golden standard of the laser angioplasty. The supposition that the arterial wall after laser recanalization is fragile and more prone to rupture from the baloon pressure is not confirmed by clinical observations.[5, 7–10]

It is currently proposed to combine thermal or mechanical angioplasty with additional thrombolytic therapy. The potency of different agents for thrombolysis and farmacologic recanalization of the artery occluded by atherosclerosis is well known. According to some observations recombinant tissue-type plasminogen activator (rTPA) presents the highest thrombolytic potency and is much more effective and safe than streptokinase or urokinase. Short time of activity of rTPA may be easely and effectively controlled, enable if neccessary, ope-

rative treatment also in emergency conditions. Indication for thrombolytic therapy is peripheral ischemia observed in some patient after angioplasty procedure. It may occur despite of successful recanalization of the main arterial trunk and is presumably caused by emboli in peripheral arteries due to remnants of arteriosclerotic plaques fragmented during the procedure. Therefore, thrombolytic treatment seems to be the logical support of transluminal angioplasty.[11–14]

Intrarterial infusion of rTPA (Actilyse Boehringer Ing.) was very well tollerated in our patients. No complications nor side effects were observed during the treatment. We did not observe any reoclusion nor peripheral thrombosis.

Our observations presented in this paper represent preliminary experience in the treatment of lower extremity ischemia due to arteriosclerosis with percutaneous, transluminal methods. The small number of patients does not permit us to draw definite conclusions. It seems, however, that transluminal laser-baloon angioplasty combined with thrombolytic treatment with rTPA is effective and may be an alternative to surgical treatment in selected cases.

Conclusions

1. Nd:YAG laser baloon angioplasty may be effective method of treatment in selected cases of femoral artery occlusion.
2. Additional intraarterial infusion of rTPA improves the effects of laser baloon angioplasty.

References

1. Bowker TJ, Cross FW, Bown SG, et al. Reduction of vessel wall perforation by the use of sapphire tipped optical fibres in laser angioplasty. *Br Heart J* 1987; **57:** 88–92.
2. Grundfest WS, Litvak F, Hickey A. Current status of angioscopy and laser angioplasty. *J Vasc Surg* 1987; **5:** 667–74.
3. Lee G, Ikeda RM, Chan MC. Limitations, risk and complications of laser recanalization. *Am J Cardiology* 1985; **56:** 181-6.
4. Lammer J, Pilger E, Kleinert R. Laser angioplasty by sapphire contact probe. *J Int Radiology* 1988; **1:** 478–86.
5. Lammer J, Pilger E, Karnel F, et al. Laser angioplasty: results of a prospective multicenter study at 3-year follow-up. *Radiology* 1991; **178:** 335-42.
6. Berengoltz-Zlochin SN, Westerhof PW, Rienks R, et al. Nd:YAG laser-assisted angioplasty in femoropopliteal artery occlusions: "hot" versus "cold" recanalization with transparent contact probe. *Radiology* 1992; **182:** 409–17.
7. Nosdstrom LA, Castaneda-Zuniga WR, Von Seegern KB. Peripheral arterial obstructions: analysis of patency 1 year after laser-assisted transluminal angioplasty. *Radiology* 1991; **181:** 515–21.
8. Rankin RN, Vellet AD, Munk PL. Excimer-laser-assisted angioplasty in chronic femoropopliteal occlusion: significance of an intimal flap in predicting reocclusion. *Canad Assoc Radiol J* 1993; **44:** 257–561.
9. Odink HF, de Valois HC, Eikelboom BC. Femoropopliteal artery occlusions: laser-assisted versus conventional percutaneous transluminal angioplasty. *Radiology* 1991; **181:** 61–9.
10. Huppert PE, Duda SH, Helber U, et al. Comparison of pulsed laser-assisted angioplasty and balloon angioplasty in femoropopliteal artery occlusion. *Radiology* 1992; **184:** 363–8.
11. LeBlang SD, Becker GJ, Benenati JF, et al. Low-dose urokinaze regimen for the treatment of lower extremity arterial ang graft occlusions: experience in 132 cases. *J Vasc Intervent Radiol* 1992; **3:** 475–9.
12. Feit F, Sherman D, Stecy P, et al. The thrombolysis in myocardial infarction (TIMI) trial. *N Engl J Med* 1985; **312:** 932–41.
13. Erbel R. Thrombolytic therapy and PTCA: acute and longtime results. In: Biamino G ed. Advances in Laser Medicine. First German Symposium on Laser Angioplasty. Berlin 1988; **1:** 34–5.
14. Schroder R. State of the art on thrombolysis in acute myocardial infarction. In: Biamino G ed. Advances in Laser Medicine. First German Symposium on Laser Angioplasty. Berlin 1988; **1:** 20–33.
15. Otto W, Gackowski W, Małkowski P. Wlew rTPA w laserowej angioplastyce tętnicy udowej. *Pamiętnik Zjazdu Chirurgii Klatki Piersiowej, Serca i Naczyń, T Ch P* Poznań 1992; **1:** 267–8.
16. Otto W, Gackowski W, Paczkowski P. Angioplastyka laserowa tętnicy udowej skojarzona z wlewem rTPA. *Pamiętnik Zjazdu T Ch P* 1993; **3:** 142-4.

Radiol Oncol 1995; 29: 190–3.

Value of ultrasound in the diagnosis of acute appendicitis

Ivan Drinković, Boris Brkljačić, Drago Odak, Andrija Hebrang

University hospital "Merkur" Center for ultrasound diagnostics, Department of Radiology, Zagreb, Croatia

Acute appendicitis is the most common surgical disease. Incidence of appendectomies performed for suspected acute appendicitis is rather high, although some other diseases may mimick appendicitis. 10–30 % of appendectomies are performed unnecessarily. Using ultrasound diagnostics the number of unnecessary operations was reduced to 2.85 %, the number of nonrecognized cases of appendicitis to 7 %, while in 24.9 % of patients prepared for surgery due to the picture of acute appendicitis, another disease was found, and operation avoided. Ultrasound specificity was 94 %, sensitivity was 89 % and accuracy 90 %. Based on the results of our investigation, ultrasound examination of the appendix has proved to be highly recommendable as a routine method in the preoperative treatment for appendectomy.

Key words: Appendicitis ultrasonography

Introduction

Acute appendicitis presents the most common, though diagnosticaly very delicate indication for surgical operation. In spite of all clinical indications, as much as 30 % of patients with a suspected appendicitis are operated on without real need because some other disease was misinterpreted as appendicitis.[1,2]

Ultrasound diagnostics using high resolute transducers, suprapubic and transvaginal examination methods, the appendix compression technique, as well as the diagnostic criterion calling for appendix visualization, wall thickness greater than 4.0 mm and transudate formation all enable the high accuracy of the diagnosis of appendicitis and its attendant complications.[3–10]

Correspondence to: Ass. prof. Ivan Drinković Ph.D. M.D. University Hospital "Merkur", Zajčeva 19, Zagreb, Croatia

UDC: 616.346.2-002-073:534-8

The aim of this study was to evaluate transabdominal and intravaginal ultrasonography in the diagnosis of acute appendicitis, that is, to evaluate its role in preventing an operative procedure indicated by the incorrect diagnosis.

Materials and methods

During a 10-year period, in collaboration with the Emergency Surgical Service of the Department of Surgery, the "Merkur" University Hospital, 570 patients suspected of having appendicitis on the basis of clinical and laboratory findings, were ultrasonographically examined. After a complete examination, transabdominal ultrasonography together with an additional intravaginal ultrasonography in women, were performed using high resolute transducers.

Of 570 patients, 385 were submitted to operation, and 185 remained under frequent clinical follow-up in order to confirm or rule out appendicitis.

Ultrasonographic examinations were performed by three well-trained sonographers. No time limits for the examination were imposed, and the diagnostic criterion of appdenicitis called for the following parameters:

1. appendix visualization
2. dosed transducer compression and pain
3. wall thickness $>4{,}0$ mm
4. perityphlitic abscess visualization

The following equipment was used for examination : the Radius CF GI, RT 4000, RT 3600, RT 2800, all provided with 7,5 MHz transducers and the first two also with additional 7,5 MHz intravaginal transducers.

Results

During a 10-year study 570 patients with clinical symptoms of appendicitis, accompanied with increased temperature and leukocytosis, were examined. Using ultrasonography, acute appendicitis was suspected in 385 patients by the above mentioned criteria, while in 185 patients the diagnosis of appendicitis was ruled out or was uncertain.

Open or laparoscopic surgery was performed in 385 patients. In 11 patients ultrasound diagnosis was not accurate, the picture of appendicitis having been simulated by inflammatory bowel diseases, adentis, or inflammatory alterations in the small pelvis.

A hundred and eighty-five patients ultrasonographically diagnosed without the signs of appendicitis or with suspected appendicitis were followed-up intensively in the course of 5 days, and in 42 patients a clinical picture of appendicitis eventually developed, in some of them subsequently recognized at sonography. These 42 patients were submitted to surgery.

Sensitivity of the examination was 89 %, specificity was 94 % and accuracy 90 %.

Discussion

Despite the apparently manifested symptoms of appendicitis in most of the patients, the diagnosis of acute appendicitis can be difficult in a smaller group of patients including especially children, pregnant women and elderly people. Certain gastrointestinal diseases, genitourinary system diseases and obstretric and gynaecological diseases present particular problems in differential diagnosis.

Even with all laboratory and clinical examinations available 10–30 % of the patients diagnosed with appendicitis are operated on without a real reason as actually suffering from a disease other than appendicitis, eg. disease of some of the systems mentioned above.

Using ultrasonography the number of unnecessary operations on our patients was reduced to only 2.85 (11 %) of patients.

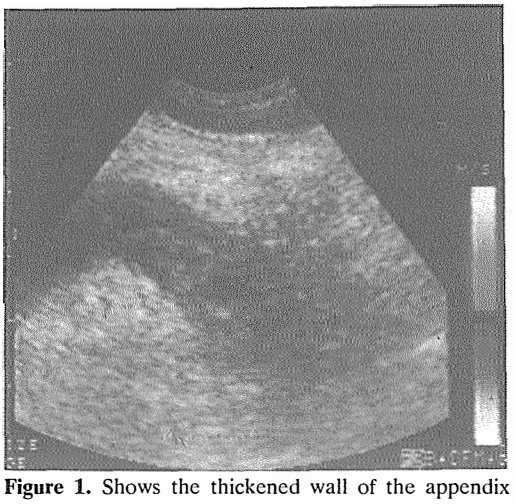


Figure 1. Shows the thickened wall of the appendix $>4{,}00$ mm.

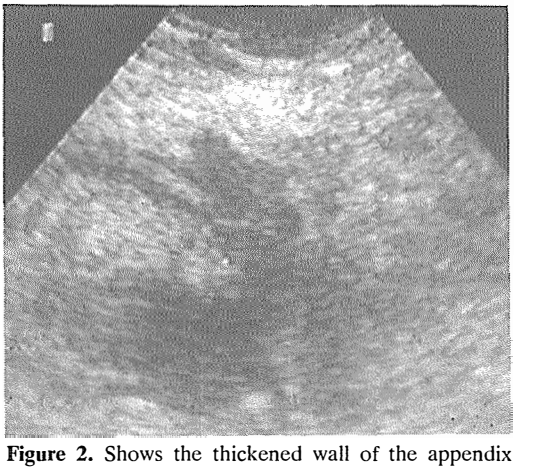


Figure 2. Shows the thickened wall of the appendix up to 4,0 mm with formed perityphlitic abscess.

It shoud be mentioned that ultrasonography prevented 185 patients (32.4%) from being operated on due to failure to recognize or establish a certain diagnosis of appendicitis, and that intensive follow-up of patients enabled a still timely operation in 42 of them (7%). thus avoiding possible complications.

The use of ultrasonography prevented an unnecessary operation in 142 (24.9%) patients.

When assessing acute appendicitis all clinical and laboratory parameters, as well as ultrasonographic parameters of inflammation including the wall thickness greater than 4.0 mm and liquid, ie. perityphlitic abscess formation should be observed. (Figure 1,2)

It is very important to use the dosed compression technique with appendix visualization, as well as pain registration, which additionaly improve examination accuracy.

Intravaginal ultrasonography was of great importance in diagnosing obstetric and gynaecological disorders in patients in whom it was not possible to diagnose appendicitis or the diagnosis was not certain at transabdominal ultrasonography. Uncertain ultrasonographic diagnoses of appendicitis despite well-founded clinical suspicion, indicate on the basis of our results, the necessity of intensive follow-up of patients in the subsequent several days because of the inability of ultrasound to approach the retrocoecal location and atipical site of the appendix, and the possibility of paretic and thickened bowel loops to simulate appendicitis.

According to our investigation, we recommend the ultrasonographic examination of acute appendicitis as a complementary diagnostic method which by its advantageous possibility of using the additional intravaginal examination technique in doubtful cases, provides a significant reduction of unnecessary surgical procedures.

In our study the use of intravaginal ultrasonography has significantly reduced the number of positive diagnosis of appendicitis in women which suggests that this examination method should be used in this population of patients paralel to suprapubic examination.[11]

Conclusion

Ultrasonographic examination of the appendix has become a complementary diagnostic method in the recognition of acute appendicitis.

It is of a particular importance in children, pregnant women, elderly people, and in all patients with atipical clinical presentation. The use of intravaginal transducer and the 7.5 MHz transducer in suprapubic examination improves the accuracy of the diagnostic procedure. This examination method reduced the number of unnecessary operations to only 2.5% of patients and was inefficient in the detection of appendicitis in only 7% of patients. Satisfactory specificity and sensitivity accompanied with sufficient accuracy argue for the desirability of the introducing ultrasonography in the routine examination procedure of acute appendicitis.

References

1. Wilson JL, JJ MC Donald. Abdominalna kirurgija – Kirurgija apendiksa. Med. knjiga Zagreb, 1969; 385–91.
2. Štulhofer M. Kirurgija probavnog sustava – Kirurgija apendiksa; 893–914.
3. Athey PA, Hacken JB, Estrada R. Sonographic appearence of mucocele of the appendix. *J Clin Ultrasound* 1984; **12:** 333.
4. Beyer D, Richer O, Kaiser C, Horsch S. Realtime-Sonographie bei akuten Appendizitis. Untersuchungstechnik – Sonomorphologie, Ergebnisse ciner prostektiven Studie, *Ultraschall Klin Prax* 1989; **4:** 124.
5. Drinkovič I, Brkljačić B, Boko H, Odak D, Vidjak V, Anić P. The treatment od appendiceal abscess by ultrasonically guided drainage. *Radiol Oncol* 1992; **26:** 96–8.
6. Hapke MR, Bigelow B. Mucocele of the appendix secondary to obstruction by endometriosis *Hum Pathol* 1977; **8:** 585–9.
7. Horgan JG, Chow PP, Richter JO, Rosenfield HT, Taylor KOW CT and sonography in the recognition of the mucocele of the mucocele of the appendix. *AJR* 1984; **143:** 959–62.
8. Hulek M, Vagner Z. Grose Mukozele der Appendix imitiert eine Ovarialzyste. *Zantralbl Gynahol* 1978; **100:** 186–186.
9. Rieber A. und Brambs H-J. Die Mukocele der Appendix in Ultrachall und CT. *Ultrachall Klin Prax* 1989; **4:** 26–7.

10 Richer OH, Beyer D, und Horsch S. Mukozele der Appendix abs Differentialdiagnose der akuten Appendizitis Sonographie und kliniche Bedeutung. *Ultraschall Klin Prax* 1991; **6:** 33–6.

11. Worrell JA, Leo F, Drolshagen, Thomas C. Kelly, David W. Hunton, Gudrn R. Durmon, Arthur C. Fleischer. Graded Compression Ultrasound in the Diagnosis of Appendicitis Ultrasound Med 1990; **9:** 145–50.

Radiol Oncol 1995; 29: 194–7.

Color-Doppler in the diagnosis and postoperative follow-up of varicoceles

Ivan Drinković, Boris Brkljačić, Vesna Stepanić, Andrija Hebrang

Center for Ultrasound Diagnostics, Department of Radiology, University Hospital Merkur, Zagreb, Croatia

Color-Doppler is a recent diagnostic method which besides palpation, ultrasonography, Doppler and phlebography is routinely used in the diagnosis of the varicocele of the testis, the disease which is the very common cause of sterility in males.
In 39 completely examined patients, we performed the color-Doppler analysis of varicoceles prior to and following the surgery, as well as the follow-up examination using phlebography.
Color-Doppler showed high sensitivity of 91 per cent and specificity of 83 per cent. At postoperative examination color-Doppler showed a persistent varicocele caused by accessory veins not visualized at phlebography in 6 per cent of patients.
The importance of color-Doppler examination as a routine preoperative and postoperative diagnostic method, is presented in this paper.

Key words: varicocele; ultrasonography, Doppler, color

Introduction

Varicocele is a disease caused by the incompetence of the valvular apparatus of the internal spermatic vein accompanied by compromised venous blood flow through the testes and increased temperature of the scrotum, which is considered the main cause of disorders in spermatogenesis.

It is the cause of sterility in as much as 40 per cent of infertile males,[1,2] and in fertile young males varicoceles can be found in 10–15 per cent of cases.[3–5]

Correspondence to: Ivan Drinković, M. D., Ph. D., Center for Ultrasound Diagnostics, Department of Radiology, University Hospital Mercur, I. Zajca 19, Zagreb, Croatia.

UDC: 616.147.22-073:534-8

The detection of a varicocele and its timely treatment can improve fertility in as much as 51–85 per cent of patients.

Besides other available methods the diagnosis of varicocele is also possible with color-Doppler, while the phlebography of the internal spermatic vein is the "golden diagnostic standard" in its detection.

In this study we present the value of color-Doppler in the detection of varicocele, as well as the feasibility of the application of this non-invasive method in determining the success of the operative procedure.

Materials and methods

In 39 patients treated endocrinologically for sterility varicocele was suspected as the main cause of sterility.

Besides endocrinologic tests, palpation, color-Doppler examination and phlebography of the internal spermatic vein were performed.

Positive finding on the phlebography of the internal spermatic vein was an indication for surgery, and 4 days following the procedure all patients operated on were examined by color-Doppler to evalute the result of the procedure, ie. the existence of accessory veins. Patients ranged from 24 years to 42 years in age.

Bimanual palpation of both testes was applied as the first diagnostic method. Color-Doppler examination in the prostrated and upright position with increased intra-abdominal pressure was performed after that. The same examination procedure was repeated 4 days after the surgery. The scanner Radius CF with a 7.5 MHz probe with possibility of low-velocity flow analysis was used.

Phlebography of the internal spermatic vein was performed using the standard technique: by introducing the catheter into the left then right internal spermatic vein and by their visualization with the radiologic contrast medium, followed by the determination of the venous insufficiency degree.

Varicoceles confirmed at phlebography were operated according to the Palomo method consisting of the high ligation of the artery and spermatic vein.

Results

Comparing clinical findings with the findings of color-Doppler examination and spectral analysis, ie. monitoring the direction of venous blood flow and the finding of phlebography as the gold standard, we found out that in 39 patients the clinical finding at inspection and palpation was a suspected or palpated incipient varicocele.

Retrograde blood flow, ie. a change of colour at the color-Doppler under increased abdominal pressure was visualized in 31 patients or 79 per cent, while in 8 patients or 20.5 per cent color-Doppler finding, ie. spectral analysis were not indicative of the existence of a varicocele. A follow-up phlebography, performed in all patients as a part of the routine preoperative treatment, revealed varicoceles in 33 patients (83.6 per cent), and normal finding in 6 patients (15.6 per cent).

The positive finding at phlebography was an indication for operative treatment, and 33 patients were operated on. Due to the possible incidence of accessory veins, ie. persistent varicocele, the color-Doppler examination was performed immediately after surgery to evaluate its success, as well as the accuracy of phlebography.

The value of ultrasonography in the preoperative treatment compared to phlebography showed sensitivity of 91 per cent and specificity of 83 per cent. In respect to phlebography 9.1 per cent were false negative, and 16.7 per cent were false positive.

Postoperative examination of 33 patients showed that phlebography failed to reveal aberrant veins in 2 patients (6 per cent), and that a varicocele persisted further as a consequence of venous drainage by veins which were not visualized by phlebography.

Discussion

Varicocele is a varicose condition of the veins of the pampiniform plexus mainly appearing on the left testis, and appearing also on the right testis, though in a smaller number of patients. Clinical symptoms can be different, varying from local discomfort to abnormal semenogram in younger males connected with infertility.

Diagnostic procedure of varicoceles can include palpation, termography, ultrasonographic examination, Doppler examination, color-Doppler examination and phlebography which is considered the golden standard for discovering varicocele, as well as for the gradation of varicoceles, resulting in the possibility of interventional therapy during the examination.[6]

Palpation has proved an uncertin method, especially in small varicoceles. In our study we compared color-Doppler finding with the finding of phlebography and spectral analysis of the Doppler curve and the result of monitoring the direction of blood flow with the contrast

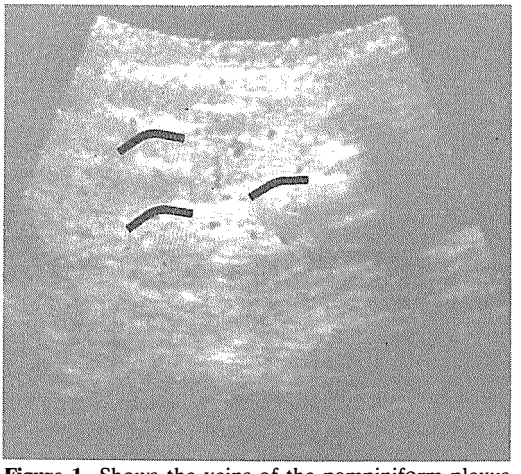


Figure 1. Shows the veins of the pampiniform plexus above the testes in which venous flow is discernible as blue colour, in this picture as dark shadows (arrows).

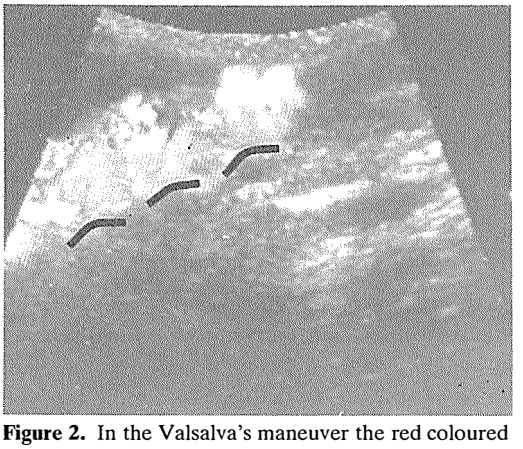


Figure 2. In the Valsalva's maneuver the red coloured pampiniform plexus is visualized above the testes which is shown in the black-and-white picture as a white shadow, and corresponds to the retrograde high velocity flow; it is an indication of the pampiniform plexus varicosity.

radiographic visualization of the spermatic vein. (Figure 1, Figure 2). By comparing these diagnostic modalities, the degree of their accuracy was found to be very similar. However, the advantages of color-Doppler are its non-invasiveness, low cost and little time needed to perform the examination.

In spite of phlebography being considered the golden standard in the diagnostics of varicoceles, color-Doppler examination must be additionally performed after phlebography, as well as after surgery because of its ability to discover the existance of a persistent varicocele, caused by the incompetence of the valvular apparatus in the accessory veins which often fail to be visualized at phlebography. High sensitivity and high specificity are comparable with the results of some other authors.[7–9]

Non-invasiveness of this diagnostic method, and good results in comparison with phlebography are suggestive of the need for introducing such examination into the diagnostic procedure as a routine method in young males with spermatogenesis disordes. In our study, unlike other diagnostic methods, especially palpation, color-Doppler has proved a much more reliable diagnostic method. Postoperative color-Doppler examination of the patients in whom varicoceles have been proved at phlebography, as well as at surgery, and of the patients treated by an interventinal radiographic procedure, is also mandatory because of the ability of color-Doppler to detect the existence of a persistent varicocele caused by the accessory veins which can further continue obstructing spermatogenesis.

References

1. Dubin L, Amelar RD. Etiologic factors in 1294 consecutive cases of male infertility. *Fertil Steril* 1971; **22:** 469.
2. Greenberg SH, Lipshultz LI, Wein AJ. Experience with 425 subfertile male patients. *J Urol* 1978; **119:** 507.
3. Uehling DT. Fertility in men with varicocele. *Int J Fertil* 1968; **13:** 58.
4. Charny CW, Baum S. Varicocele and infertility. *JAMA* 1968; **204:** 1165.
5. Oster J. Varicocele in children and adolescents. An investigation of the incidence among Danish school children. *Scand J Urol Nephrol* 1971; **5:** 27.
6. Ahleberg NE, Bartley O, Chidekel N, Fritjofsson A. Phlebography in varicocele scroti. *Acta Radiol Diagn* 1966; **4:** 517.
7. Petros JA, Andriole GL, Middleton WD, Picus DA. Correlations of testicular color - Doppler ultranosonography, physical examination and venography in the detection of the left varicoceles in men with infertility. *J Urol* 1991; **145:** 785.

8. Geatti O, Gasparini D, Shapiro B. A Comparison of scintigraphy, termography, ultrasound and phlebography in grading of clinical varicocele. *JNM* 1991; **32:** 2092.

9. Basile-Fasolo C, Izzo PL, Canale D, Menchini Fabris GF. Doppler-sonography, contact scrotal termography and venography: A comparative study in evaluation of subclinical varicocele. *Int J Fertil* 1986; **30:** 62.

Radio Oncol 1995; 29: 198–202.

Venous thrombosis of the portal system. Etiology, diagnosis and treatment – analysis of 225 cases

Piotr Małkovski,[1] Bogdan Michałowicz,[1] Jacek Pawlak[1], Włodzimierz Otto,[1] Elżbieta Leowska,[2] Olgierd Rowiński,[3] Rafał Paluszkiewicz,[1] Paweł M. Paczkowski,[1] Krzystof Zieniewicz[1]

[1]Department of General Surgery and Liver Diseases [2]Department of Nuclear Medicine [3]Department of Radiology, Medical Academiy, 02-097 Warsaw, Banacha 1a, Poland.

The authors present the material of 225 patients, treated since 1975, with various forms of portal system venous thrombosis (PSTV), of various origin and etiology. The largest group (120 patients) were the young people suffering from portal hypertension due to pre-hepatic venous obstruction of uncertain etiology, lasting since childhood. The next group consisted of 75 patients with liver cirrchosis coexisting with PSTV. In other cases PSVT was diagnosed as coincident with: Budd-Chiari Syndrome (8 cases), liver tumors (9 cases), chronic pancreatitis (3 cases), and polycythemia (2 cases). In 3 cases PSVT developed postoperatively and in 5 was the result of oral contraceptives. The course of the disease depended on extensivity and dynamism of thrombosis, but consequently led to the development of portal hypertension. The most effective diagnostic procedures were: computed tomography (CT) and ultrasonography Doppler flowmetry (SG), detecting PSVT in 96 % and 95 % of cases, respectively. Bleeding esophagal varices required either sclerotherapy (152 cases) or surgical treatment-decompressive shunts (26 cases) or »non-shunts« procedures (20 cases). In the cases of recent thrombosis, without bleeding varices, thrombolytic therapy was effective in all 6 cases.

Key words: portal vein: thrombois

Introduction

Portal system venous thrombosis (PSVT) was believed to be a rare phenomenon. Not more than 1000 cases of this pathology have been reported in the literature since 1901.[1–6] Recently, thanks to the development of noninvasive diagnostic imaging procedures (Doppler ultrasound and dynamic CT-scan) the diagnosis of PSVT is being established much more frequently.[3,5,7–10]

UDC: 616.147.4-005.6

Liver cirrhosis is recognised as the most common condition coexisting with PSVT.[1,3,6] Decrease of the portal blood flow is probably the main factor enhancing the development of thrombosis.[4,6,9] The frequency of PSVT in cirrhotic patients is estimated by different authors at 5 to 25 per cent.[1,3,6,9] The clinical features of liver cirrhosis coexisting with PSVT (»double block« of portal flow) do not essentially differ from those of portal hypertension caused by cirrhosis alone. The dominating symptoms are: large esophageal varices with high bleeding tendency and progressive impairment of liver function.[1,6,9]

The other conditions predisposing to PSVT are liver tumours (often accompanying liver cirrhosis), carcinoma of the gallbladder, pancreas and stomach, inflammatory processes within the abdominal cavity (pancreatitis, peritonitis, Crohn disease).[3,9,11–13] In liver tumours thrombosis involves mainly the intrahepatic branches of the portal vein,[12,14] while in the other cases its' main trunk and splenic vein.[13] The less frequent causes of PSVT are trauma, including iatrogenic lesions at the time of surgery (most commonly splenectomy)[15,16] and hypercoagulation conditions (puerperium, polycythaemia, paroxysmal nocturnal hemoglobinuria and congenital antithrombin III deficiency).[16,17] More recently the coexistence of PSVT with Budd-Chiari syndrome was reported.[16,18] The increasing incidence of PSVT in young women using oral contraceptives is also noteworthy.[7,16,18,19]

In a considerable number of cases of PSVT the etiology remains unknown.[16,20] It concerns most of patients treated for portal hypertension due to pre-hepatic obstruction of portal flow, second, after cirrhosis, reason of gastroesophageal varices.[21,22] According to some authors the role of neonatal umbilical infection, resulting in umbilical and portal thrombosis is overestimated.[16,21] Retrospective investigations, only in some cases of pre-hepatic block, have proved it's relationship to umbilical infection or thrombosis.[21,22] Anyway, the etiology of pre-hepatic portal obstruction remains unclear.[16,21]

In the symptomatology of PSVT, apart from the symptoms of primary disease (if present) the clinical features of portal hypertension dominate. These include extensive collateral venous circulation, gastroesophageal varices, and splenomegaly accompanied sometimes by abdominal pain, ascites and jaundice. Their intensity depends upon the degree of hemodynamic disorders of the portal venous system.[1,6,9,13,16,20]

Material and methods

From 1975 to 1993 the diagnosis of PVST was established in 225 patients treated in the Department of General Surgery & Liver Diseases of Warsaw Medical Academy. There were 100 females and 125 males aged from 17 to 74 (mean 38 years). In 197 cases the reason of admission was active or controlled bleeding from esophageal varices, accompanied in 35% of patients by symptoms of liver function impairment (jaundice, ascites, coagulopathy). Some of these patients had a long history of portal hypertension. Other indications for admission were: suspected liver tumour (9 cases), chronic pancreatitis (3 cases), upper abdominal pain (6 cases), ascites of unknown origin (6 cases), splenomegaly alone (3 cases) and ultrasonographic suggestion of portal vein obstruction (1 case).

All actively bleeding patients were treated by esophageal balloon tamponade and/or emergency sclerotherapy with simultaneous i. v. infusion of Vasopressin. As soon as the bleeding was controlled and the patients recovered, they were submitted (except the previously diagnosed patients) to diagnostic procedures including Doppler sonography (SG-94 pts), CT-scan (CT-62 pts), celiac arteriography with venous phase (61 pts) and splenoportography (SPG-4 pts).

Subsequently the patients were treated either surgically (26 decompressive shunting procedures and 20 non-shunt operations) or by repeated endoscopic sclerotherapy. Patients with portal and spenic vein thrombosis due to chronic pancreatitis were treated conservatively. In 5 patients with liver tumors a partial hepatectomy was performe (in 4 cases the tumour were inoperable). Two patients with polycythaemia were referred to Hematology Department for chemotherapy.

All patients with recent PSVT admitted during 1975–1980 (3 with coexisting hepatic vein thrombosis and 2 with portal trunk thrombosis alone) were treated conservatively. Further 8 patients, hospitalised after 1980, were submitted to thrombolytic treatment with Streptokinase (3 cases) and recently with recombinant tissue plasminogen activator (rt-PA, Actilyse).

The analysis of the above presented group of patients with PSVT included the results and reliability of diagnostic imaging procedures and results of treatment regarding the etiology of

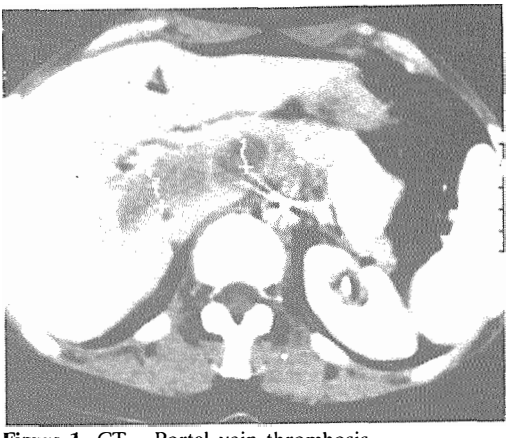


Figure 1. CT – Portal vein thrombosis.

PSVT or coexistence with predisposing diseases.

Results

SPG showed the presence of portal obstruction in each of 4 cases. The venous phase of arteriography was conclusive in only 38/61 cases (62%). Apart from the SPG, which is not performed now, the highest reliability was attributed to SG and CT (Figure 1), detecting PSVT in 90/94 patients (96%) and 59/62 cases (95%) respectively.

Results of various methods of treatment in particular groups of patients are presented in Table 1.

Discussion

The most numerous was the group of patients presenting clinical symptoms of portal hypertension due to pre-hepatic venous occlusion, in whom the diagnosis of PSVT was established in childhood and followed by long-lasting treatment including surgery and sclerotherapy. After having grown up they have been referred to us by pediatric centers for continuation of treatment. Most of them are young people in good general condition, often with partly recanalized portal system. They require, however, permanent medical attendance and (not infrequently) repeated sclerotherapy.[21,22] Regarding their past history, only few of them can be considered as candidates for surgical treatment. In our experience only in 5 cases we were able to perform a venous shunt; 2 patients with uncontrollable recurrent variceal bleeding required a non-shunt surgery (splenectomy with gastroesophageal devascularisation, esophageal stapling). Generally, the results of treatment in this group are satisfactory, fatal cases of uncontrollable hemorrhage bein rare.[21,22]

The coexistence of PSVT with liver cirrhosis ("double block") deteriorates the prognosis.[1,6,9,16] Gastroesophageal varices are usually very large and the frequency of recurrent massive bleedings, followed by hepatic insufficiency is remarkably higher compared to other cases

Table 1. Results of various methods of treatment in particular groups of patients.

Number of patients	Etiology or coexisting disease	Sex		Treatment					Hospital deaths
				Surgical		Non-surgical			
		F	M	Shunt	Non shunt	ES,S–B,V	Thrombolytic	Other	
75	Liver cirrhosis	23	52	21	8				16 (55%)
						46			9 (20%)
120	Unknown etiology	62	58	5	12				1 (5,8%)
	PSVT since childhood					103			4 (3,8%)
9	Liver tumors	3	6			5	2	4	2
8	Budd-Chiari	6	2					3	3 (100%)
	syndrome						3 SK, 3 rtPA		0
5	Oral contraceptives	5						2	2 (100%)
							3 rtPA		0
2	Polycythaemia		2					2	0
3	Intraoper. trauma	1	2			3			0
225	Total	100	125						

S-B = Balloon tamponade, V = Vasopressin infusion, SK = Streptokinase, rtPA = Actilyse, ES = Endocsopic sclerotherapy.

of portal hypertension.[1,9] It was proved that the percentage of rebleedings and postoperative deaths is three times higher compared with patients with portal hypertension caused by liver cirrhosis alone.[9] Intensive sclerotherapy improves the results of treatment of patients with "double block".[9]

In the group of patients with liver tumours there were 4 cases of hepatoma in the cirrhotic liver. Two patients required sclerotherapy. The resectability of the lesion depended on dimensions of the tumour itself, as well as the extent of intrahepatic portal thrombosis. The final intraoperative estimation has significantly improved since the intraoperative sonography is used. It enables the exact identification of the affected parts of the liver tissue and occluded branches of portal vein.[13,14]

Our patients with PSVT and chronic pancreatitis, as well as those observed by other authors, did not require any special treatment.[13] Splenomegaly observed in 2 cases and ascites in 1 case, were slowly decreasing during 2 years of follow-up, as the recanalization of occluded veins progressed.

Chemotherapy (Hydroxycarbamide) administered to patients with polycythaemia led to regression of thrombotic occlusions after 6 and 9 months with decrease of ascites. One patient with PSVT, caused by intraoperative lesion required sclerotherapy. In these cases thrombosis did not result in total portal occlusion and severe hemodynamic disorders, which explains a relatively mild course of the disease.

Much more dramatic course, despite the initially slight symptoms, was observed in patients PSVT, coexisting with trombosis of hepatic veins. All of 3 conservatively treated patients died of progressing liver failure and massive variceal bleeding. Better results were achieved by thrombolytic treatment – Streptokinase in 3 and rt-Pa in 2 cases.[7,18] Significant clinical improvement appeared in the first day of treatment with rt-PA and after 2–3 days of Streptokinase therapy. Although the full recanalization of the occluded veins was not recorded, the Doppler flowmetry allowed to document a significant increase of both portal and hepatic venous flow.

Thrombolytic therapy with rt-PA was also administered in 3 cases of isolated portal thrombosis caused by oral contraceptives. All these women had a short history (less than 1 month) of abdominal pain, splenomegaly and slight ascites.[7] Also in these cases the therapy was started at the moment of diagnosis and resulted in rapid clinical improvement. In no case an immediate full recanalization of the thrombosed veins was seen at SG, but progressing improvement in portal flow was recorded at repeated Doppler examinations. After two years all 3 patients are doing well, with proved repermeabilisation of the portal system and hepatopetal blood flow. It has to be stressed that in none of our patients with esophageal varices thrombolytic therapy caused variceal bleeding.

Conclusions

The etiology of PSVT is not uniform, in many cases it remains unknown. In cirrhotic patients the diagnosis of coexisting PSVT seriously deteriorates the prognosis. Clinical features of PSVT vary in dependence upon the extensiveness and dynamism of thrombotic process, but sooner or later portal hypertension develops with all its consequences.

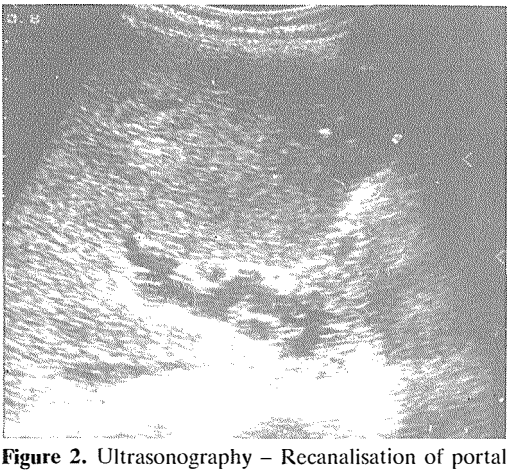


Figure 2. Ultrasonography – Recanalisation of portal vein.

The most effective diagnostic methods are SG and CT, with preference for SG (Figure 2) because of it availability and safety. Repeated SG allovs a systematic monitoring of the disease and treatment results. In the cases of recent thrombosis early diagnosis enables effective treatment.

In our opinion, every case of recent, progressing PSVT requires thrombolytic tgreatment, as the only means to achieve radical improvement, if not full recovery.

References

1. Belli R, Romani F, Sansalone CV et al. Portal thrombosis in cirrhotics. A retrospective analysis. *Ann Surg* 1986; **203:** 286–91.
2. Bockus HL. Diseases of the hepatic vessels and Cruveilhier-Baumgarten syndrome. In: *Gastroenterology.* Philadelphia, London: WB Saunders, 1949; 224.
3. Nonami T, Yokoyama I, Iwatsluki S, Starzi TE. Vein thrombosis at liver transplantation. *Hepatology,* 1992; **16:** 1195–998.
4. Okuda K, Ohnishi K, Kimura K et al. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. *Gastroenterology* 1985; **89:** 279–86.
5. Perisic M, Colovic R, Milosavljevic T, Ivanovic L. Splenic vein thrombosis diagnosed with Doppler ultrasonography. *Hepato-gastroenterol* 1991; **38:** 557–60.
6. Sarfeh IJ, Portal vein thrombosis associated with cirrhois. *Arch Surg* 1979; **114:** 902–5.
7. AL Karawi MA, Quaiz M, Hilali A et al. Mesenteric vein thrombosis. Non-invasive diagnosis and follow-up and non-invasive therapy by streptokinase and anticoagulants. *Hepato-gastroenterol* 1990; **37:** 507–9.
8. Haddad MC, Clark DC, Sharif HS et al. MR, CT and ultrasonography of splanchnic venous thrombosis. *Gastrointest radiol* 1992; **17:** 34–40.
9. Małkovski P, Michałowicz B, Pawlak J et al. Diagnosis and treatment of portal hypertension caused by concomittant liver cirrhosis and thrombosis of the portal vein. *Pol Przegl Chir* 1993; **65:** 131–8.
10. Tessler FN, Gehgring BJ, Gomes AS et al. Diagnosis of portal vein thrombosis: value of color Doppler imaging. *AJR* 1991; **157:** 293–96.
11. Brinberg DE, Stefansson TB, Greicius FA et al. Portal vein thrombosis in Crohn's disease. *Gastrointest Radiol* 1991; **16:** 245–7.
12. Kumada H, Ozawa K, Okamoto K et al. Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. *Surgery* 1990; **108:** 821–7.
13. Rattner DW, Warshaw AL. Venous, biliary and duodenal obstruction in chronic pancreatitis. *Hepato-gastroenterol* 1990; **37:** 301–6.
14. Lygidakis NJ, Makuuchi M. Clinical applications of perioperative ultrasonography in liver surgery. *Hepato-gastroenterol* 1992; **39:** 232–6.
15. Henderson JM, Millikan WJ, Chipponi J et al. The incidence and natural history of the portal vein following distal splenorenal shunt. *Ann Surg* 1982; **196:** 1–7.
16. Abbitt PL. Portal vein thrombosis: imaging features and associated etiologies. *Curr Probl Diagn Radiol* 1992; **21:** 115–47.
17. Valla D, Casa Deuvall N, Lecombe CF. Primary myeloproliferative disorders and hepatic vein thrombosis. *Ann Intern Med* 1986; **103:** 329–
18. Pawlak J, Palester-Chlebowczyk M, Michałowicz B et al. Thrombolytic treatment of the Budd-Chiari syndrome with portal venous thrombosis. *Pol Arch Med Wewn* 1993; **89:** 171–7.
19. Valla D, Lee MG, Poynard T. Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives. *Gastroenterology* 1986; **90:** 807–
20. Sugiura N, Matsutani S, Ohto M et al. Extrahepatic vein obstruction in adults detected by ultrasound with frequent lack of portal hypertension signs. *J Gastroenterol Hepatol* 1993, **8:** 161–7.
21. Voorhees AB, Price JB. Extrahepatic portal hypertension. A retrospective analysis of 127 cases and associated clinical implications. *Arch Surg* 1974; **108:** 338–41.
22. Pinkerton JA, Holcomb GW, Foster JH. Portal hypertension in childhood. *Ann Surg* 1972; **175:** 870–6.

Radiol Oncol 1995; 29: 203–6.

Direct sagittal computed tomography in diagnosis and treatment of internal derangements of the temporomandibular joint

Goran Roić,[1] Tatjana Klarić Jurković,[2] Josip Pandurić,[2] Slavko Čop[1]

[1] Children's Hospital, Zagreb, Croatia, [2] School of Dentistry, Department of Removable Prosthodontic, Zagreb, Croatia

Direct sagittal computed tomography (CTI), as a diganostic modality in the diagnosis and treatment of internal derangements of the temporomandibular joint (TMJ), is reviewed. Direct sagittal CT demonstrates well the position and functioning of the TMJ disc and is an excellent non-invasive diagnostic aid when using dental splint therapy to treat disc disfunctions and internal derangements of the temporomandibular joint. Furthermore, this practicable non-invasive method allows direct visualisation and evaluation of the TMJ disc, bony structures and particular soft-tissue.

Key words: temporomandibular joint diseases; tomography, x-ray computed

Introduction

Temporomandibular joint (TMJ) dysfunction causes a variety of symptoms in the masticatory system and kynesiologically related regions of the body, particulary in the cranial and cervical regions.[1–3] The main symptoms described in the literature are: temporomandibular sounds, sensitivity or pain in the masticatory muscles, temporomandibular joint pain, impaired mobility of the mandible and irregular path of movement of the mandible.[4] Headache and facial pain are often described as being connected with functional disturbances of the masticatory system.[5,6] Conventional radiographic methods do not permit adequate evaluation of this complex joint. The use of computed tomography has been found to be superior to conventional radiography and tomography in evaluating internal derrangements of the TMJ.

Correspondence to: Dr. Goran Roić, Department of Radiology, Children's Hospital, Klaićeva 16, 41000 Zagreb, Croatia. Phone: +3841441611.

UDC: 616.724-073.756.8

Two techniques of computed tomography of the TMJ have been described. Helms et al.[7] use multiple axial images of the TMJ, with computerized reconstructions in the sagital plain (Figure 1). Since the resolution of recon-

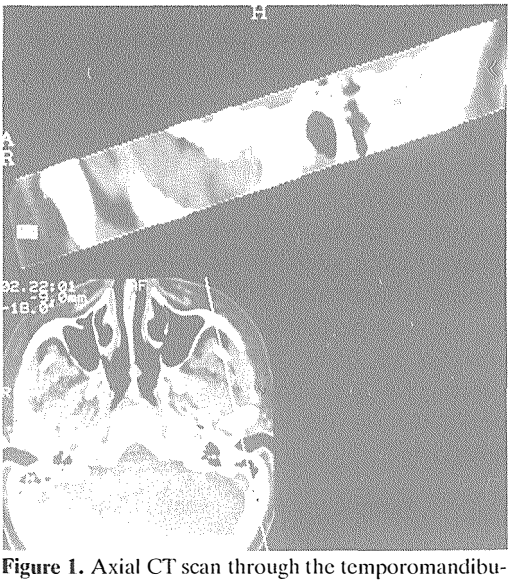


Figure 1. Axial CT scan through the temporomandibular joint with sagittal reconstruction.

structed CT images is usually less than that of slices imaged in the primary direction, it has proved more useful to perform TMJ scanning using a direct sagittal projection.[8,9] CT can show the position of the meniscus relative to the condyle and articular eminence, without the need of injecting intraarticular radiopaque contrast media. The meniscus, as seen during CT imaging, has a density greater than the adjacent pterygoid musculature and surrounding adipose and connective tissue.[9]

Anatomy of the TMJ

The TMJ is a complex synovial articulation between the mandibular condyle and the mandibular fossa of the temporal bone. Interposed between the head of the condyle and the surface of the temporal bone is a biconcave articulating disk, or meniscus, that serves as a buffeting pad between the head of the condyle and the temporal bone. The meniscus is thin in the center (1 mm) and thick peripherally (2,8 mm posteriorly and 2 mm anteriorly).[10]

Of radiographic interest is the relationship of the superior and inferior heads of the lateral pterygoid muscles. The superior head is attached to the meniscus, and the inferior head is attached to the neck of the condyle. Between the two heads of the lateral pterygoid muscle is a layer of adipose and connective tissue.[9] This structure has been identified by Manzione who designated it "as the lateral pterygoid fat pad".[8,11] The fatty tissue serves as the anatomic basis for detection of internal derangements of the disk during CT imaging. CT can show fine anatomic soft tissue structures because of its sensitive discrimination of density. The low-density adipose tissue of the lateral pterygoid fat pad may be seen easily within surrounding complex of bony, cartilaginous and muscle tissues. When the meniscus is displaced anteriorly, the fat pad may be seen to be shifted anteriorly.[9]

Technique of CT examination

Direct sagittal computed tomography scanning of the TMJ provides exceptional detail of anatomic structures. Soft-tissue and bone algorithms, thin sections and multiple tomographic images can be used to obtain details of osseous structures and the intraarticular menisco-ligamentous complex. Positioning is of critical importance in this study. An attempt is made to minimize radiation to the orbit, especially to the lens of the eye. A sagittal scout view is obtained and cursor lines are placed through to the area of interest (Figure 2). The external auditory canal has been shown to be a helpful landmark for vizualizing the TMJ on the scout view. The patient must be turned to perform scans of the right and left sides.

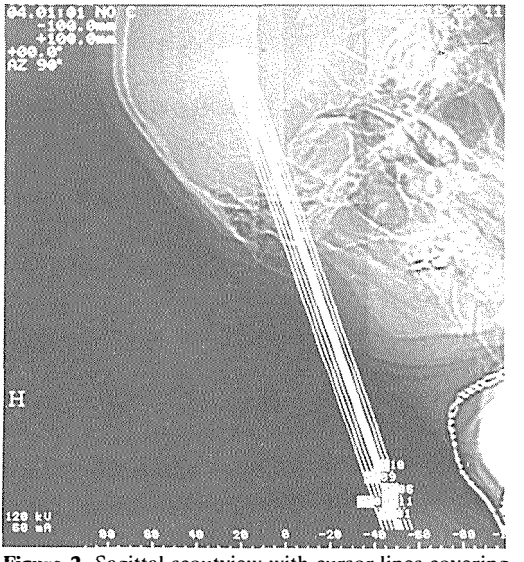


Figure 2. Sagittal scoutview with cursor lines covering the area of the TMJ. An attempt is made to avoid scanning within the orbit and especially to avoid the lens of the eye.

Radiographic evaluation of pathological changes of the TM

Internal derrangement of the TMJ is defined as disc disfunction and damage. Anterior disc displacement is the most common type in TMJ disc, disfunction. This category of disfunction is easiest to diagnose with CT scanning. Characteristically, meniscus density is seen in the anterior perycondylar space separated from the condyle by a few milimeters of intervening normal soft-tissue density.[10] According to the

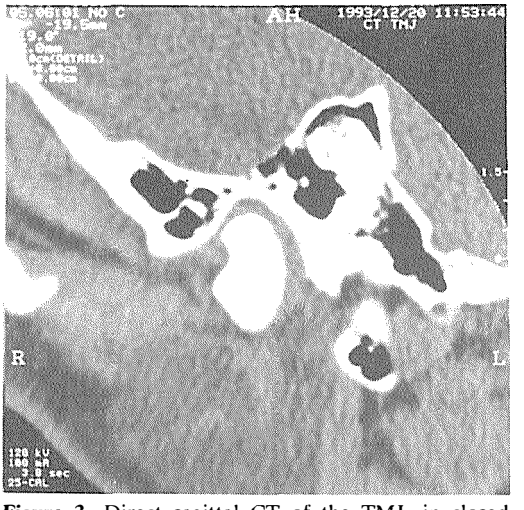


Figure 3. Direct sagittal CT of the TMJ, in closed position the disk is located anteriorly to the condyle – Anterior disk dislocation.

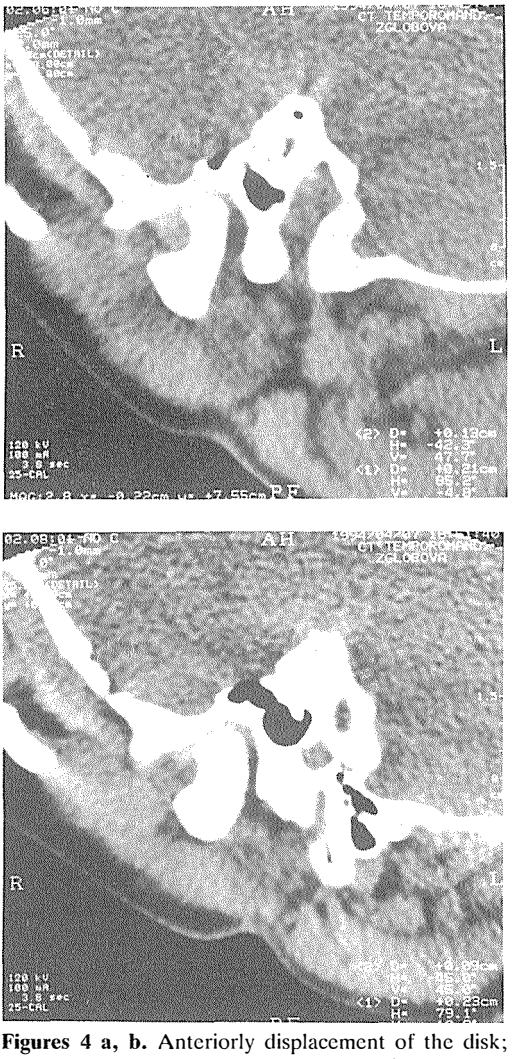
literature anterior displacement of the TMJ disc can be subdivided into displacement with reduction and without reduction.[12] Anterior disc displacement with reduction means that disc is abnormaly located when the condyle is in the closed position but resumes a normal position at some point in condylar motion.

Anterior disc displacement without reduction implies that the disc has migrated or slipped from its normal position between the articular surfaces of the mandibular condyle and temporal bone without reduction at any point during joint movement.

Anterior disc dislocation is a condition in which the meniscus density is seen in the anterior pericondylar space to varying degrees, depending on the amount of anterior displacement (Figure 3). This condition is generally preceded by a history of painful TMJ with clicking. Later, the patient notices that there is no click and may complain of a "locked jaw". Patients also experience limited jaw opening during this phase.

This is due to a lateral "balling up" of the meniscus in front of the condyle, which limits jaw opening because the condyle, impinges on the soft-tissue of the menisco-ligamentous complex. With time, most patients regain more normal jaw opening as they push the menisco-ligamentous complex forward with repeated openings.

Direct saggital computed tomography of tempotomandibular joints also allows the assessment of therapeutic effects of dental splint by analysing position and movements of the intraarticular disc and condyles as well as by direct measuring of the intraarticular distances (Figures 4 a, b). Mandibular anterior re-



Figures 4 a, b. Anteriorly displacement of the disk; recapturing with oral splint in place – a) the closed mouth view shows anteriorly displaced disk that appears as an area of increased density, b) the closed mouth view with the oral splint in place shows reduction of the disk to a normal location posteriorly.

positioning by dental splint therapy has been used successfully as a conservative treatment modality for anterior disc displacement with reduction and also in cases without reduction after mobilization of the TMJ.[10, 11, 13]

Conclusion

Computed tomography is a useful noninvasive method of imaging complex anatomic structures such as temporomandibular joint. Direct sagittal CT has proved to be an excellent method for the diagnosis of disc disfunction and internal derrangements of the TMJ. Scanning directly in the plain of interest provides images of better spatial resolution than reconstructed sagittal images. Furthermore, direct sagittal CT scanning allows noninvasive evaluation of the disc, bony architecture and paraarticular soft-tissue. CT is also a practical diagnostic aid at the follow-up stage after treating anterior disc displacement by dental splint therapy.

Used with clinical history and physical examination, CT is an excellent diagnostic modality that can provide information important for the better care for patients with internal derangement of the TMJ.

References

1. Friedman MH, Weisberg J. Application of orthopedic principles in evaluation of the temporomandibular joint. *Phys Ther* 1982; **62:** 597–603.
2. Friedman MH, Waisberg J. Pitfalls of muscle palpation in TMJ diagnosis. *J Prosthet Dent* 1982; **48:** 331–
3. Danzing WN, VanDayke, A, R. Physical therapy as as adjunct to temporomandibular joint therapy. *J Prosthet Dent* 1983; **49:** 96–9.
4. Helkimo M. Epidemiological surveys of dysfunction of the masticatory system. In: Zarb GA, Carlsson GE, eds. *Temporomandibular Joint – Function and dysfunction.* Copenhagen: Munksgaard, 1979: 175–92.
5. Gelb H, Bernstein I. Clinical evaluation of two hundred patietns with temporomandibular joint syndrome. *J Prosthet Dend* 1903; **49:** 234–43.
6. Reider CE, Martinoff. The prevalence of mandybular dysfunction. Part II: Amultiphasic dysfunction profile. *J Prosthet Dent* 1983; **50:** 237–44.
7. Helms CA, Vogler JB, Morrish RBJr, Goldman SM, Capra RE, Proctor E. Temporomandibular joint internal derangements: CT diagnosis. *Radiology* 1984; **152:** 459–
8. Manzione JV, Seltzer RW, Katzberg SB, Hammerschlag SB, Chiango BF. Direct sagittal computed tomography of the temporomandibular joint. *AJR* 1983; **140:** 165–7.
9. Hoffman DC, Berliner L, Manzione J, Saccaro R, McGivern BEJr. Use of direct sagitall computed tomography in diagnosis and treatment of internal derangements of the temporomandibular joint. *JADA;* **113:** 407–11.
10. Bell KA. Computed Tomography of the Temporomandibular Joint. In: eds. Palacios E, Valvassori GE, Shanon M, Reed CF. *Magnetic Resonance of the Temporomandibular Joint.* Stuttgart, Georg Thieme Verlag, 1990: 28–39.
11. Manzione JV, Katzberg RW, Brodsky GL, Seltzer SE, Mellins HZ. Internal derangement of temporomandibular joint: diagnosis by direct sagittal computed tomography. *Radiology* 1984; **150:** 111–5.
12. Raustia AM. Diagnosis and treatment of temporomandibular joint dysfunction. *Proc Finn Soc* 1986; **82** (Suppl IX–X): 9–41.
13. Raustia AM, Pyhtinen J. Direct sagittal computed tomography as a diagnostic aid in the treatment of an anteriorly displaced temporomandibular joint disk by splint therapy. *The Journal of Craniomandibular Practice* 1987; **5** (3): 241–5.

Radiol Oncol 1995; 29: 207–10.

Changes in some collon mucosal cells after irradiation

Ruda Zorc-Pleskovič

Institute of Histology and Embriology, Medical Faculty, University of Ljubljana, Slovenia

The aim of the present investigation was to study the histological and stereological changes in lymphocytes and mast cells after irradiation. For experimental model we used 20 Beagle dogs, 1–2 years old. Ten dogs were irradiated 20 days with 32 Gy onto the whole pelvis and tail. Another 10 dogs represented a control group.

Histological and stereological analysis were performed on a Wild sampling microscope M 501. In the nonirradiated group volume, numerical density and average volume of lymphocytes were significantly lower in comparison with the irradiated group. Volume density and average volume of mast cells were significantly lower in nonirradiated group. Numerical density of mast cells in this group was significantly higher.

The results of our experiments show that mast cells and lymphocytes in the intestinal mucosa are deeply involved in the tissue fibrosis occurring as the response to irradiation.

Key words: colon-irradiation effects; intestinal mucosa-pathology

Introduction

Several years after irradiation severe fibrous changes of the colon often cause for a surgeon an unsolvable problem in surgical intervention. The purpose of our study was to investigate experimentaly the histological and stereological changes in the colon occuring after irradiation in view of an early diagnosis and prevention of fibrosis. The intestinal epithelium is a tissue most sensitive to irradiation.[1,2,3] Individual cells in the intestinal mucosa such as lymphocytes and mast cells participate in the defense system of the body or in the protection against tumor invasion. Therefore we paid special attention to them in our study. The literature data describe changes in the intestinal mucosa,[1,4,5,6] yet no stereological data could be found in the available literature.

Correspondence to: doc. dr. Ruda Zorc-Pleskovič, Institute of Histology and Embriology, Medical Faculty, University of Ljubljana, 61000 Ljubljana, Slovenia

UDC: 616.348-001.29

Materials and methods

20 Beagle dogs weighting 8 to 13 kg, 1 to 2 years old were included in our study. Ten dogs were irradiated (I) with γ rays on telecobalt (Phillips) with 32 Gy over the pelvis region and tail. The size of the irradiated region on the skin was 10 × 15 cm. Ten dogs represented the nonirradiated group (N). Ten days after concluded irradiation, a 1-cm wide piece of colon transversum was excised from the middle third of the colon of the anesthetized dogs. Tissue was fixed in Bouin's fluid, embedded in paraffin

and cut in 5 μm step serial sections. The step section was 20 μm thick. The obtained preparations were stained with hematoxylin-eosin (HE), toluidine-blue and solution alcian blue (SAB) reaction.

An accurate histological analysis of the step serial sections was used to establish the changes in the mucosa of the colon in individual groups. The lymphocyte infiltration and presence, size, form as well as distribution of the mast cell's granules were studied.

Histological analysis[7] were performed on a Wild sampling microscope, using Weibel's test system. Volume density (V_v) of lymphocytes and mast cells were estimated at an objective magnification x40 using the M-42 test system. Numerical density (N_v) of I and m were estimated according to the Weibel-Gomez method at an objective magnification x40 using the M-100 test system. For these cells average volume was also calculated.

The results were statistically evaluated. Significant differences were determined by Student's "t" test.

Results

Histological analysis

In the N group lymphocyte infiltration of lamina propria in the intestinal mucosa was well expressed while in the irradiated group (I) there were some rare lymphocytes only in the connective tissue. The individual ones infiltrated the epithelium (Figure 1).

In the N group the mast cells were equally distributed in the connective tissue. Their cytoplasm was full of metachromatically stained granules. Oval nuclei were visible in the middle of cells (Figure 2). In the I group the mast cells were mainly in the connective tissue at a basal part of the cryptes. Their shapes were mainly irregular. Numerous metachromatic granules were dispersed around the cells (Figure 3).

Stereological analysis

In the N group all the measured stereological values of lymphocytes such as V_v (Figure 4), N_v (Figure 5) and average volume of the indi-

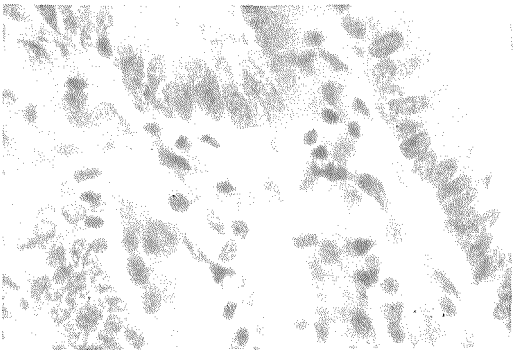


Figure 1. Rare lymphocytes in the irradiated group (HE, obj. 40×).

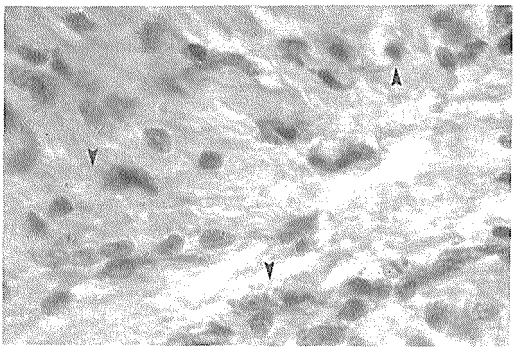


Figure 2. Degranulated mast cells in the intestinal mucosa in the irradiated group (SAB, obj. 40×).

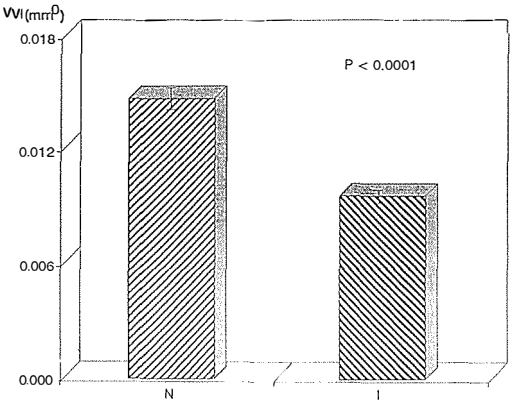


Figure 3. Volume density (V_{vl}) of lymphocytes in the nonirradiated (N) and the irradiated (I) group ($V_{vl} \pm 2SE$).

vidual lymphocytes V_I (Figure 6) were significantly lower in comparison with the I groups.

V_v of mast cells (Figure 7) and V_m mast cells (Figure 8) were significantly lower, while the N_v (Figure 9) was significantly higher in the N group compared to the I group.

Discussion

Stereological analysis of lymphocytes after irradiation revealed reduction of V_v, N_v and V of lymphocytes. This demonstrates that irradiation reduces the number and the size of the cells.

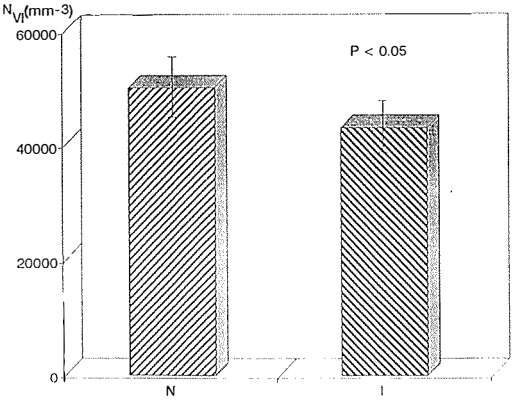


Figure 4. Numerical density (N_{vl} of lymphocytes in the nonirradiated (N) and the irradiated (I) group ($N_{vl} \pm 2SE$).

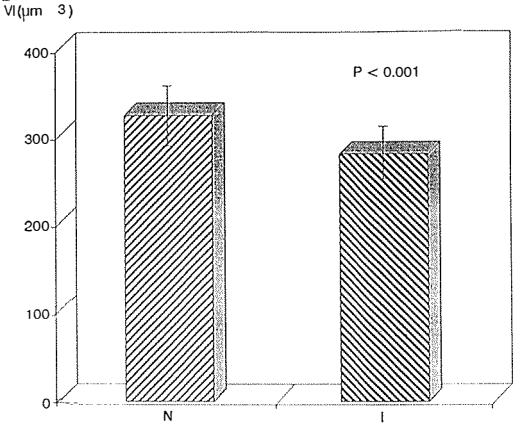


Figure 5. Average volume (VI) of lymphocytes in the nonirradiate (N) and the irradiated (I) group ($VI \pm 2SE$).

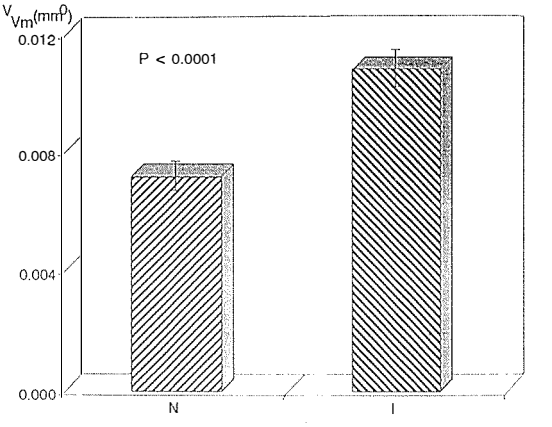


Figure 6. Volume density (V_{vb}) of mast cells in the nonirradiated (N) and the iradiated (I) group ($V \pm 2SE$).

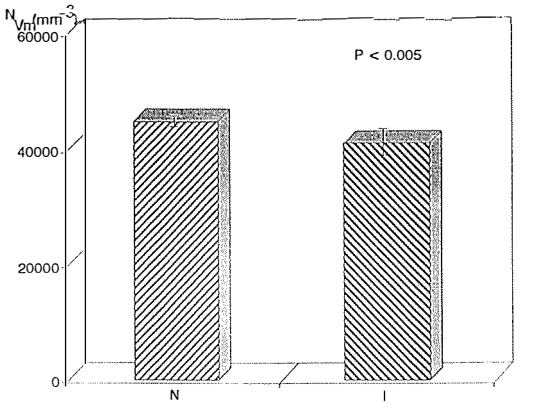


Figure 7. Average volume (V_b) of mast cells in the nonirradiated (N) and the irradiated (I) group ($V \pm 2SE$).

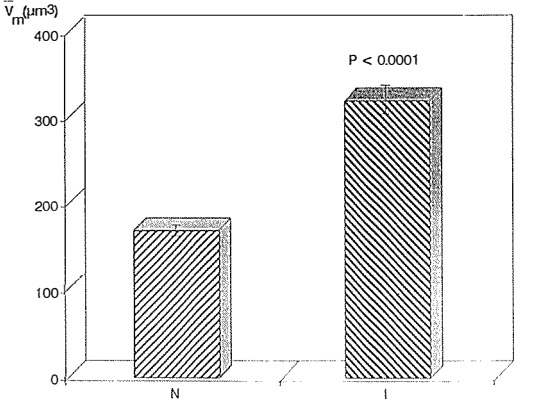


Figure 8. Numerical density (N_{vb}) of mast cells in the nonirradiated (N) and the irradiated (I) group ($N \pm 2SE$).

The findings of Black[8] and Breiter[9], who investigated histological changes of lymphocytes in the intestinal mucosa, agree with our findings. The authors state that numerous lymphocytes and plasma cells, penetrating the intestine with blood or being produced by proliferation of the lymphocytes in the mucosa, are smaller after irradiation. This most probably reflects the change in the immune system resulting in the progression of irradiated tissue impairment. It is also possible that X rays damage the chromosomes and so diminish the capacity of lymphocytes. The consequence is the reduction of their number and the inhibition of normal response to antigenic stimulation.[10,11] It is also possible that the irradiated lymphocytes release nucleoproteins which affect proliferation of fibroblasts and formation of collagen fibers in the irradiated tissue.[3–5]

Our stereological analysis of the irradiated mast cells revealed a significantly increased V_v and V of an individual cell and reduced N_v. Irradiation also caused degranulation. These results agree with the findings of Grand[12] and Sedgwick[13], who investigated mast cells in the mucous membrane of the small intestine of irradiated mice and rats. The literature data demonstrate that histamine is released from the mast cell granules during irradiation.[3,14] The literature data state that mast cells are the only cells in the body with receptors for IgE and can therefore bind IgE.[15,16] Literature data and our results suggest that new antigens are produced in the damaged intestinal mucosa after irradiation. Binding of neo-antigens to the antibodies IgE fixed to the mast cells caused the degranulation and the release of vasoactive amines and other inflammatory mediators so as leukotrienes.[17] Such leukotrienes can induce long-term contraction of the intestinal vessels. All mentioned changes cause poorer oxygenation of intestinal tissue and finally fibrosis of the intestinal wall.

The results of our experiments have confirmed our hypothesis that mast cells and lymphocytes in the intestinal mucosa are deeply involved in the tissue fibrosis occuring as the response to irradiation.

References

1. Anderson WD, Scotti A. Synopsis of Pathology. St. Louis, Toronto, London, Mosby 1980; 220–32.
2. Astorquiza MI, Ojeda F. Mast cells degranulation by low doses of irradiation. *Ircs Bioch* 1984; **13:** 30–9.
3. Norrby K, Enerback L, Franzen L. Mast cells activation and tissue cell proliferation. *Cell Tis Res* 1986; **170:** 289–303.
4. Smiht DH, Jerome J. Radiation damage to the small intestine. *World J Surg* 1986; **10:** 189–94.
5. Lukič F, Škrk J, Simčič J, Zorc R. Early detection of the thoracic duct lymphocytes damage in irradiated dogs. ESSO Workshop, Farmitalia Carlo Erba 1989; **4:** 1–9.
6. Lukič F, Simčič V, Adamič Š, Zorc R, Porenta O. Promene limfocita duktus toracikusa posle zračenja, kao mogući faktor prevencije intestinalne fibroze. *Acta Chirurg Iugosl* 1985; **32:** 537–9.
7. Kališnik M. Fundamental Stereology. *Acta Stereol* 1985; **1:** 1–148.
8. Black WC, Gomez LS, Yuhas JM. Quantification of the late effect of X-radiation on the large intestine. *Cancer* 1980; **45:** 444–51.
9. Breiter N, Trott KR. Chronic radiation damage in the rectum of the rat after protracted fractionated irradiation. *Radiat Biol* 1986; **7:** 155–63.
10. Rodgers VD, Fasset R, Kagnoff MF. Abnormalities in intestinal mucosal T cells in homosexual populations including those with the lymphadenopathy syndrome and acquired immunodeficiency syndrome. *Gastroenterol* 1986; **90:** 552–8.
11. Goetzl EJ, Foster DW, Payan DG. A Basopsil-activating factor from human T lymphocytes. *J Immunol* 1984; **53:** 227–31.
12. Grand GD, Tuffan DM, Vassali P. Gut mucosal mast cells, origin, traffic and differentiation. *J Exp Med* 1984; **160:** 12–28.
13. Sedgwich DM, Ferguson A. Dose-response studies of defletion and repopulation of rat intestinal mucosal mast cells after irradiation. *Int J Radiat Biol* 1994; **65:** 484–95.
14. Dvorak AM. Human mast cells. *Adv Anat Embr Cell Biol* 1989; **114:** 15–73.
15. Haig DM, Mckee TA, Jarett EE. Generation of mucosal mast cells is stimulated in vitro by factors derived from T cells of helminthinfected rats. *Nature* 1992; **300:** 188–99.
16. Crapper RM, Thomas WR, Schrader JW. In vivo transfer of persisting (P) cells. Further evidence for their identity with T-dependent mast cells. *J Immunol* 1984; **133:** 2174–80.
17. Vanloveren H, Dennoter W, Meade R, Terheggem PM, Askenase PW. Role of mast cells and the vasoactive a,ome serptpmom om T cell immunity to tumors. *J Immunol* 1985; **134:** 1292–303.

Radiol Oncol 1995; 29: 211–7.

Glutathione concentration and glutathione S-transferase activity in gynecological normal and tumor tissues: A preliminary report

Maja Osmak,[1] Damir Babić,[2] Marija Abramić,[3] Duško Miličič,[4], Lidija Bizjak,[1] Lidija Beketić-Orešković,[1] Egidio Čepulić,[4] Slavko Orešković,[4] Stanko Jukić[2] and Damir Eljuga[5]

[1]Department of Molecular Medicine, Ruđer Bošković Institute, [2]Department of Gynecological and Perinatal Pathology, Medical School, University of Zagreb, [3]Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, [4]Department of Obstetrics and Gynecology, Medical School, University of Zagreb, [5]Department of Gynecology, University Hospital for Tumors, Zagreb, Croatia

Drug resistance is a major problem in cancer therapy. In vitro *studies have suggested that glutathione (GSH) and glutathione transferase (GST) may be associated with alkylating agents resistance. In this study, we determined GSH concentrations and GST activity in 41 samples of gynecological tissues, which include: normal tissue of cervix uteri (7 samples), normal tissue of corpus uteri (14 samples), benign tumors of corpus uteri (4 samples) malignant tumors of corpus uteri (7 samples), the normal tissue of ovary (5 samples), benign ovarian tumors (2 samples) and 2 malignant ovarian tumors. The GSH concentrations were similar in normal tissue of cervix uteri, corpus uteri and ovary. Similar levels of GSH were also found in malignant tumors of corpus uteri, but these levels were lower in benign tumors. In the ovarian tissue, lower levels of GSH were found in benign and malignant tumors. The GST activities were similar in the normal tissue of cervix uteri, corpus uteri and ovary. In corpus uteri, similar values were obtained for normal tissue and benign tumors, but higher ones for malignant tumors. This difference was statistically significant if two malignant Muller mixed tumors (with very low GST levels) were excluded from the analysis. Similar GST activities were obtained for the normal ovarian tissue and benign ovarian tumor, but higher activities for ovarian malignant tumors. In spite of a modest number of samples, our data nevertheless suggest that the activity of glutathione transferase is increased in tumor tissues. The GST activity may contribute to resistance of tumor cells to alkylating drugs in chemotheraphy.*

Key words: ovarian neoplasms-analysis; uterine neoplasms-analysis; glutathione; glutathione transferases; drug resistance

Correspondence to: Dr. Maja Osmak, Ruđer Bošković Institute, Department of Molecular Medicine, Bijenička cesta 54, 41000 Zagreb, Croatia.

UDC 618.14-006.6-074:612.398.192

Introduction

The intrinsic and acquired drug-resistance are rate-limiting step in successful antineoplastic

therapy. Until recently the mechanisms underlying drug-resistance have received little attention, in spite of the fact that this phenomenon was observed as early as in 1948. A wide variety of factors are now implicated as causes of the resistance.[1,2,3] One mechanism may involve overexpression of plasma membrane P-glycoprotein P170. It decreases the drug-accumulation in cells by facilitating the drug efflux from cells, leading to multidrug resistant phenotype. The other mechanism may involve the increased protection by cellular detoxification systems: glutathione (GSH), glutathione transferases (GST), gluthathione peroxidases, and/or metallothioneins. DNA repair, the altered activity of topoisomerase II, changes in drug metabolism and drug transport are also implicated in drug resistance. In many cases, several different mechanisms were found in resistant cells.[4,5,6] In patients, the values of these various parameters might allow us to predict the response of tumors to the particular therapy.

The thiol-mediated detoxification of anticancer drugs is of considerable interest. GSH is the main intracellular nonprotein sulphydryl compound. It has a variety of functions, such as the transport of amino acids into the cells, detoxification of xenobiotics, scavenge of free radicals, biosynthesis of deoxyribonucleotides and biosynthesis or metabolism of prostaglandins and leukotriens. GSH has been shown to have an important role in cell resistance to different drugs.[7,8,9] It affects drug-efficiency by non-catalytic nucleophilic reactions, or by the reactions catalyzed by GST. GSH can express its activity at two levels: cytoplasmatic – by increasing drug inactivation and elimination, or nuclear – by affecting formation and repair of DNA lesions.[10]

GSTs are a group of multifunctional enzymes that catalyze the conjugation of GSH with the various electrophilic agents. This reaction is the initial step in the formation of mercapturic acids, a pathway important in eliminating potentially cytotoxic or mutagenic compounds from the body. GST also act as intracellular blinding proteins for many hydrophobic compounds.[11] In humans, there are three main classes of GSTs in cytosol: α, π and μ; they differ in structural and functional characteristics. Regarding GST in anticancer drug resistance, the following data are well documented: a) tumors express the high level of GST, especially GSTπ; b) nitrogen mustards are good substrates for GSTα; c) most drugs associated with multidrug resistant phenotype are not GST substrates; d) transfection with GST complementary DNAs have produced some lines with increased resistance to alkylating agents.[12,13]

In addition to being important for chemotherapy, GSH[7,9,14] and GST[15] may also play a role in the cellular response to oxidative stress generated by ionizing radiation.

Chemotherapy alone or combined with surgery or radiotherapy, is the usual strategy for treatment of patients with gynecological cancers. Therefore, we compared GSH concentrations and GST activities in gynecological tissues (cervix uteri, corpus uteri and ovary) in an attempt to determine whether they can be used as diagnostic and prognostic factors.

Materials and methods

Tissues

The tissues were obtained from fresh specimens removed during surgery or biopsy at the Department of Obstetrics and Gynecology, School of Medicine, University of Zagreb. Each sample was divided in two halves, for histological and biochemical studies.

The samples were frozen and maintained at – 196°C.

Fortyone samples of normal, benign and malignant tumor tissue from cervix uteri, corpus uteri and ovary were analyzed (Table 1). They were divided as: gradus I (normal), gradus II (benign) and gradus III (malignant).

The protocol was approved by the Ethics of Research Committee at the School of Medicine, University of Zagreb.

Glutathione determination

The total intracellular glutathione (GSH) level was measured by modified Tietze's method.[16]

Briefly, the samples were cut into small pieces, covered with buffer (50 mM TRIS, 250 mM saccharose, 134 mM KCl, pH = 7.6) and homogenized on ice (Ika-Kunkel, Labor Technick, Germany; three strokes for 5 sec). The suspension was centrifugated at 4°C for 45 mit at 15000 g. The total GSH content in the supernatant was determined by the enzymatic recycling assay.[16] The absorbance of 5,5-dithiobis-2-nitrobenzoic acid (Boehringer Mannheim GmbH, Germany) at 412 nm was monitored spectrophotometrically. Values were normalized according to the total protein assessed by Bradford's method.[17] Each sample was divided into two halves and GSH was determined in each of them two times.

Glutathione transferase determination

The intracellular glutathione transferase (GST) activity was determined as described by Habig and Jacoby.[18] GST activity was measured in the supernatant prepared for GSH determination, using 1-chloro-2,4-dinitrobenzene as the electrophilic substrate. GST activity was expressed as nanomoles of GSH-1-chloro-2,4-dinitrobenzene conjugate formed per min per mg protein. In each clinical sample GST activity was determined four times.

Statistics

The significance of differences between the particular groups was tested by analysis of Mann-Whitney or Kruskal-Wallis. The level of significance was set to 0.05.

Results

In this study, we examined the glutathione concentrations and glutathione S-transferase activities in 41 samples that originated from the normal tissues (26 samples), benign tumors (6 samples) and malignant tumors (9 samples) (Table 1). Glutathione concentrations in normal and tumor tissues are given in Figure 1. The data reveal that the concentration of glutathione was about the same in the normal tissue of cervix uteri, corpus uteri and ovary. It contrast, the values obtained for benign tumors of corpus uteri were significantly lower than that for the normal tissue. However, GSH concentration in normal and malignant tumors was not statistically different (Figure 1b).

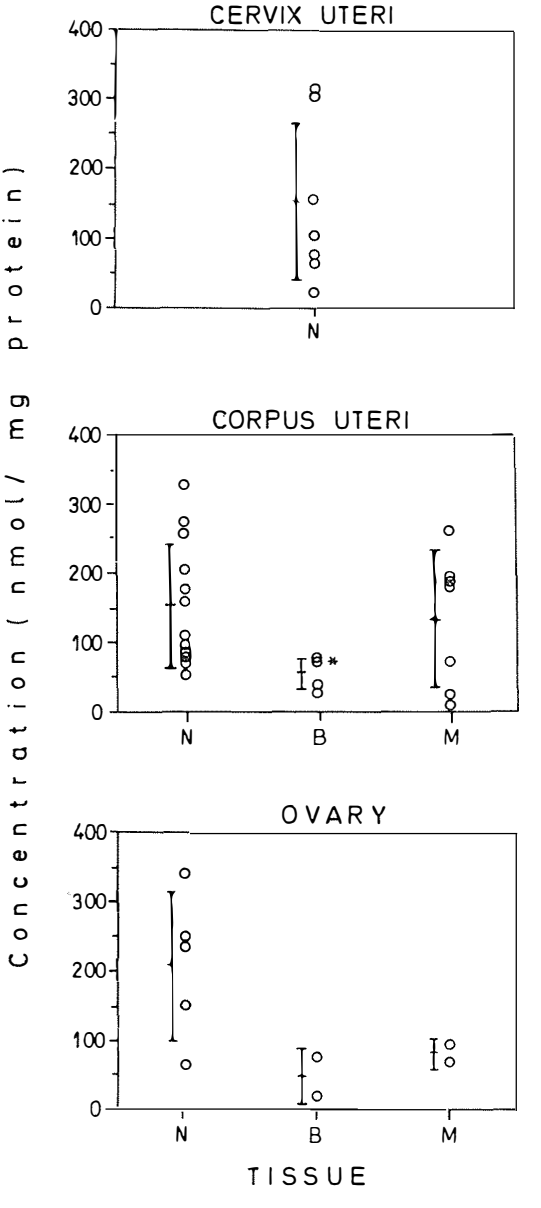


Figure 1. Glutathione concentrations in cervix uteri, corpus uteri and ovary. Individual values are given for N = normal tissues, B = benign tumors, M = malignant tumors. The mean values ± SD are presented.
* Statistically different from normal tissue.

The statistical analysis of the data of the GSH concentrations in ovary was impossible because the number of samples was too low. Therefore, we were also unable to make statistical comparison of the data obtained for tumors of corpus uteri and ovary (Figure 1b and 1c). Figure 1c shows, however, that the mean values for GSH concentrations were lower in benign and malignant tumors than in the normal ovarian tissue.

We next examined the activity of glutathione transferase in gynecological tissues. The results are given in Figure 2. We found no significant differences in the GST activity in normal tissues (cervix uteri, corpus uteri or ovary). The GST activities in benign and malignant tumors were similar to those found in the normal tissue of corpus uteri. If, however, the two lowest values are excluded from the analysis (marked with arrows in Figure 2b), significant differences in the GST activity between normal and malignant tumor tissue are found. These two exceptions are two carcinosarcomas (MMMT, see Table 1) that differ from malignant adenocarcinoma tumors by their composition: they have less glandular and more stromal components, indicating a possible explanation for lower GST activities. Again, we are unable to make the statistical analysis of the GST activity in ovary because of a low number of samples. As can be judged from Figure 2c, however, is the GST activity similar in the normal tissue and benign tumors, but higher in malignant tumors.

The comparison of the GST activity in corpus uteri and in ovarian carcinomas points to higher GST activities in ovary, although it is still in the range of values obtained for carcinomas of corpus uteri. When the data for MMMT are excluded, the GST activities in ovarian and endometrial tumor are quite similar.

Discussion

Resistance to chemotherapy is a serious problem in the management of patients with cancer. Some of the most active anticancer-drugs are electrophiles that damage DNA either directly by alkylation (melphalan, phenylalanine mustard, BCNU, cyclophosphamide, cisplatin) or indirectly through free-radical mechanism (Adriamycin). *In vitro* studies have suggested that GSH can participate in detoxification of antineoplastic drugs like alkylating agents and Adriamycin.[8,9] These studies have been extended to clinic to see whether tumor and normal tissues display phenotypic differences relevant to potential cytostatic drug resistance.

In this preliminary study we examined the level of GSH in different normal gynecological tissue (cervix uteri, corpus uteri and ovary) and found similar values. If these values were compared to those obtained for tumor tissue, similar (corpus uteri) or even lower (ovary) concentrations were found. Therefore, our data suggest that GSH concentrations cannot be used as a diagnostic and prognostic factor, at least not for tumors of corpus uteri and ovary.

The literature data concerning clinical studies suggest that differences in the GSH level between normal and tumor tissue depend on the tumor type. No significant difference between the GSH concentration in the tumor and the normal tissue of lung was obtained.[19] Moreover, a certain decrease in the GSH concentration in adenocarcinoma was found as compared to the

Table 1. Normal and tumor samples analyzed in this study

	Normal	Benign tumors	Malignant tumors
Cervix uteri	7	–	–
Corpus uteri	14	3 myomas	5 endometrial adenocarcinomas
		1 endometrial polyp	2 malignant Muller mixed tumors*
Ovary	5	1 mucinous ovarian cystadenoma	2 serous ovarian carcinoma
		1 ovarian endometriotic cyst	
Total	26	6	9

* = MMMT, carcinosarcoma

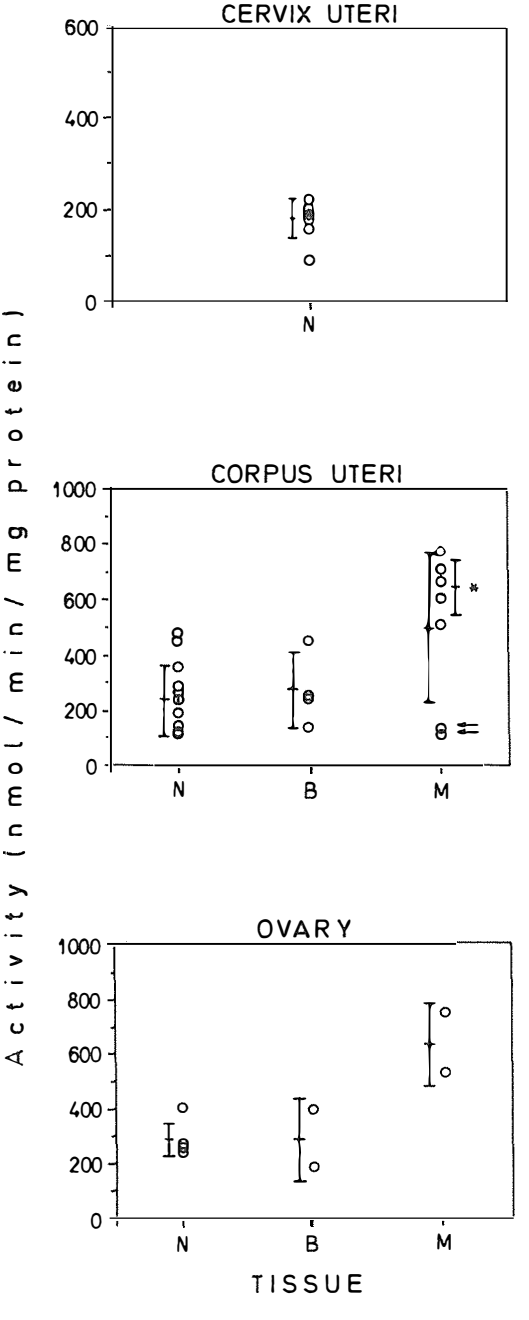


Figure 2. Activity of glutathione S-transferases in cervix uteri, corpus uteri and ovry. Individual values are given for N = normal tissues, B = benign tumors, M = malignant tumors. The mean values ± SD are presented.
* Statistically different from normal tissue.

normal lung specimens. A drop in the GSH concentration in tumors of sigmoid colon was also reported.[20] In contrast, the increased levels of GSH were found in the tumors of colon[21] and rectum.[22]

The activity of GST enzymes in normal and tumor tissues is of great importance. The levels in normal tissue may determine the susceptibility of the tissue to cytotoxic damage from chemical toxins, carcinogens and some anticancer drugs. In tumors, by contrast, the GST level may cause the resistance to chemotherapy.

Anticancer drugs that are substrates for GST can be divided in two categories: those for which convincing substrate/kinetic data are known (chlorambucil melphalan, nitrogen mustard, phosphoramide mustard, acrolein, BCNU, hydroxyalkenals, ethacrynic acid and steroids) or those for which only some indirect evidence exist (bleomycin, hepsulfan, mitomycin C, adriamycin, cisplatin, carboplatin).[12] So far, the involvement of GST in the resistance to classical alkylating agents, cisplatin based drugs and anthacyclines has been documented.[12,13]

In this study, we examined the activity of GST in normal cervix uteri, corpus uteri and ovary, and found similar values in these tissues. If the activity of GST for corpus uteri (with the exception of MMMT) and ovary were compared, similar values were again obtained. If, however, the GST activities in normal tissues were compared to the tumor tissue, a significant increase in the tumor tissue was observed. This is the main finding of our study. It suggests that for the gynecological tissue, GST activity may be used as a diagnostic and prognostic factor.

Our findings that gynecological tumors have higher GST activities than the corresponding normal tissues, are in agreement with the literature data. Higher GST activities have been found in various cancers, including cancer of colon, rectum, stomach, lung and breast, but not of kidney and liver.[21–26] In these studies, as well as in ours, GST activities varied considerably (1.3 to 2.7 -fold), and even higher variations were observed among individual tumors.

Promising strategies to overcome resistance are emerging from basic and preclinical studies. They seem likely to lead to the improved therapeutic regimens based on the modulation of chemotherapy. One approach could involve the elevation of the host cells GST enzyme level. On the other hand, inhibition or inactivation of GST enzymes of the tumor can be the principal goal. For this, the specific GST inhibitors can be used: inhibitory peptide analogues of GSH, the quinone inactivators of GST, the prostaglandin I_1 analogue piriprost or the diuretic agent ethacrynic acid. Ethacrynic acid is of particular interest, because it is applied in Phase II preclinical trial for chlorambucilrefractory chronic lymphatic leukemia.[12]

To sum up, in this preliminary study we did not find the elevated glutathione levels in tumor of corpus uteri and ovary as compared to the corresponding normal tissue. We found an increase in the activity of glutathione transferase in tumor tissues. This GST activity may contribute to resistance of tumor cells to alkylating drugs in chemotherapy. We started the clinical followup study to examine the correlation between the high tumor GST activity and prognosis of the ilness.

Acknowledgement

We are very grateful to Dr. Ž. Trgovčević for his helpful suggestions and Mrs. Lj. Krajcar for her technical assistance. This project was supported by the Ministry of Science and Technology of the Republic of Croatia (Grant 1-08-210 given to dr. M. Osmak) and by Croatian League against Cancer.

References

1. Borst B. Genetic mechanisms of drug resistance. A review. *Rew Oncol* 1991; **30:** 87–105.
2. Dietel M. What's new in cytostatic drug resistance and pathology. *Path Res Pract* 1991; **187:** 892–905.
3. Moscow JA, Cowan KH. Review Multidrug resistance. *J Natl Canc Inst* 1989; **80:** 14-20.
4. Osmak M, Užarević B. Mechanisms involved in resistance of preirradiated Chinese hamster V79 cells to cytotoxic drugs are multifatorial. *Res Exp Med* 1991; **191:** 413–21.
5. Osmak M, Eljuga D. The characterization of two human cervical carcinoma HeLa sublines resistant to cisplatin. *Res Exp Med* 1993; **193:** 389–96.
6. Beketić-Orešković L, Osmak M, Jakšić M. Human larynx carcinoma cells resistant to *cis*-diammine-dichloroplatinum (II): mechanisms involved in resistance. *Neoplasma* 1994; **41:** 163–9.
7. Arrick BA, Nathan CF. Glutathione metabolism as a determinant of therapeutic efficacy: a review. *Cancer Res* 1984; **44:** 4224–32.
8. Meister A. Glutathione, ascorbate, and cellular protection. *Cancer Res* 1994; **54:** 1969S–75S.
9. Russo A, Carmichael J, Friedman N. DeGraff W, Tochner Z, Glatstein E, Mitchell JB. The roles of intracellular glutathione in antineoplastic chemotherapy. *Int J Radiation Oncology Biol Phys* 1986; **12:** 1347–54.
10. Meijer C, Mulder NM, Timmer-Boscha H, Zilstra JG, De Vries EGE. Role of free radicals in an adriamycin – resistant human small cell lung cancer cell line. *Cancer Res* 1987; **47:** 4613–7.
11. Pickett CB, Lu AYH. Glutathione S-transferases: gene structure, regulation, and biological function. *Annu Rev Biochem* 1989; **58:** 743–64.
12. Tew KD. Glutathione-associated enzymes in anticancer drug resistance. *Cancer Res* 1994; **54:** 4313–20.
13. Waxman DJ. Glutathione S-transferases: role in the alkylating agent resistance and possible target for modulation chemotherapy-a review. *Cancer Res* 1990; **50:** 6449–54.
14. Miura M, Sasaki T. Role of glutathione in the intrinsic radioresistance of cell lines from a mouse squamous cell carcinoma. *Radiat Res* 1991; **126:** 229–36.
15. Cholon A, Giaccia AJ, Lewis AD, Hickson I, Brown JM. Wtat role do glutathione S-trasferases play in the cellular response to ionizing radiation? *Int J Radiation Oncology Biol Phys* 1992; **22:** 759–63.
16. Tietze F. Enzymatic method for quantitative determination of nanogram amounts of total and oxidized glutathione: applications to mammalian blood and other tissues. *Analyt Biochem* 1969; **27:** 502–22.
17. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem* 1976; **72:** 248–53.
18. Habig WH, Jacoby WB. Assays for differentitation of glutathione-S-transferases. *Methods in Enzymol* 1981; **77:** 398–405.

19. Cook JA, Pass HI, Iype SN, Friedman N, DeGraff W, Russo A, Mitchell JB. Cellular glutathione and thiol measurements from surgically resected human lung tumor and normal lung tissue. *Cancer Res* 1991; **51:** 4287–94.

20. Siegers C-P, Bose-Younes H, Thies E, Hoppenkamps R, Younes M Glutathione and glutathione-dependent enzymes in the tumorous and nontumorous mucosa of the human colon and rectum. *J Cancer Res Clin Oncol* 1984; **107:** 238–41.

21. Butler RN, Butler WJ, Moraby Z, Fettman MJ, Khoo KK, Roberts-Thomson IC. Glutathione concentrations and glutathione S-transferase activity in human colonic neoplasms. *J Gastroenterol Hepatol* 1994; **9:** 60–3.

22. Redmond SMS, Joncourt F, Buser K, Ziemiecki A, Altermatt H-J. Fey M, Margison G, Cerny T. Assesment of P-glycoprotein, glutathione-based detoxifying enzymes and O^6-alkylguanine-DNA alkyltransferase as potential indicators of constitutive drug resistance in human colorectal tumors. *Cancer Res* 1991; **51:** 2092–7.

23. Howie AF, Forrester LM, Glancey MJ, Schlager JJ, Powis G, Beckett GJH, Hayes JD, Wolf CR. Glutathione S-transferase and glutathione peroxidase expression in normal and tumor human tissues. *Carcinogenesis* 1990; **11:** 451–8.

24. Peters WHM, Wormskamp NGM, Thies E. Expression of glutathione S-transferases in normal gastric mucosa and in gastric tumors. *Carcinogenesis* 1990; **11:** 1593–6.

25. Singh SV, Brunnert SR, Roberts B, Krishan A. Differential expression of glutathione S-transferase, glutathione peroxidase and glutathione reductase in normal and malignant human breast tissues. *Cancer Lett* 1990; **51:** 43–8.

26. Moorghen M, Cairns J. Forrester LM, Hayes JD, Hall A, Cattan AR, Wolf CR, Harris AL. Anhanced expression of glutathione S-transferases in colorectal carcinoma compared to nonneoplastic mucosa. *Carcinogenesis* 1991, **12:** 13–7.

Radiol Oncol 1995; 29: 218–22.

High rate of complications in patients with carcinoma of the cervix surgically treated after radical radiotherapy

Albert Peter Fras

Institute of Oncology, Ljubljana, Slovenia

With the aim to improve the results of treatment of patients who had advanced carcinoma of the uterine cervix and were radically irradiated, a group of 49 patients underwent hysterectomy two to 24 months after completion of radiotherapy, among whom for only 43 patients data were available.
Radiotherapy consisted of 40 Gy external beam irradiation to true pelvis, low dose intracavitary treatment to a total dose 40 Gy to point A, and parametrial irradiation 16 to 20 Gy, shielding the place where radioactive sources were positioned during intracavitary therapy.
Necrosis, persistent cervical carcinoma, recurrent carcinoma, and in patients younger than 50 years no evidence of disease (NED) with dysplasia were indications for the surgical treatment.
Hysterectomy with bilateral oophorectomy was as conservative as possible but severe complications, such as ureteral stenosis (five cases), recto-vaginal fistula (three cases), vesico-vaginal fistula (two cases), recto-vesico-vaginal fistula (one case) occurred. Asymptomatic frozen pelvis as a mild complication occurred in 10 cases. One patient died postoperatively because of dehiscence and abdominal wall necrosis. In 17 (39.5%) of 43 patients complications occurred, although asymptomatic frozen pelvis was not taken in account. We believe that such a combined treatment is only for selected cases.
Key words: cervix neoplasms-radiotherapy; hysterectomy, surgical treatment; postoperative complications

Introduction

Radical radiotherapy is the treatment of choice for carcinoma of the uterine cervix stages IIB and III.[1] With radical radiation therapy and careful intracavitary techniques, central recurrences are extremely rare, an incidence of approximately 1 %.[2] In another report, in a significantly larger group (1801 patients) treated with radiation alone, the central failure rate was approximately 3 %.[3]

At the Hammersmith Hospital after radical radiotherapy, usually combined with cisplatin, simple total abdominal hysterectomy with bilateral salpingo-oophorectomy may be indicated as a "central debulk" to remove central disease if the cervical smear or biopsies should remain positive or if the smear or biopsies, having been negative, become positive again.[4]

Correspondence to: Assist. Prof. Albert Peter Fras, M.D., Ph.D., Institute of Oncology, Zaloška 2, 61105 Ljubljana, Slovenia.

UDC: 618.146-006.6:615.849.2:618.14-089.87

There are some controversy about the benefit of preoperative irradiation in the treatment of cervical carcinoma. Data from the M.D. Anderson Hospital showed an improved pelvic control rate, as well as a small increase in survival, when patients with bulky Stage IB-IIA-B carcinoma of the cervix were treated with preoperative irradiation followed by extrafascial hysterectomy. In such a combination of irradiation and surgery a high rate of complications was observed (from 8 to 17.5%).[5]

To define the complications after radical radiotherapy and surgical therapy we retrospectively analysed the patients who had undergone such sort of treatment at the Institute of Oncology in Ljubljana

Material and methods

In a non-randomized group of 49 patients, in the years from 1981 to 1991, all patients who underwent hysterectomy with bilateral oophorectomy were, prior to the surgical treatment, radically irradiated. But the data were available only for 43 patients, others came out of control because they were from another country.

With combined tele- and brachytherapy doses to the central portion of the cervical tumor were over 80 Gy (40 Gy teletherapy and 40 Gy intracavitary insertion of Cesium-137). As most of the patient were still irradiated to the pelvic wall, although the center where Cesium was positioned was shielded by a led block, doses under the shield were approximately 2 to 3 Gy.

So we believe, the center was overirradiated. Among our patients persistent and recurrent carcinoma was evidently present in 7 out of 43 (16.2%) patients although the intracavitary irradiation was carefully performed. In these cases we did not try to reirradiate the center. As in necrosis recurrent or persistent carcinoma could not be established before operation, these patients underwent surgical treatment as well (9 out of 43 patients or 20.9%).

In all patients hysterectomy with bilateral oophorectomy was performed.

Indications for surgical treatment were as follows: residual disease, recurrent carcinoma, cervical necrosis, and vaginal dysplasia with no evidence of recurrent or persistent carcinoma. In only one elderly patient the indication for the surgical treatment was enlarged uterus due to the piometra with consequent general symptoms, whereas the second patient underwent surgery because of ovarian tumours (Table 1).

Patients ranged from 26 to 78 years (median 44 years). At the beginning of the treatment the disease was classified according to FIGO stages as stage IB four cases, stage IIA two cases, stage IIB 27 cases, and 10 cases as stage III.

All patients underwent surgical treatment between the second and 24th month (median 6th month).

Residual and recurrent disease was preoperatively verified. In patients with no evidence of disease (NED) with vaginal dysplasia in the operative specimen in 10 cases carcinoma was present, in one case, only in an enlarged lymphnode, micrometastasis was found and in 15 cases no carcinoma was present. In patients with necrosis of cervix they underwent surgical treatment and in three out of 9 carcinoma were still present (Table 2).

Table 1. Indications for surgical treatment after radical radiotherapy.

Indications	No. of pts.
Residual disease	5
Recurrent disease	2
NED and dysplasia	25
Necrosis of cervix	9
Other	2
Total	43

NED - No evidence of disease.

Table 2. Postoperative pathohystology of patients without evident carcinoma after radiotherapy (n = 34).

Preoperative status	Pathohystology	
	Positive	Negative
NED and dysplasia	9 (+ 1)*	15
Necrosis of cervix	3	3
Total	13	21

NED – No eveidence of disease.
* Patient with positive lymph nodes.

According to the glossary for reporting complications of treatment in gynaecological cancers, we divided complications to the complications of gastrointestinal tract, urinary tract and pelvic soft tissues.[9] No evident complications were observed on vascular tissue, cutaneous tissue, peripheral nerves and hemopoetic tissue.

Results

Gastrointestinal complications

Evident gastrointestinal complications developed in 8 (18.6%) of 43 patients (Table 3).

Three patients suffered from rectal bleeding (G1b), but bleeding was occasional and required only conservative treatment.

In three patients recto-vaginal fistula developed (G3a), in one patient combined with vesico-vaginal fistula. All of them required surgical treatment. One patient died after bowel resection due to rectal necrosis after stool derivation (G4).

In one patient rectal bleeding required stool derivation, she died six months later. After brachytherapy of recurrent disease a huge necrosis developed in the true pelvis.

In one patient sigmoid fistula developed (G3a), and transversostomia was performed.

Urinary complications

Evident urinary complications developed in 10 (23.2%) of 43 patients (Table 4).

Bladder and urethra

Mild or occasional hematuria (G1b) developed in three patients. In one patient hematuria, combined with urine incontinence, required major surgery with urinary derivation (G3a). Vesicovaginal fistula (G3d) developed in two patients. In one patient surgical closure was done and the patient is quite well. The other patient died of recurrent disease.

Ureter

Unilateral ureteral stenosis developed in three patients, bilateral in two cases (G3a). In one patient with bilateral ureteral stenosis surgical ureterolysis was performed, in one patient with unilateral ureteral stenosis reimplantation was done. The other three patients have had only percutaneous nephrostomy because of the evident recurrent carcinoma.

Complications of pelvic soft tissue

Asymptomatic frozen pelvis developed in 10 (23.2%) of 43 patients, in two patients it was

Table 3. Gastrointestinal complications after radiotherapy and surgery according to propose glossary[9] (n = 43).

Complications		No. of pts.
Rectum	G1b	3
	G3a	3
	G4	1
Sigmoid colon	G3a	1
Total		8 (18.6%)

Rectum:
G1b:Mild or occasional rectal bleeding with or without mucosal hyperemia and/or oozing of blood and/or teleangiectasia. G3a:Recto-vaginal fistula. G4:Death due to complication.
Sigmoid colon: G3a:Fistula.

Table 4. Urinary complication after radiotherapy and surgery according to propose glossary[9] (n = 43).

Complications		No. of pts.
Bladder	G1b	2
	G3a	1
	G3d	2
Ureter	G2b	2
	G3a	3
Total		10 (23.2%)

Bladder:
G1b:Mild or occasional hematuria with or without mucosal hyperemia and/or teleangiectasia.G3a:Hematuria requiring major surgery or embolisation.G3d:Early or late vesico-vaginal fistula with permanent anatomical and/or functional damage.
Ureter:G2b:Ureteral stenosis requiring surgery with subsequent normal renal function.G3a:Uretero-vaginal fistula and/or ureteral stenosis with subsequent inadequate renal function, or which resulted in a non-functioning kidney, or which required either nephrectomyor permanent nephrostomy.

combined with ureteral stenosis in one patient with vesico-vaginal fistula, in one patient with proctitis and in two patients with cistitis (Table 5).

Discussion

Following the patients during radiation therapy it is allowed to conclude about evolutionary aspects of the cervical lesion and its relative radiosensitivity. As the uterus is mobile, and parametrial infiltration had disappeared after radiotherapy, in some instances, especially in younger patients, they may undergo surgical intervention to remove the residual tumor.[10]

Complications developed after radical radiotherapy and surgeries are quite often, up to 39.5% (Table 6), when we do not take in account asymptomatic frozen pelvis. Some authors reported high rate complications after radical radiotherapy up to 20.4%, although fistulas developed only in 1.6%.[11] Radiation doses to the rectum and bladder within the range 60 to 65 Gy are not found to be in relationship among bowel complications and we never exceed them during radiation treatment. The total dose 80 Gy to the point A and 60 Gy to the pelvic wall and parametria had been giving an acceptably low rate of late major complications.[12]

Rectal complications after remote afterloading intracavitary therapy for carcinoma of the uterine cervix are reported higher to 30%, among them severe only 2%.[13]

Minor complications after combined radiotherapy and surgery are reported after preoperative radiation, although ureteral fibrosis in the pelvis are also described, but doses to the cervix do not exceed 70 Gy.[14]

Conclusion

This study does not define the therapeutic value of combined radical radiotherapy and surgery in patients with residual or recurrent carcinoma of the uterine cervix. As in our material four different stages of disease were treated by the same mode, it is impossible to get the real survival for these patients. However, due to the nature of this disease, successful treatment will be at the price of a high complication rate. But we believe that such a treatment could be obtained only in a selected cases.

Table 5. Pelvic soft tissues complications after radiotherapy and surgery according to propose glossary[9] (n = 43).

Frozen pelvis		No. of pts.
Asymptomatic (G2a)		10
Combined with:	ureteral stenosis	2
	vesico-vag. fistula	1
	cystitis	2
	proctitis	1
Total		16

Frozen pelvis:G2a:Fibrosis involving at least one parametrium as far asthe pelvic side wall, and/or asymptomatic frozen pelvis.

Table 6. Gastrointestinal and urinary complications after radiotherapy and surgery (n = 43).

Complications	No. of pts.
Gastro-intest. complications	7
Urinary complications	9
Combined gastro-intest. and urinary complications	1
Total	17 (39.5%)

References

1. Wang CC. Principles of radiation therapy of gynecologic cancers. *Cancer* 1981; **48**: 530-42.
2. Weems DH, Mendenhall WM, Bova FJ, Marcus RB, Morgan LS, Million RR. Carcinoma of the intact uterine cervix, stage IB-IIA-B, 6cm in diameter: irradiation alone vs preoperative irradiation and surgery. *Int J Radiat Oncol Biol Phys* 1985; **11**: 1911-4.
3. Paunier JP, Delclos L, Fletcher GH. Causes, time of death and sites of failure in squamous cell carcinoma of the uterine cervix on intact uterus. *Radiology* 1967; **88**: 555-62.
4. Shaw LMA, Webb JB, Blake PR. Cervical cancer: a two-pronged attack. *Practitioner* 1983; **228**: 555-9.
5. Perez CA, Zivnuska F, Askin F, Camel HM, Ragan D, Powers WE. Mechanisms of failure in

patients with carcinoma of the uterine cervix extending into the endometrium. *Int J Radiat Oncol Biol Phys* 1977; **2**: 651-9.

6. Nelson AJ, Fletcher GH, Wharton JT. Indications for adjunctive conservative extrafascial hysterectomy in selected cases of carcinoma of the uterine cervix. *Am J Roentgenol* 1975; **123**: 91-9.
7. Perez CA, Camel HM, Askin F, Breaux S. Endometrial extension of carcinoma of the uterine cervix: a prognostic factor that may modify staging. *Cancer* 1981; **48**: 170-80.
8. Perez CA, Bedwinek JM, Breaux S. Patterns of failure after treatment of gynecologic tumors. *Cancer Treat Symposia* 1983; **2**: 217-23.
9. Chassagne D, Sismondi P, Horiot JC et al. A glossary for reporting complications of treatment in gynecological cancers. *Radiother Oncol* 1993; **26**: 195-202.
10. Pilleron JP, Durand JC, Lenoble JC. Carcinoma of the uterine cervix, stages I and II, treated by radiation therapy and extensive surgery (1000 cases). *Cancer* 1972; **29**: 593-7.
11. Allert J, Jimenez J, Beldarrain L, Montalvo J, Roca C. Complications from irradiation of carcinoma of the uterine cervix. *Acta Radiol Oncol* 1980; **19**: 13-5.
12. Teshima T, Chatani M, Hata K, Inoue Ta, Inoue To, Suzuki T. Rectal complication after remote afterloading intracavitary therapy for carcinoma of the uterine cervix. *Strahlentherapie* 1985; **161**:343-7.
13. Singh K. Two regims with the same TDF but differing morbidity used in the treatment of stage III carcinoma of the cervix. *Br J Radiol* 1978; **51**:357-62.
14. Perez CA, Camel HM, Kao MS, Hederman MA. Randomized study of preoperative radiation and surgery or irradiation alone in the treatment of stage IB and IIA carcinoma of the uterine cervix: final report. *Gynecol Oncol* 1987; **27**: 129-40.

Radiol Oncol 1995; 29: 223–8.

Staging laparotomy for Hodgkin's disease in adults: One center experience

Marjeta Vovk,[1] Tatjana Šumi-Križnik,[1] Marija Jenko-Fidler,[1] Gabrijela Petrič-Grabnar,[1] Marinka Kremžar,[1] Janez Novak,[1] Mojca Senčar,[1] Branko Zakotnik,[1] Alenka Vodnik-Cerar,[1] Branimir Jakšić[2]

[1] Institute of Oncology, Ljubljana, Slovenia; [2] Klinička bolnica Merkur, Zagreb, Croatia

The results of 124 staging laparotomies (SL) for Hodgkin's disease (HD) in adults, 95 with supradiaphragmatic clinical state (CS) I-II, and 29 with CS III, performed at the Institute of Oncology in Ljubljana in the years 1974–1989 are presented in a retrospective analysis. After SL, clinical stage was changed in 36 % of all cases, with 34 % of CS I-II cases upstaged and 45 % of CS III cases downstaged. 88 % (28/32) of CS I-II patients with positive SL had upper abdominal involvement (pathological stage – PS III_1) most frequently in the spleen, 84 % (27/32); in 31 % (10/32) the spleen was the only localization of HD. Only 5 % of the patients had early, while 5 % had late complications after SL; there were no procedure-related deaths.

Key words: Hodgkin's diseases; staging laparotomy

Introduction

The extent of Hodgkin's disease (HD) at the time of diagnosis is one of the most important data needed to determine therapy Staging laparotomy (SL) is the most accurate method for diagnosis of HD in the subdiaphragmatic sites. The first experiences with SL were published by the Stanford University in 1969.[1] Since then SL has become accepted in many centers. Considering great differences in the experience and competence of therapeutic teams in different centers as well as in the quality of investigations and the accuracy of SL, the evaluation of our own results seems to be all the more important.

Correspondence to: Marjeta Vovk, MD, Institute of Oncology, Zaloška 2, 61105 Ljubljana, Slovenia.

UDC: 616-006.442:616.381-089.85

The purpose of this study was to review the results of SL in our center, and to compare them with those obtained by other authors, in order to establish the degree of realiability of this method in our hands.

Patients and methods

From January 1974 to December 1989, 421 formerly untreated adult patients with HD were treated at the Institute of Oncology in Ljubljana. Their age ranged between 15 – 83 yrs (mean 40 yrs). The diagnosis was histologically[2] confirmed in all except 17 patients. SL has been performed since 1974 in patients with clinical stage (CS) I-II above the diaphragm, and in those suspected of having HD under the dia-

phragm (suspected CS III), whereas SL was never indicated in clear CS III and CS IV. SL was performed in a third, 31% (130/421) of all patients with CS I-IV; 43% (95/219) of these were with CS I-II above the diaphragm, and only 20% (29/144) with CS III (Table 1). For various reasons SL was performed in less than a half of patients with early stages, the selection of candidates for SL was not randomised. Six of 130 patients with CS I-II under the diaphragm had only diagnostic laparotomy performed, and were excluded from the study. Thus, our retrospective study was carried out in 124 patients with CS I-III (95 with supradiaphragmatic CS I-II, and 29 with suspected CS III) who underwent SL. Their age ranged from 15–63 (mean 32.4) years.

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 (99/124), Ga-scintiscan of the whole body (103/124), and in last years also CT and/or US of the abdomen.

Stage was determined according to Ann Arbor criteria.[3] For the needs of this study, five supradiaphragmatic lymph node regions were defined as follows: 1. left neck and/or supraclavicular: 2. right neck and/or supraclavicular; 3. left axillary and/or subclavicular; 4. right axillary and/or subclavicular; 5. mediastinal and/or hilar nodes on the right/left or bilaterally.

Laparotomy consisted of wedge and needle biopsy of both liver lobes, splenectomy, biopsy of multiple lymph nodes (celiac, portal, splenic, paraaortic, mesenteric and iliac), biopsy of all lymph nodes that appeared to be involved with disease or the involvement was suspected on lymphangiogram and appendectomy. Metallic clips were placed at biopsy sites. An oophoropexy was performed in premenopausal women. Pneumococcal vaccine has been administrated preoperatively to patients since 1984.

Results

After laparotomy 34% (32/95) of patients with supradiaphragmatic CS I-II were upstaged (Table 2) while 45% (13/29) of patients with CS III were downstaged (Table 3).

Table 4 shows the distribution of HD by subdiaphragmatic site. The distribution by the frequency of subdiaphragmatic lymph node involvement is presented in Table 5, while the number and sites of biopsies are shown in Table 6.

Early complications were noted in 5% (7/130) and late in 5% (6/130) of patients; there were no SL-related deaths (Table 7). Three of 291 non–splenectomized patients had acute myeloblastic leukemia, and one of 130 splenectomized patients had refractory anemia with myeloblastostis; all four patients received chemotherapy according to MOPP schedule, and radiotherapy.

Because of laparotomy, the beginning of treatment had to be postponed for more than 3 weeks on average (Table 8).

Discussion

The reassessment of stage after SL may alter the treatment, which remains the major argument in favor of SL.

According to the data from literature, 25–35% of patients with supradiaphragmatic CS I-II are found to have HD under the diaphragm.[4-10] These findings are consistent with our results (34%) (Table 2). However, when comparing our findings by stage (CS I 44%, CS II 27%) with data from literature (CS I 17–32%, CS II 27–30%)[6,7,11] a high rate of positive SL in our patients with CS I is clearly evident. Perhaps the reason for this is a diffe-

Table 1. Hodgkin's disease: Number of staging laparotomies by clinical stage (Ljubljana, Sovenija 1974–1989).

Clinical Stage	Lapartomy	Non--laparotomy	Total
I-II supradiaphragmatic	95	124	219
subdiaphragmatic	6	16	22
III	29	115	144
IV	0	36	36
Total	130 (31%)	291 (69%)	421

Table 2. Hodgkin's disease with clinical stage I-II: Results of laparotomy.

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

CS = clinical stage, PS = pathological stage

Table 3. Hodgkin's disease with clinical stage III: Results of laparotomy.

CS	No. of pts.	Unchanged stage PS II	Upstaging PS IV	Downstaging PS I	Downstaging PS II	Downstaging %
III	29	12	4	5	8	45

CS = clinical stage, PS = pathological stage

Table 4. Hodgkin's disease with clinical stage I-III (n = 124): Sites of subdiaphragmatic disease after laparotomy.

Site	CS I 16 + SL/36 SL No.	CS II 16 + SL/59 SL No.	CS I-II 32 + SL/95 SL No.	CS III 16 + SL/29 SL No.
Spleen alone	6	4	10	0
Spleen + lgl III_1	9	6	15	7
Spleen + lgl III_2	0	0	0	1
Spleen + lgl III_{1+2}	1	1	2	5
Lgl alone III_1	0	3	3	0
Lgl alone III_2	0	1	1	1
Lgl alone III_{1+2}	0	0	0	1
PS III_1	15	13	28	6
PS III_2	1	2	3	6
PS IV	1	0	1	4

CS = clinical stage, SL = staging laparotomy, PS = patological stage, lgl = lymph nodes

Table 5. Hodgkin's disease with clinical stage I-III (n = 124): Subdiaphragmatic lymph node sites after laparotomy.

Site	CS I 16 + SL/36 SL No.	CS II 16 + SL/59 SL No.	CS I-II 32 + SL/95 SL No.	CS III 16 + SL/29/ SL No.
III_1:				
celiac	6	9	15	7
splenic hilus	3	4	7	10
liver hilus	1	0	1	2
III_2:				
paraaortal	1	1	2	7
mesenteric	0	0	0	0
iliac R	0	0	0	2
iliac L	0	0	0	1

CS = clinical stage, R = right, L = left

Table 6. Hodgkin's disease with clinical stage I-III (n = 124): Number and sites of biopsies, and rate of histologically positive biopsies on laparotomy.

Site of biopsy	Rate of histologically positive biopsies	
	No.	%
Liver	4/124	3
Spleen	40/124	32
Bone-marrow	1/124	0.8
Lymph nodes:		
periportal	3/11	27
spleenic hilus	17/49	35
celiac	22/64	34
paraaortal	10/94	11
iliac right	2/41	5
iliac left	2/38	5
mesenteric	0/75	0

Table 7. Hodgkin's disease with clinical stage I-III (n = 130): Laparotomy related complications.

Complications		No.	%
Early (5%):	bleeding from a. lienalis (surg)	1	0.8
	bronchopneumonia	3	2.3
	dehiscence	2	1.5
	severe wound infection	1	0.8
Late (5%):	ileus	3	2.3
	requiring surgery	2	
	herniation in the surgical scar	3	2.3
	sepsis	–	–
Death (0%)		–	–

Table 8. Hodgkin's disease with clinical stage I-II:Time from diagnosis to the beginning of therapy – laparotomized vs. non-laparotomized patients.

Laparotomy	No. of pts	Range days	$\bar{x}$ days	Chi^2	df	p
Yes	95	22–334	66.8			
				3.75	1	0.0002
No	124	23–243	43.3			

rent definition for the number of involved regions. For instance, we defined the localizations in the mediastinum and/or right and/or left hilus as one site, while other authors may have defined them differently.

In our patitents with advanced disease, the stage after Sl was found to have decreased in 45% (Table 3) while other authors[5,6,11] report decrease in only 11–27% of patients. A high percent of downstaging in our patients probably indicates a high false positive rate of diagnostic procedures under the diaphragm.

In approximately one third of patients with supradiaphragmatic CS I-II, i.e. in 28% (27/95) of our cases (Table 4) and 26%–30% of those reported by other authors,[6,11] HD in the spleen is confirmed by SL. This fact actually proves how difficult it is to prove the presence of splenic involvement by menas of clinical examinations. In patients with CS I-II and positive SL, the spleen was affected most frequently; in our series this was the case in 84% (27/32) (Table 4), while in other reports the rate ranges between 85–100% of patients.[4,6,10,12] The spleen was found to be the only subdiaphragmatic HD site in 31% (10/32) of our patients and in 20–50% of those reported by others.[10–12] According to our data, which are consistent with other reports,[11] all patients with HD in the liver also had splenic involvement. In CS I-II, HD was most frequently localized in the upper abdomen (pathological stage – PS III_1) 88% (28/32) in our series (Table 4) vs. 75–86% in other reports),[6,11] and rarely also in the lower abdomen (PS III_2) 9% (3/32) in our series vs. 8.5–18% in other reports)[6,11] while the extranodal involvement (PS IV) was rare 3% (1/32) in our series vs. 5.3–6.5% in others).[6,11] In our patients (Table 5) as well as in those reported by other authors,[5,11,13] lymph nodes of the splenic hilus and celiac lymph nodes among those of the upper abdomen (PS III_1), and the paraaortal among the lower abdominal lymph nodes (PS III_2), were affected most frequently. According to Smithers, HD, which is initially situated supradiaphragmatically, spread hematogenously under the diaphragm, first into the spleen, thereafter lymphogenously (or hematogenously) into the lymph nodes of the splenic hilus and further into other lymph nodes (but not vice versa) as well as into extranodal organs (liver, bone-marrow).[4] This theory is supported by the following facts: 1. in 25–35% of patients with CS I-II the disease is situated under the diaphragm, 2. the spleen is the most frequent and often the only site of involvement, 3. upper abdominal lymph nodes are most frequently affected together with the

spleen and rarely alone, 4. liver involvement always goes hand in hand with splenic involvement, and 5. the spleen is supplied only by efferent lymphatics.

The quality of SL can be evaluted by the assessment of its technical performance, and in patients with PS I-II treated by mantel field irradiation (MFI) also by the number of subdiphragmatic recurrences outside the radiotherapy field.

The basic criteria for quality SL were fulfilled. All the patients underwent splenectomy, biopsy of both liver lobes, biopsy of the bone marrow and biopsy of all suspicious lymph nodes, while biopsy of all lymph nodes was not done (Table 6). Premenopusal women had "oophoropexy". In ours as well as in other centers[11, 14] biopsy was most frequently performed in the following lymph nodes: those of the splenic hilus, celiac, paraaortal and mesenterial.

However, it would be unrealistic to base our assessment of the quality of SL solely on the number of subdiaphragmatic recurrences, taking into account that 2/3 of laparotomized patients were treated with subtotal nodal irradiation (STNI), for which it is difficult to find a reason. In those patients the radiation field included upper abdominal lymph nodes, which are most frequently affected in CS I-II.

Our data for the occurence of early and late SL-related complications (Table 7) are comparable to those reported by other centers.[5, 6, 10, 13] None of our patients had sepsis, though some authors[5, 10, 13, 15–17] associate splenectomy with an increased risk of sepsis (0.1–10%), while others[18] failed to prove any difference in the frequency of infection between splenectomized and non-splenectomized patients. SL is associated with 0–3% mortality[5, 10, 13, 19–22] although no procedure-related deaths have been registered by the majority of centers in the last decade, probably due to advanced SL technique, better pre- and postoperative care, as well as due to a more appropriate selection of SL candidates.[5, 10] None of our patients have died.

Some authors[23, 24] report an increased incidence of acute myeloblastic leukemia in splenectomized patients receiving MOPP chemotherapy, however, no such association has been confirmed by our results.

The onset of primary (initial) treatment was postponed for almost a month due to SL (Table 8); this data is consistent with other reports.[25]

Conclusion:

There are great differences between individual centers with respect to ghe quality of diagnostic workup, accuracy of SL performance, and the experience and competence of therapeutic team. Nevertheless, the fact that our results are comparable with those obtained elsewhere confirms our competence to perform SL safely. Despite new diagnostic procedures, SL remains the most accurate albeit aggressive diagnostic method for the verification of subdiaphragmatic spread of HD. However, the opinions about when and whether this method is still indicated at all are controversial.

References

1. Glatstein E. Guernsey JM, Rosenberg SA, Kaplan, HS. The value of laparotomy and splenectomy in the staging of Hodgkin's disease. *Cancer* 1969; **24:** 709–18.
2. Lukes RJ, Craver LF, Hall TC et al. Report of the Nomenklature Commitee. *Cancer Res* 1966; **26:** 1311–6.
3. 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.
4. Mann JL, Hafez RG, Longo WL. Role of the spleen in the transdiaphragmatic spread of Hodgkin's disease. *Am J Med* 1986; **81:** 959–61.
5. 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.
6. 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.
7. Brada M, Easton DF, Horwich 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.

8. Aragon De La Cruz G, Cardenes H, Otero J, et al. Individual risk of abdominal disease in patients with stages I and II supradiaphragmatic Hodgkin's disease: A rule index based on 341 laparotomized patients. *Cancer* 1989; **63:** 1799–803.

9. Worthy TS. Evaluation of diagnostic laparotomy and splenectomy in Hodgkin's disease (Report No 12). *Clin Radiol* 1981; **32:** 523–6.

10. 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.

11. 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.

12. Vlasak MC, Martin RG, Fuller LM, Hagemeister FB, Da Cunha MF, Shullenberger CC. Clinical staging of Hodgkin's disease: results of taging laparotomy. *Cancer Bull* 1983; **35:** 209–17.

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

14. Moxley JH, DeVita VT, Brace L, et al. Intensive combination chemotherapy and x-irradiation in Hodgkin's disease. *Cancer Res* 1967; 27: 1258–63.

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. Infection 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. Abrahamsen AF, Borge L, Holte H. Infection after splenectomy for Hodgkin's disease. *Acta Oncol* 1990; **29:** 167–70.

19. Brogadir S, Fialk MA, Coleman M, et. al. Morbidity of staging laparotomy in Hodgkin's disease. *Am J Med* 1978; **64:** 429–33.

20. Kaiser CW. Complications from staging laparotomy for Hodgkin's disease. *J Surg Oncol* 1981; **16:** 319–25.

21. Straus DJ. Strategies in the treatment of Hodgkin' s disease. *Semin Oncol* 1986; **13:** 26–34.

22. Tubiana M, Hayat M, Henry-Amar M, Breur K, Van der Verf, Messing B, Burgers M. Five-year results in the E. O. R. T. C. randomized study of splenectomy and spleen iradiation in clinical stages I and II of Hodgkin's disease. *Eur J Cancer* 1981; **17:** 355–63.

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

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

25. 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.

Radiol Oncol 1995; 29: 229–35.

Electrochemotherapy with bleomycin. The first clinical experience in malignant melanoma patients

Zvonimir Rudolf,[1] Borut Štabuc,[1] Maja Čemažar,[1] Damijan Miklavčič,[2] Lojze Vodovnik[2] and Gregor Serša[1]

[1] *Institute of Oncology, Ljubljana,*[2] *Faculty of Electrical and Computer Engineering, University of Ljubljana, Slovenia*

Electrochemotherapy offers a new approach to increase chemotherapeutic drug delivery. Exposure of cells or tissues to electric pulses potentiates the antitumor effectiveness of bleomycin and cisplatin, as demonstrated in vitro and in vivo on murine tumor models and in clinical trials in head and neck carcinoma patients. To determine the antitumor effectiveness of electrochemotherapy with bleomycin in malignant melanoma patients, cutaneous and subcutaneous tumor nodules were treated with electric pulses after intravenous administration of bleomycin. Nodules of various sizes were treated with single or multiple treatment. Also, antitumor effectiveness of electrochemotherapy with bleomycin was evaluated after several runs of electrochemotherapy treatment in the same patient with an interval of at least three weeks. The treatment effect was not dependent only on the tumor size, but also on the even distribution of the electric field for electropermeabilization of the nodules. Therefore, nodules which were treated either with a single or several runs of electric pulses, and were completely covered by the treatment, regressed within two to three weeks after therapy. Electrochemotherapy was equally effective in the same patient when it was repeated after a three weeks interval. In reported 2 malignant melanoma patients complete response was achieved in 22 out of 24 nodules treated. The preliminary results demonstrate that electrochemotherapy with bleomycin is effective in eradicating cutaneous and subcutaneous tumor lesions of malignant melanoma. Therefore, electrochemotherapy with bleomycin offers a successful approach to the treatment of cutaneous and subcutaneous tumor lesions in patients, without side effects and with high response rate. The treatment is applicable in nodules of varying sizes, since the nodules can be treated with multiple electric pulses to cover the whole tumor area and electrochemotherapy can be safely repeated several times.

Key words: melanoma-therapy; bleomycin; electric stimulation therapy

Correspondence to: Gregor Serša Ph.D., Institute of Oncology, Department of Tumor Biology, Zaloška 2, 61105 Ljubljana, Slovenia. Tel: + 386 61 323 063 ext. 29 33, Fax: + 386 61 131 41 80.

UDC: 616.5-006.81-085.84:615.277.3

Introduction

In cancer treatment electrochemotherapy utilizes electric pulses to potentiate delivery of chemotherapeutic drugs into cells. Exposure of cells or tissues to short intense electric pulses increases permeability of plasma membrane without impairing cell viability. This nonselec-

tive plasma membrane permeabilization enables drugs to diffuse into the cells and reach their intracellular targets.[1-7]

Antitumor effectiveness of electrochemotherapy was extensively studied in murine tumor models using bleomycin or cisplatin as chemotherapeutic drugs.[8-17] In these studies it has been demonstrated that for an effective antitumor action of electrochemotherapy very low drug concentration is needed, which is ineffective when used without electric pulses.[8-17] The chemotherapeutic drug can be given either systemically or locally, thus providing many possibilities of clinical application.[15,17,18]

The first reports on antitumor effectiveness of electrochemotherapy in patients have already been published. In head and neck squamous cell carcinoma patients it was demonstrated that the treatment with bleomycin (10 mg/m^2) followed by four or eight short intense electric pulses (100 μs, 1300 V/cm, frequency 1 Hz) administered through two external electrodes located on each side of the treated nodule was well tolerated. Objective responses were obtained in a majority of the 40 treated nodules (72 %) with 57 % complete response rate.[19]

The aim of our study was to determine antitumor effectiveness of electrochemotherapy with bleomycin in malignant melanoma patients with terminal disease. In the study cutaneous and subcutaneous malignant melanoma nodules of various sizes were treated with single or multiple electrochemotherapy treatments. Also, the antitumor effectiveness of electrochemotherapy with bleomycin was evaluated after several runs of treatment in the same patient.

In this preliminary communication we report 2 cases with repeated treatment for cutaneous and subcutaneous metastases of malignant melanoma.

Patients and methods

Patient description

Patient 1: The female patient, born in 1968 (H.F.No.: 731/92), had a nevus on her right thigh removed 6 months after her first childbirth, i.e. in October 1991, because during pregnancy, it grew bigger and became hemorrhagic. Histological examination after radical removal revealed a nodular type of melanoma, Breslow 2.1 mm, Clark V. Due to the metastases of the melanoma in the inguinal lymph nodes on the right, a radical inguinal dissection was carried out in December 1991. After the operation, the patient was treated with human leukocyte interferon alpha given in 2 MU doses once a week for 6 months.

In April 1993, a number of skin metastases were detected on the gluteal part of the right thigh as well as in two inguinal lymph nodes on the right. The metastatic nodes in the inguino-femoral region and two skin metastases of melanoma origin on the right thigh were removed by surgery. In June 1993, after the third of total five cycles of chemo-immunotherapy with vinblastine (4 mg/m^2 intravenous (i.v.) on day 1), lomustine (60 mg/m^2 per os on day 1), cisplatin (20 mg/m^2 given in a two-hour infusion on days 2-5) and interferon alpha-2b (6 MU subcutaneously on days 3-7), a complete response of the skin metastases in the right gluteal region was established.

In March 1994, chemotherapy with dacarbazine (400 mg/m^2 i.v. on days 1-5) was applied due to recurrent melanoma growth on the skin and in the inguinal and retroperitoneal lymph nodes. The four-month treatment resulted in a complete response of skin metastases, whereas a partial response was noted in the inguinal and retroperitoneal lymph nodes.

Four months after completed therapy, skin metastases of melanoma were cytologically confirmed in the right gluteo-femoral region extending over a 30 x 20 cm surface. The inguinal and retroperitoneal lymph glands were not found to have enlarged since the previous examination. US and CT examinations failed to detect metastases in the visceral organs. Performance status by Karnofsky scale was 100. The total blood count and chemistry were within normal limits.

Patient 2: The patient, born in 1951 (H.F.No.: 2721/92), was operated on in January 1992 in order to have a rapidly growing pigmen-

ted nevus on the left thigh removed. Histological examination after radical removal revealed a nodular type of melanoma, Breslow 3.9 mm, Clark III. In July 1992, a radical inguino-femoral dissection of the lymph nodes on the left was carried out because of cytologically confirmed melanoma metastases in the inguinal lymph nodes. After surgery, the patient was receiving human leukocyte interferon alpha, 2 MU once weekly for 2 months. During the treatment with human leukocyte interferon alpha, a number of skin metastases emerged on the left thigh. In October 1992, the patient received radiotherapy for the skin metastases on the left thigh and was simultaneously also treated by chemo-immunotherapy with dacarbazine (interferon alpha-2b days 1-4, 3 MU daily; and dacarbazine 800 mg/m^2 on day 5 i.v. bolus repeated every three weeks). Altogether, the patient had undergone four treatment cycles. In January 1993, a complete response of the skin metastases was observed in the irradiated area whereas further progression of metastases was noted in the area outside the radiation field. Between January and July 1993, the skin metastases with the largest diameter not exceeding 5-15 mm were treated with several intratumoral applications of interferon alpha-2b. This treatment resulted in a complete response of all skin metastases, which was maintained until June 1994, when further progression of the disease was noted in the iliac lymph nodes on the left and in the inguinal lymph nodes bilaterally, together with the occurrence of skin metastases on the left thigh and shank, and pulmonary metastases. After three cycles of chemo-immunotherapy with dacarbazine and interferon alpha-2b a complete response of the pulmonary metastases was observed along with further progression of skin and lymph node metastases. The systemic treatment was therefore stopped and replaced with irradiation of the bilateral inguinal lymph node metastases. The patient received daily dose of 600 cGy twice a week to an irradiation field of 9 x 13 cm; left and right inguinal lymph node sites were irradiated with a total dose of 3000 cGy each.

Before electrochemotherapy treatment of skin metastases, the patient's performance status by Karnofsky scale was 60; several subcutaneous metastases with the largest diameter ranging from 2 mm to 3 cm were noted on the left thigh and shank. The metastatic inguinal lymph nodes were enlarged on both sides. No melanoma metastases could be found in the lung and liver. The total blood count and chemistry were within the limits of normal values.

Electrochemotherapy treatment

Electrochemotherapy consisted of i.v. administration of bleomycin (Mack, Germany) followed by exposure of melanoma nodules to electric pulses. Bleomycin was administered i.v. in 30 seconds at the dose of 10 mg/m,^{2} regardless of the number of nodules treated. The interval between bleomycin administration and electric pulse application was 8 minutes. The nodules to be treated were sprayed few minutes before electric pulse application with xylocaine (Astra, Germany) in order to avoid pain. Square wave electric pulses of 100 μs, 910 V amplitude (1300 V/cm), frequency 1 Hz were delivered through two parallel stainless steel electrodes (distance 7 mm; width 7 mm; length 14 mm, with rounded tips) with an electropulsator Jouan GHT 1287 (Jouan, France). Electrical parameters were controlled using oscilloscope HM 205-3 (Hameg Instruments, Germany). Electric pulses were delivered in two trains of four pulses with one second interval, delivered in two perpendicular directions (4 + 4 configuration). Good contact between the electrodes and the skin was assured by means of conductive gel. When several nodules were treated in the same session electric pulses were delivered one after the other at the intervals of at least one minute. Large nodules were treated with several runs of electric pulses, administered in adjacent position in the way that the whole tumor area was covered.

Follow up

During the electrochemotherapy treatment patients were carefully monitored for evaluation

of treatment effects. After the treatment the patients remained in the outpatients clinic for two hours, when they were examined and released. As outpatients they were examined weekly and the treatment response was evaluated. Tumor nodules were measured with caliper and were photographed before and after the treatment. The therapeutic response of electrochemotherapy was scored according to WHO guidelines as progressive disease (PD) if tumors increased more than 20 % in size, no change (NC) if the tumors decreased in size less than 50 %, partial response (PR) if the tumors decreased more than 50 % and complete response (CR) if they became unpalpable.

Results

Case reports

Patient 1 received bleomycin 10 mg/m^2 i.v. on December 6, 1994; 8 minutes later electric pulses were applied to two metastases measuring 5 x 5 x 3 mm (39 mm^3) and 5 x 3 x 2 mm (16 mm^3), respectively; another two lesions untreated by electric pulses served as controls. Both electrochemotherapy treated lesions underwent complete response after 14 days while the control lesions progressed. (Table 1, session A). Second electrochemotherapy session (Table 1, session B) was introduced on December 21, 1994 for a skin metastasis of 22 x 27 x 2 mm (622 mm^3). Electric pulses were applied consecutively in 12 runs, administered in adjacent position, covering the whole tumor area. After 21 days a complete response of the treated skin metastases was confirmed, as illustrated in Figure 1A and B.

Table 1. Patient 1: electrochemotherapy conditions and effects.

Session	No. of treatments*	No. of nodules	Size of the treated nodules (mm^3) Before treatment	– 4 weeks later	Response+
A	none	1	39	188	PD
	none	1	9	56	PD
		1	39	0	CR
	1	1	16	0	CR
B	12	1	622	0	CR

* treatment = application of 4 + 4 electric pulses
+ PD – progressive disease; CR – complete response

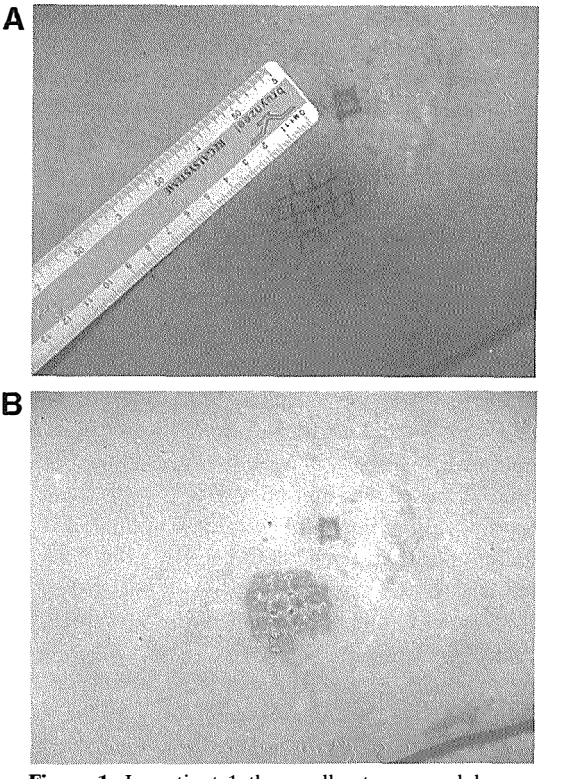


Figure 1. In patient 1 the smaller tumor nodule was treated with single application (4 + 4) of electric pulses in the first session. The marks where the electrodes were positioned are still visible (A). In the bigger tumor nodule the positions of the electrodes for the 12 treatments with electric pulses in 4 + 4 configuration were marked with ballpen. Three and five weeks after the first and the second electrochemotherapy session, both tumor nodules were in complete response (B). Electrode marks and superficial scabs on the bigger tumor nodule are clearly visible.

In January 1995, the patient was referred to irradiation of the central nervous system due to two inoperable brain metastases. Because of severe neurological symptoms and epilepsy, no further electrochemotherapy treatment of skin metastases was indicated or applied. The patient was maintained on symptomatic therapy until May 1995, when she died of brain edema due to further progression of brain metastases.

All electrochemotherapy treated metastases remained in complete response until the patient's death.

Patient 2 received bleomycin 10 mg/m^2 i.v. on October 24, 1994, 8 minutes later two metastases measuring 29 x 24 x 8 mm (2915 mm^3)

and 16 x 11 x 5 mm (461 mm^3), respectively, on the left thigh and shank were treated by electric pulses, while another metastasis measuring 18 x 13 x 5 mm (613 mm^3) untreated by electric pulses served as a control (Table 2, session A). The control metastasis and smaller metastasis treated with electrochemotherapy progressed, while the bigger one underwent a decrease.

On November 28, 1994, after the application of bleomycin, 5 skin metastases on the left thigh and one on the left forearm, their largest diameters ranging from 4 to 15 mm, were treated with electric pulses (with tumor volumes 251, 88, 17, 17, 17 mm^3, respectively). The biggest one (on the left thigh, 251 mm^3) was treated with two runs of electric pulses, covering the whole tumor area. All the electrochemotherapy treated lesions underwent complete response (Table 2, session B).

On December 14, 1994, after the application of bleomycin, 13 skin metastases, with the largest diameters from 4 to 6 mm, on the back of the right thigh and on the right side of the thorax were treated with electric pulses (average tumor volume 20 mm^3). All electrochemotherapy treated lesions underwent complete response (Table 2, session C).

In January 1995, there were metastases detected in the lung, liver, spleen, and in the retroperitoneal lymph nodes. The patient died of liver metastases in February 1995. When he died, all the metastases treated with electrochemotherapy on November 28 and December 14, 1994 were found to have regressed completely; the bigger of the two metastases treated on October 24, 1994 was in regression, whereas the smaller one was in progress.

Table 2. Patient 2: electrochemotherapy conditions and effects.

Session	No. of treatments*	No. of nodules	Size of the treated nodules (mm^3) Before treatment	– 4 weeks later	Response+
A	none	1	613	1253	PD
	4	1	2915	2027	NC
	1	1	461	785	PD
B	2	1	251	0	CR
	1	1	88	0	CR
	1	4	17	0	CR
C	1	13	20	0	CR

* treatment = application of 4 + 4 electric pulses
+PD – progressive disease; NC – no change;
CR – complete response

Side effects

There were no major local or general side effects noted. Muscle contractions were observed after each pulse. The contractions were instantaneous, disappearing immediately at the end of each pulse. Although the contractions were tolerable in treated regions, an unpleasant sensations described as a local pain or shock were reported by the patients. Several hours after treatment, the only noticeable effect was the occurrence of erythema and slight edema at the treated area. These symptoms disappeared in one day. Marks of the electrodes were visible for several weeks after the treatment. No significant changes in blood count and biochemistry were observed.

Discussion and conclusion

The preliminary results of an on-going trial on malignant melanoma patients demonstrated that electrochemotherapy with bleomycin is effective in eradicating cutaneous and subcutaneous tumor lesions of malignant melanoma. In the two reported malignant melanoma patients complete response was achieved in 22 out of 24 nodules treated.

Our results support the outcome of the first clinical trial with electrochemotherapy with bleomycin of head and neck squamous cell carcinoma, where 57 % of the treated nodules were in complete response after the treatment.[19] The treatment protocol of our study on malignant melanoma and the study on squamous cell carcinoma are similar except some modifications. Melanoma patients with cutaneous and subcutaneous nodules were treated without general anesthesia, with electric pulses delivered in 4 + 4 configuration. Furthermore, treatment protocol was extended to several runs of electric pulses being applied to bigger tumor nodules, and repeated treatment with electrochemotherapy in the same patient with a few weeks interval.

As reported, antitumor effectiveness of electrochemotherapy was dependent on tumor size, the best response being noted in smaller nodules up to 20 mm^3 of volume. Nevertheless, it seems that the response is dependent also on the even distribution of the electric field for electropermeabilization of nodules, since bigger nodules that were treated with several runs of electric pulses completely covering the tumor area regressed within two to three weeks after treatment. Also, electrochemotherapy was equally effective in the same patient when it was repeated after a three-week interval. These first results demonstrate that electrochemotherapy is feasible as a local form of treatment since it does not cause significant side effects, either immediate or delayed. All the observed side effects appear to be reversible. A clear antitumor effect was observed in patients with disease resistant to conventional methods. Furthermore, electrochemotherapy could be safely repeated.

Acknowledgement

This work was supported by the Ministry of Science and Technology of the Republic of Slovenia.

References

1. Melvik JE, Pettersen EO, Gordon PB, Selgen PO. Increase in cis-dichlorodiammineplatinum (II) cytotoxicity upon reversible electropermeabilization of the plasma membrane in cultured human NHIK 3025 cells. *Eur J Cancer Clin Oncol* 1986; **22:** 1523-30.

2. Nutt AK, Mansouri A, Henle KJ. Response of cisplatin resistant tumor cells to electroporation and cisplatin. *Proc Annu Meet Am Assoc Cancer Res* 1991; **32:** A2229.

3. Rols MP, Teissie J. Electropermeabilization of mammalian cells. Quantitative analysis of the phenomenon. *Biophys J* 1990; **58:** 1089-98.

4. Orlowski S, Mir LM. Cell electropermeabilization: a new tool for biochemical and pharmacological studies. *Biochim Biophys Acta* 1993; **1154:** 51-63.

5. Orlowski S, Belehradek Jr J, Paoletti C, Mir LM. Transient electropermeabilization of cells in culture. Increase in cytotoxicity of anticancer drugs. *Biochem Pharmacol* 1988; **37:** 4727-33.

6. Poddevin B, Orlowski S, Belehradek Jr J, Mir LM. Very high cytotoxicity of bleomycin introduced into the cytosol of cells in culture. *Biochem Pharmacol* 1991; **42:** S67-S75.

7. Belehradek Jr J, Orlowski S, Ramirez LH, Pron G, Poddevin B, Mir LM. Electropermeabilization of cells in tissues assessed by the qualitative and quantitative electroloading by bleomycin. *Biochim Biophys Acta* 1994; **1190:** 155-63.

8. Okino M, Mohri H. Effects of a high-voltage electrical impulse and an anticancer drug on in vivo growing tumors. *Jpn J Cancer Res* 1987; **78:** 1319-21.

9. Mir LM, Orlowski S, Belehradek Jr J, Paoletti C. Electrochemotherapy potentiation of antitumor effect of bleomycin by local electric pulses. *Eur J Cancer* 1991; **27:** 68-72.

10. Belehradek Jr J, Orlowski S, Poddevin B, Paoletti C, Mir LM. Electrochemotherapy of spontaneous mammary tumours in mice. *Eur J Cancer* 1991; **27:** 73-6.

11. Okino M, Esato K. The effects of a single high voltage electrical stimulation with an anticancer drug on in vivo growing malignant tumors. *Jpn J Surg* 1990; **20:** 197-204.

12. Salford LG, Persson BRR, Brun A, Ceberg CP, Kongstad PCh, Mir LM. A new brain tumor therapy combining bleomycin with in vivo electropermeabilization. *Biochem Bioph Res Co* 1993; **194:** 938-43.

13. Heller R, Jaroszeski M, Leo-Messina J, Perrot R, Van Voorhis N, Reintgen D, Gilbert R. Treatment of B16 mouse melanoma with the combination of electropermeabilization and chemotherapy. *Bioelectrochem Bioenerg* 1995; **36:** 83-7.

14. Serša G, Čemažar M, Miklavčič D, Mir LM. Electrochemotherapy: variable anti-tumor effect on different tumor models. *Bioelectrochem Bioenerg* 1994; **35:** 23-7.

15. Čemažar M, Miklavčič D, Vodovnik L, Jarm T, Rudolf Z, Štabuc B, Čufer T, Serša G. Improved therapeutic effect of electrochemotherapy with cisplatin by intratumoral drug administration and changing of electrode orientation for electropermeabilization on EAT tumor model in mice. *Radiol Oncol* 1995; **29:** 121-7.

16. Serša G, Čemažar M, Miklavčič D. Antitumor effectiveness of electrochemotherapy with cis-diamminedichloroplatinum(II) in mice. *Cancer Res* 1995; **55:** 3450-5.

17. Heller R, Jaroszeski M, Leo-Messina J, Glass F, Perrot R, Van Voorhis N, Reintgen D, Gilbert R. Electropermeabilization/chemotherapy parameter examination for effective anti-tumor treatment. XIIth international symposium on bioelectrochemistry and bioenergetics, Sevilla 1994, Book of abstracts, OIII-3.

18. Mir LM, Orlowski S, Belehradek JJr, Tessie J, Rols MP, Serša G, Miklavčič D, Gilbert R, Heller R. Biomedical applications of electric pulses with special emphasis on antitumor electrochemotherapy. *Bioelectroch Bioenerg* 1995; **38:** 203-7.

19. Belehradek, M., Domenge, C., Luboinski, B., Orlowski, S., Belehradek, Jr. J., Mir, L. M. Electrochemotherapy, a new antitumor treatment. First clinical phase I-II trial. *Cancer* 1993; **72:** 3694-700.

Radiol Oncol 1995; 29: 236–9.

Cytostatic chemotherapy for small cell lung cancer in patients of age 75 years or older

Peter Berzinec, Milan Kroslak, Stefan Petricek, Magdalena Arpasova, Helena Kuzmova

Institute of TB and Respiratory Diseases, Nitra, Slovakia

Eleven patients of age 75 years or older with histologically and/or cytologically proven small cell lung cancer (SCLC) were treated at our institution during the period of 5 years 1990–1994.
Patients characteristics: 10 men, 1 woman, age: median: 77, range: 75–82 years, performance status WHO ≤ 3.
Treatment: different treatment schedules were used according to patients status and comorbidity. Single drug therapy with teniposide or etoposide was used in five patients, in six patients further cytostatics (mostly carboplatin) were used in addition.
Results: response rate after 2 courses of therapy: complete response: 1 (9%), partial response: 5 (45%), stable disease: 3 (27%), progression: 2 (18%), survival time: median: 7.5, range: 1–32 + months, adverse effects: except for 3 leukopenias (2x WHO grade 3, 1x WHO grade 4) no serious adverse effects.
Conclusion: currently available cytostatics for SCLC, especially epipodophyllotoxins alone or in combination with carboplatin, seem to be effective and (with adequate premedication) well tolerated even in very old patients.

Key words: lung neoplasms-drug therapy; carcinoma, small cell; antineoplastic agents; aged

Introduction

Small cell lung cancer accounts for approximately 25% of all cases of lung cancer.[1] Cytostatic chemotherapy is the standard treatment modality as initial therapy and favorably influences both quality and quantity of survival. However, very old patients are regarded as a poor candidates for aggressive combination chemotherapy. Chronological age per se should not, in our view, exclude patient from the standard protocol of treatment. Most of these patients, if not all, may have, however, comorbid conditions such as chronic obstructive lung disease, congestive heart failure, coronary artery disease, or others, that will influence the decision of chemotherapy. Further, there is an age-related reduction in creatinine clearance.[2] The wishes and expectations of the elderly patient may differ and must be considered before treatment decision as well.

There are only a few data in the literature about the cytostatic chemotherapy for small cell lung cancer in elderly patients and in fact

Correspondence to: Peter Berzinec, M. D., Head, Department of Oncology, Institute of TB and Respiratory Diseases, Puskinova 134, 949.88 Nitra, Slovakia; Fax: 42 87 513092.

UDC: 616.24-006.6-085-053.9

Table 1. Patients characteristics.

No. of patients	11
Male	10
Female	1
Age (yrs)	
median	77
range	75–82
Performance status	
WHO 1	3
WHO 2	5
WHO 3	3
Disease stage	
Limited disease	5
Extensive disease	6

none aimed specifically at the very old patients. The aim of our retrospective study was to assess the results of cytostatic chemotherapy for small cell lung cancer in 75 years or older patients, i. e. the patients who are considered to be very old.

Patients and methods

Eleven patients of 75 years or older with histologically and/or cytologically proven small cell lung cancer were treated at our institution during the period of 5 years: 01. 01. 1990 – 31. 12. 1994. Characteristics of the patients are shown in Table 1.

By the start of chemotherapy 5 patients were considered to have limited disease (LD), 6 extensive disease (ED) – defined as a tumor dissemination beyond the hemithorax and its regional node drainage (mediastinal, scalene and supraclavicular).

Different cytostatic treatment schedules were used according to patients status and comorbidity. Single drug therapy with epipodophyllotoxins – teniposide or etoposide – was used in five patients, in six patients further cytostatics (mostly carboplatin, in one case cyclophosphamide) were used in addition. The overview of treatment schemes most often used in our patients is in Table 2. Chemotherapy was planned for at least 2 courses and maximum 6 courses in responders. Chest radiotherapy was suggested to 2 patients with LD after the chemotherapy, but it was accepted only by 1 patient.

Table 2. Therapeutic protocols.

No.	Drug	Daily dose mg/m^2	Administration route	Day	Frequency
1.	Etoposide	150	p. o	1–5	3 weeks
2.	Etoposide	120	i. v.	1–3	3 weeks
3.	Teniposide	30	i. v.	1–5	15 days
4.	Etoposide	120	i. v.	1–3	3 weeks
	Carboplatin	300	i. v.	1	

Patients evaluation before therapy included a history and physical examination, complete blood count, urinanalysis, electrolyte levels, chemical survey, roentgenograms and ultrasound investigation. These investigations were repeated before each course of therapy. CT was used only selectively, bone radionuclide scans were used in the same manner.

A complete response was defined as the disappearance of all evidence of tumor for at least 4 weeks. A partial response was defined as a 50 % or greater decrease in the sum of the products of the diameters of all measured leasions persisting at least 4 weeks. No lesion could increase in size and no lesion could appear. Progressive disease was defined as any increase greater than 25 % in the sum of the products of diameters of any observed lesion or as the appearance of any new lesion. Survival was calculated from the start of chemotheraphy.

Results

Response data

The response data after 2 courses of therapy are shown in Table 3.

The overall response rate was 6/11 (54 %). The response rate in the group of patients treated with single drug therapy – teniposide or etoposide – was 3/5 (60 %), in the group of patients treated with combination of cytostatics: 3/6 (50 %).

Eleven patients received total 32 courses of chemotherapy, mean 2.9 courses per patient, range: 1 – 6 courses. Despite our intention to administer at least 2 courses of chemotherapy, 2 patients received only 1 course of treatment.

Table 3. Response data and survival.

No. of patients	11
Complete response	1 (9 %)
Partial response	5 (45 %)
Stable disease	3 (27 %)
Progression	2 (18 %)
Overall response	6 (54 %)
Survival (month)	
median	7.5
range	1–32 +
Follow-up (month)	
median	7.5
range	1–32

This resulted from rapidly progressive disease in one patient and from overall somatic deterioration in second patient by progressive cancer disease. These patients were included into the analysis of the results, as well as one patient with chest radiotherapy followed after 4 courses of chemotheraphy with teniposide (the survival time in this last patient was 9 months).

Toxicity

Except for 3 leukopenias (WHO grade 3: 2x, WHO grade 4: 1x) no serious side effects were observed. All patients received antiemetics, mostly oral ondansetron alone or in combination with intravenous dexamethason, given as a standard before the chemotherapy and repeated if needed, so there was virtually no vomitus.

Discussion

Elderly patients were frequently excluded from clinical trials until recently,[3] so it is not surprising that the data in the literature about the treatment of small cell lung cancer in this group of patients are limited. Smit et al.[4] reported overall response rate 71 % in 35 patients older than 70 years treated with oral etoposide 800 mg/m^2 over 5 consecutive days. Toxicity was minimal and there were no hospitalizations needed for drug-related toxicity. Carney et al.[5] observed with the same treatment scheme overall response rate 79 % in a group of 53 patients in the age 70 years or older.

Bork et al.[6] observed response rates 77 % and 66 % respectively in the comparative study of teniposide and etoposide in a dose 70 mg/m^2 for 5 days for both drugs and median survival time 11 v 8.5 months in 92 patients of age 70 years or older. Other authors[7,8] have reported response around 50 % in elderly patients treated with teniposide as single drug therapy, but Cerny et al.[8] reported high toxic death rate 5 of 30 in their group of patients with a fixed dose of teniposide 100 mg/m^2 every 3 weeks.

Bishop[9] and Raghavan et al.[10] studied the outcome in 26 patients treated with carboplatin + etoposide combination who were aged 70 years or older. An objective response was seen in 88 % of patients. Neutropenia and trombocytopenia were seen more often than in younger patients, but none of the elderly patients had infective or bleeding sequelae.

The overall response rate to the chemotherapy seen in our patients in the age of 75 years or older was 54 % – similar to the results of the other, above mentioned authors. Median survival time was 7.5 months after the start of chemotherapy. In one patient the long – term survival has been achieved and the patient continues to live in good overall status 32 months after the start of chemotherapy i. e. 28 months after finishing 4 courses of carboplatin/etoposide chemotherapy. The toxicity of chemotherapy in our group of patients as a whole was acceptable.

Considering the fact, that the median survival time for untreated patients with small cell lung cancer is only 2 or 7 weeks for extensive or limited disease respectively,[11] we may conclude, that the currently available cytostatics, especially epipodophyllotoxins alone or in combination with carboplatin, seem to be effective and with adequate premedication well tolerated even in very old patients.

References

1. Ihde CD, Pass IH, Gladstein JE. Small cell lung cancer. In: DeVita TV, Hellman S, Rosenberg AS, eds. *Cander, Principles and Practice of Onco-*

logy. 4th Edition. Philadelphia: J. B. Lippincott Company, 1993: 723–58.

2. Einhorn HL. Approaches to drug therapy in older cancer patients. *Oncology* 1992; **6** (Suppl 2): 69–73.

3. Keane M, Carney DN. Treatment of elderly patients with small cell lung cancer. *Lung Cancer* 1993: **9** (Suppl 1): 91–8.

4. Smit EF, Carney DN, Harford P, Slejfer DT, Postmus PE. A phase II study of oral etoposide in elderly patients with small cell lung cancer. *Thorax* 1989; **44:** 631–3.

5. Carney DN, Grogan L, Smit EF, Harford P, Berendsen HH, Postmus PE. Single-agent oral etoposide for elderly small cell lung cancer patients. *Semin Oncol* 1990; **17** (Suppl. 2): 49–53.

6. Bork E, Ersboll J, Dombernowsky P, Hansen M, Hansen HH. Teniposide and etoposide in previously untreated small-cell lung cancer: a randomised study. *J Clin Oncol* 1991; **9:** 1627–31.

7. Holoye PY, Winn RJ, Craig K. Phase II study of teniposide in small cell bonchogenic carcinoma. *Proc Am Soc Clin Oncol* 1989; **8:** 243 [abstr.].

8. Cerny T, Pedrazzini A, Joss RA. Unexpected high toxicity in a phase II study of teniposide (VM-26) in elderly patients with untreated small cell lung cancer (SCLC). *Eur J Cancer Clin Oncol* 1988; **24:** 1791–4.

9. Bishop JF. Carboplatin/etoposide in small cell lung cancer. *Oncology* 1992; **49** (Suppl. 1): 11–8.

10. Raghavan D, Bishop JF, Stuart-Harris R, Zalcberg J, Morstyn G, Kefford RF, Matthews JP. Carboplatin-containing regimens for small cell lung cancer: implications for management in the elderly. *Semin Oncol* 1992; **19** (Suppl. 2): 112–6.

11. Sunder-Plassman L, Fink U. *Bronchialkarzinom*. München: Tumorzentrum, 1991.

Radiol Oncol 1995; 29: 240–7.

Analytical representations of clinical electron beam central axis depth doses

Wieslaw Wierzbicki[1] and Ervin B. Podgorsak[2]

[1] Département de physique biomédicale, Hôpital Notre-Dame; [2] Department of Medical Physics, Montreal General Hospital Montréal, Québec, Canada

Analytical expressions proposed to date to approximate central axis electron beam depth dose distributions are reviewed and their quality of fitting discussed. A recently developed analytical expression based on only four fitting parameters is analyzed. The expression approximates well the measured electron beam data from two commercial linear accelerators in the field size range from $4\times4\,cm^2$ to $25\times25\,cm^2$ and in the energy range from 4 MeV to 22 MeV in all four regions of the depth dose curve: build-up, dose maximum, dose fall-off, and bremsstrahlung contamination.

Key words: electrons, particle accelerators, depth doses

Introduction

The particular energy loss characteristics of electrons as they penetrate into tissue make electrons suitable for use in treatment of superficial malignant diseases. Advantages of electrons over superficial x-rays and brachytherapy are a better dose homogeneity in the target volume and a lower dose in tissues surrounding the target. The electron beam depth dose distributions consist of four regions: buildup, dose maximum, dose fall-off, and bremsstrahlung contamination. Ever since the first depth dose distributions of clinical electron beams were measured in water, attempts have been made to describe the measured distributions with analytical expressions. In the individual dose regions, it is relatively easy to approximate the dose distributions analytically; however, the distributions are difficult to describe accurately with a single expression covering all four regions simultaneously.

In 1953 Laughlin et al.[1] proposed the first analytical expression to reproduce electron depth doses in water. Since then, attempts to describe analytically depth doses of clinical electron beams have continued with varying degrees of success.[2–12] With each subsequent new proposal, the analytical expressions became more accurate but also, to a certain degree, more complicated, as they depended on an ever-increasing number of empirical parameters involved in the curve fitting process.

In this note, we present a summary of expressions that were proposed to date by various authors to describe electron beam depth dose data analytically. For each expression, we show the fit it provides to a typical measured depth dose distribution. We also provide an analysis of an analytical expression which we developed

Correspondence to: Wieslaw Wierzbicki, Ph.D., Département de physique biomédicale, Hôpital Notre-Dame, 1560, rue Sherbrooke Est, Montréal, Québec H2L 4M1.

UDC: 615.849.5:621.384.64

recently for description of electron beams of various energies and field sizes.[12] The expression reproduces electron beam central axis depth doses well in all four regions of the depth dose curve, and it achieves this with a smaller number of empirical parameters than does the most accurate approximation proposed previously.[11]

Analytical expressions for electron beam depth doses

The first analytical representation of clinical electron depth doses was proposed by Laughlin et al.[1] as follows:

$$D(x) = 110 - 10 \exp [\mu (x - x_m)] , \quad (1)$$

where D(x) is the percentage depth dose at depth x in the medium, μ is an attenuation coefficient, and x_m is the depth of dose maximum. The equation is simple, depends on only two parameters (μ and x_m), but agrees with measured data only for relatively low energy electrons in the dose fall-off region. The equation is valid neither for the dose build-up region nor for the bremsstrahlung region.

To provide a better analytical description of electron depth doses, Bagne[2] proposed a modification to Eq. (1) through the addition of a cubic term in the exponent:

$$D(x)=110-10 \exp[\mu_m ((x-x_m) \rho - \lambda (x-x_m)^3 \rho^3)] , \quad (2)$$

where D(x), x and x_m were defined above, μ_m is a mass attenuation coefficient, ϱ the density of the medium, and λ a third adjustable parameter. This equation, although an improvement over Eq. (1), is also only valid for the dose fall-off region.

Pacyniak and Pagnamenta[3] derived the following equation based on physical arguments:

$$D(x)=100\left(\frac{R-x}{R-x_m}\right)^A\left(1 + A\frac{x-x_m}{R-x_m}\right) , \quad (3)$$

where R is the practical electron range in the medium and x_m again the depth of maximum dose. The third parameter A is defined as $A = \mu (R/E)$, where μ represents an attenuation coefficient and E the average electron energy. In contrast to Equations (1) and (2), Eq. (3) provides a fairly good approximation to the measured depth doses in the build-up region, dose maximum region as well as in the dose fall-off region. At depths beyond the range R, however, the equation generates high negative percent depth doses and therefore cannot account for the bremsstrahlung contamination of the electron beam.

Further attempts to parametrize electron depth dose data were based on different types od mathematical functions which can mimic the dependence of measured depth doses on the depth in phantom. One group the these proposed approximations[4–7] uses polynomial functions as follows:

$$D(x)=100 + (x-x_m)^2[a_2 + a_3 x + a_4 x^2 + a_5 x^3] , \quad (4)$$

$$D(z) = 100 + \sum_{m=2}^{m=5} a_m z^m \text{ with } z = \frac{x-x_m}{E} \quad (5)$$

$$D(x) = 100\left[a_0 + a_1 \frac{x}{x_m} + a_2\left(\frac{x}{x_m}\right)^2\right]^{\left(\frac{x}{x_m}-1\right)} , \text{ and} \quad (6)$$

$$D(x) = a_0 (a_1 - 2 a_2 s + a_3 a_4 s^{(a_4-1)} + a_5 a_6 s^{(a_6-1)}) \exp[- (a_1 s + a_2 s^2 + a_3 s^{(a_4)} + a_5 s^{(a_6)}] + B \quad (7)$$

where x_m again is the depth of the dose maximum, a_i are adjustable parameters, and parameter B in Eq.(7) is a bremsstrahlung dose-related function. Variables z and s in Equations (5) and (7), respectively, are normalized depths defined as $z = (x-x_m)/E$ where E is the electron beam energy, and $s = x/R_p$ where R_p is the measured practical range of electrons.

It was shown[4–6] that Equations (4), (5) and (6) fit the measured electron depth doses relatively well in the build-up region, dose maximum region, and in the sharp dose fall-off region for electron energies from 5 MeV to 20 MeV and for field sizes from $5\times5\,cm^2$ to $25\times25\,cm^2$. However, they fail, similarly to Eq. (3), to provide an acceptable approximation in the bremsstrahlung background region in which they generate high negative depth dose values, a property typical of all proposed polynomial

representations of electron depth doses. Equation (7) approximates all four electron depth dose regions but is obviously quite complicated as it depends on a large number of fitting parameters.

Another group of mathematical approximations to electron beam depth doses is based on a modified Fermi-Dirac distribution function:[8–10]

$$D(x) = \frac{100}{1 + \exp\left[\frac{(x - x_{50})}{a}\right]}, \tag{8}$$

$$D(x) = \frac{108}{1 + a\exp[\mu (x - x_s)]}, \text{ and} \tag{9}$$

$$D(x) = \frac{a_1 x^2 + a_2 x + a_3}{1 + \exp[a_4 (x - a_5)]}, \tag{10}$$

where x_{50} in Eq.(8) is the depth in the dose fall-off region at which the dose reaches 50 % of the maximum value and x_s in Eq. (9) is the depth in the fall-off region at which the dose is equal to the surface dose. Parameter a in Equations (8) and (9) and parameters a_i in Eq. (10) are adjustable parameters. Equations (8) and (9) give much better approximations to electron depth doses in the build-up region than Equations (1) and (2), but they are considerably less efficient than the polynomial Equations (3 through 7) in simultaneously approximating both the build-up region and the dose fall-off region. Moreover, they still tend to generate negative percent depth doses in the bremsstrahlung contamination region.

An excellent quality of curve fitting was achieved with Eq. (10), which has five fitting parameters and gives a very good approximation for electron depth doses in the build-up region, dose maximum region, and the dose fall-off region. However, at large depths Eq. (10) yields either zero or negative values and thus cannot reproduce the dose behaviour in the bremsstrahlung region.

A more recent and very successful analytical representation of electron depth doses as a function of the depth in phantom was proposed by Strydom[11] as follows:

$$D(x) = \frac{(100-B)}{1 - a_1 (x - x_m)} \exp\{-(x - x_m)^2[a_2 + a_3 (x - x_m) + a_4 (x-x_m)^2]\} + B \tag{11}$$

where x_m again is the depth of the dose maximum, B represents the bremsstrahlung dose bakcground, and a_i are adjustable parameters. This equation has in effect six varying parameters: (four fitted parameters: a_1, a_2, a_3, a_4 and two measured parameters: x_m and B), and describes very well the electron depth doses in all dose regions, including the bremsstrahlung dose background region.

The various approaches to analytical descriptions of electron beam depth dose distributions discussed above and given by Equations (1) though (11) are illustrated in Figure 1. A typical elecron beam depth dose curve measured in water (9 MeV, field size: $10\times10\,cm^2$), and shown as data points, is approximated by various expressions (solid curves) proposed to date, starting (a) with the rudimentary initial proposal of Laughlin et al.[1] with two parameters and ending with (j) the excellent fitting based on six parameters proposed by Strydom.

The varying quality of the curve fitting results for each to the approaches proposed to date is clearly evident from Figure 1, which also gives for each of the approaches the number of parameters required for the curve fitting procedure and the year of the proposal. It is evident that the curve fitting proposals improved with time but they also became considerably more complicated as they depended on ever-increasing numbers of fitted and measured parameters.

As shown in Figure 1 (j), Strydom's equation based on six parameters provides an excellent approximation to measured electron depth doses with four fitted parameters in addition to two measured parameters: the depth of dose maximum and the bremsstrahlung contamination. Thus, the objective of an accurate approximation of the whole electron beam central axis dose distribution has been met successfully with six parameters in Eq. (11). It is clear that new approaches will not be able to improve the quality of fitting; however, they might simplify the fitting procedure by using equations which

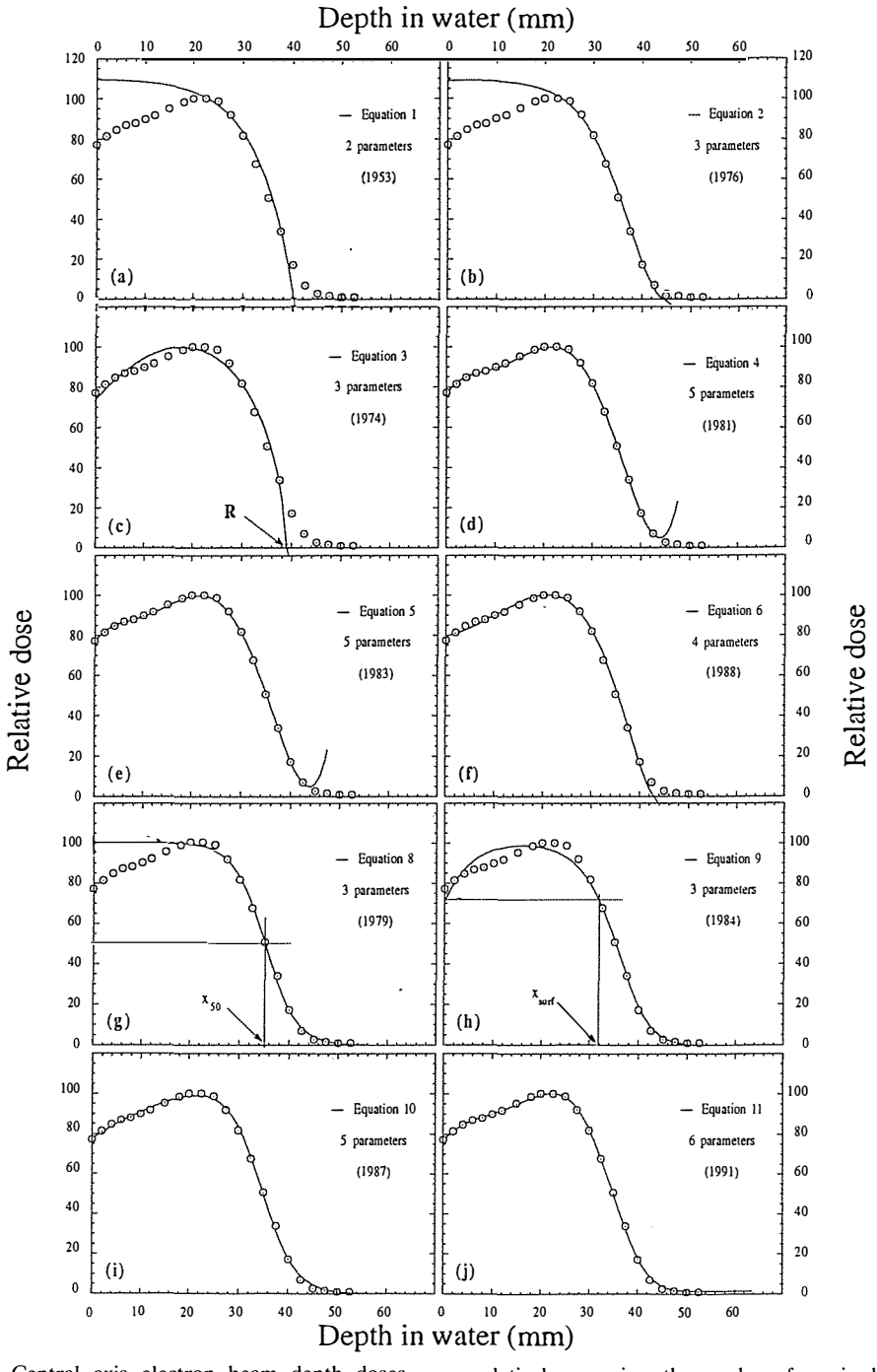


Figure 1. Central axis electron beam depth doses calculated from analytical expressions given by Equations (1) through (6) and (8) through (11), compared to data measured for a 9 MeV electron beam with a field size of $10 \times 10\,cm^2$. Calculated data are shown with solid curves, measured data as points. For each analytical expression, the number of required parameters and the year the expression was developed are also given. Equations (1) through (6) correspond to parts (a) through (f), respectively. Equations (8) through (11) correspond to parts (g) through (f), respectively.

achieve a similar quality fit with a lower number of parameters.

We have recently proposed[12] a new analytical equation which contains only four parameters and is able to fit the measured electron depth doses in all four regions for various nominal energies of the electron beam as well as for various field sizes. The equation is given as follows:

$$D(x) = \frac{(100 - B)}{1 + a(x + c)(x - c)^2 \exp[b\,x\,(x + c)(x - c)^2]} \cdot 5 \exp\left(-\frac{3x}{c}\right) + B \quad , \tag{12}$$

where a, b, and c are the fitted parameters, B is a measured parameter representing the bremsstrahlung contamination, and x is the depth in medium.

Materials and methods

The validity of the approximation given by Eq. (12) was verified with electron beam depth dose data which were measured in water at a source-surface distance (SSD) of 100 cm using a 3-D isodose plotter with a p-type semi-conductor detector. In the build-up region the percentage depth doses were measured in polystyrene with a parallel-plate ionization chamber (Markus-type PTW, model 329). Two linear accelerators (Philips SL-25 and Varian Clinac 2300 C/D) were used as sources of electron beams with square field sizes in the range from $4 \times 4\,cm^2$ to $25 \times 25\,cm^2$ and beam energies in the range from 4 MeV to 22 MeV.

Nonlinear curve-fitting was performed with a commercially available graphics software package (KaleidaGraph by Abelbeck Software) on a MacIntosh computer. The general curve fitting space is missing program, based on a Marquardt algorithm,[13] is both powerful and efficient, able to fit any arbitrary single variable function containing up to nine fitted parameters. Moreover, the program allows fitting of weighted data as well as the use of partial derivatives. In our curve fitting procedure we used wqually-weighted data points.

Results and discussion

The fitting of Eq. (12) to measured electron beam percent depth doses resulted in a set of optimized numerical values for parameters a, b and c as a function of field size and nominal electron beam energy. The numerical values of parameters a, b, c and B depend on the field size as well as on the nominal energy of the beam. The second term in the right-hand side of Eq. (12) adjusts the shape of the function to the dose measured at the phantom surface and in its vicinity.

For curve fitting purposes, the initial values of the four parameters are set as follows: the initial value of c is set equal to x_m, the measured depth of dose maximum; the initial value of a is obtained from Eq. (12) for the phantom surface, i.e., $x = 0$ and $D(0) = D_s$ as:

$$a = \frac{100 - (D_s + 5)}{c^3 (D_s + 5 - B)} \tag{13}$$

The initial value of b is set a few (typically six) times smaller than the initial value of a; and B is set equal to the measured bremsstrahlung contamination which is assumed constant for a given electron beam energy. The non-linear curve fitting starts with the initial values for a, b, and c and reaches the optimal values for a, b, and c through an iterative process. Note that Eq. (13) is used only for estimation of the initial value of parameter a using measured values for the surface dose D_s and bremsstrahlung contamination B, and the initial value for c as equal to x_m. The final optimal values for parameters a and c are generally not related through Eq. (13).

An example of Eq. (12) used in fitting experimental electron depth doses is shown in Figure 2 for a field size of $10 \times 10\,cm^2$ and electron beams produced by two of our high energy linear accelerators. Measured data are shown as data points and the corresponding calculated depth doses by solid curves. Parts (b) and (d) of Figure 2 show on an expanded scale the build-up regions of parts (a) and (c), respectively. The agreement between the measured data and the fitted data in all four regions of the

electron depth dose curves is excellent, proving that Eq. (12) with four parameters offers an excellent analytical approximation to measured data. Optimized parameters a, b, and c as well as the two measured parameters B and D_s for beams of Figure 2 are given in Table 1.

The quality of fitting Eq. (12) to the electron beam data set of Table 1 was evaluated for percentage depth doses above 20%. The results of a statistical comparison between calculated and measured data representing 655 analyzed points ($10 \times 10\,cm^2$ field size, six beam energies for each of the two linear accelerators) are as follows: at the phantom surface, in the build-up region, and in the dose fall-off region, 61% of calculated points matched the measured data within 1%, 92% within 2%, and 98% within 3%. In the fall-off region, the difference between the measured and calculated depths corresponding to the 50% depth dose was within 0.4 mm for all electron energies produced by the two linear accelerators.

Fitting of Eq. (12) to other sets of measured electron beam data gave results similar to those shown in Figure 2. for the $10 \times 10\,cm^2$ field size. Thus a conclusion can be made that the quality of fitting is independent of electron beam machine, field size, or electron beam energy, and all four regions of the electron depth dose curves are approximated well with

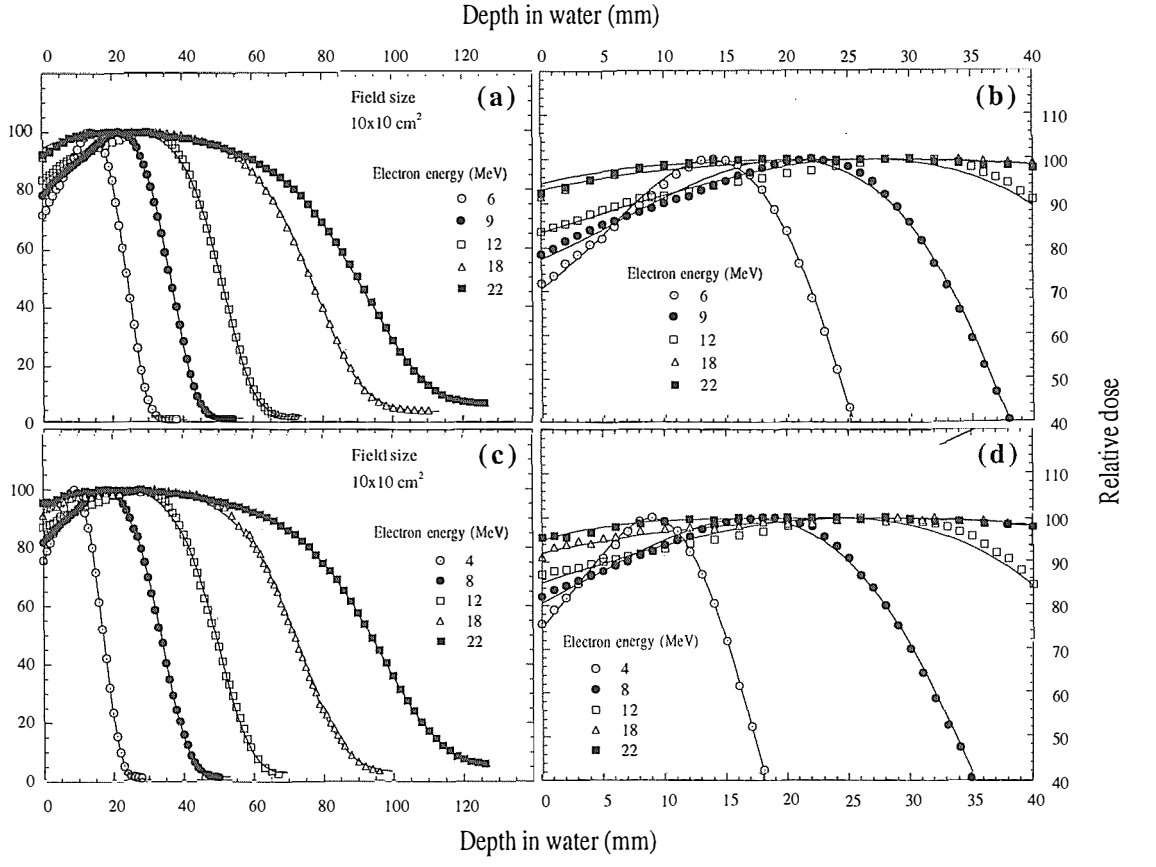


Figure 2. Central axis percentage depth doses for a field size of $10 \times 10\,cm^2$ and various clinical electron beams produced by two linear accelerators: (a) and (b) Varian Clinac 2300 C/D; and (c) and (d) Philips SL-25. Measured data are shown as data points and corresponding dose distributions calculated with Eq. (12) are represented by solid curves. Parts (b) and (d) show in greater detail the build-up and dose maximum regions of parts (a) and (c), respectively.

Table 1. Optimized values of fitting parameters a, b, and c and measured parameters B and D_s for $10 \times cm^2$ electron beams with various nominal energies for two commercial linear accelerators: a Varian Clinac 2300C/D and a Philips SL-25.

	Nominal electron energy (MeV)	Parameter $a \times 10^7$ (mm^{-3})	$b \times 10^8$ (mm^{-4})	c (mm)	B	D_s
VARIAN	6	1283.3	595.82	13.65	0.65	70.6
CLINAC	9	278.29	146.30	19.89	1.31	77.3
2300 C/D	12	76.647	42.505	25.96	2.14	83.4
	15	24.050	15.052	27.71	3.44	90.3
	18	11.810	6.1579	25.88	4.13	93.1
	22	7.1493	2.2432	20.44	5.14	94.4
PHILIPS	4	3652.7	1295.1	8.86	0.036	74.7
SL-25	6	1104.0	406.77	12.5	0.54	77.3
	8	369.59	135.71	16.74	1.08	80.5
	10	178.34	78.031	20.54	1.47	81.8
	12	85.550	39.118	23.54	2.49	85.2
	15	33.882	16.287	24.52	3.12	90.4
	18	15.922	8.5102	27.14	3.31	92.0
	20	8.3512	4.1550	23.33	3.68	94.0
	22	4.7616	1.9890	15.79	4.06	94.8

the fitting procedure. Equation (12) with four fitting parameters thus provides a relatively simple yet precise means for expressing clinical electron beams analytically.

Conclusions

Ever since electron beams have been used clinically, attempts have been made to describe analytically the measured central axis depth dose distributions. These distributions consist of four regions: dose buildup, dose maximum, dose falloff and bremsstrahlung contamination. Numerous analytical expressions to approximate electron depth doses in all four regions have been proposed to date. The quality of fitting generally improved with each new proposal but the curve fitting equations were becoming increasingly more complex as they depended on larger and larger numbers of fitting parameters.

Analytical expressions developed in recent years for descriptions for electron beam depth doses provide an excellent fit to measured data. Improvements in this area can in the future only be achieved in developing simpler expressions which rely on a smaller number of parameters. We have recently developed a relatively simple expression based on only four parameters. We show in this paper that the expression represents, with a high degree of precision, measured electron beam depth doses for various beam energies from two commercial linear accelerators. The conclusion can be made that the expression may be applied to describe the electron beam depth doses generally for any linear accelerator, any field size, and any beam energy.

References

1. Laughlin JS, Ovadia J, Beattie JW, Henderson WJ, Harvey BS, and Hass LL. Some physical aspects of electron beam therapy. *Radiol* 1953; **60:** 165–83.

2. Bagne F. Electron beam treatment-planning system. *Med Phys* 1974; **3:** 31–8.

3. Pacyniak JM and Pagnamenta A. Central axis percentage depth-dose for high energy electrons. *Radiat Res* 1974; **60:** 342-6.

4. Jette D, Lanzl LH, Rozenfeld M, Pagnamenta A. Analytic representation of electron central-axis depth dose data. *Med Phys* 1981; **8:** 877–81.

5. Nelson CE, Heneman W, Young K, O'Foghludha F. Analytic calculation of electron beam isodose distributions. *Med Phys* 1984; **11:** 242-6.

6. Chen FS. An analytical equation of electron beam percentage depth ionization curve along the central axis. *Med Phys* 1988; **15:** 407–9.

7. Tabata T, Ito R. Precision fitting to depth-dose curves of clinical electron beams. *Jpn Radiol Phys* 1988; **8:** 73–84.

8. Shabason L, Hendee WR. An analytical expression for central axis electron depth dose distributions. *Int J Radiat Oncol Biol Phys* 1979; **5:** 263–7.

9. Strydom WJ. An analytical expression for central axis depth-dose of electrons. *Phys Med Biol* 1984; **29:** 267–9.

10. Meigooni AS, Das IJ. Parametrization of depth dose for electron beams. *Phys Med Biol* 1987; **32:** 761–8.

11. Strydon WJ. Central axis depth dose curve for electron beams. *Med Phys* 1991; **18:** 1254–5.

12. Wierzbicki W, Podgorsak EB. An analytical expression for electron beam central axis depth doses. *Med Phys* 1994; **21:** 827–9.

13. Marquardt DW. An algorithm for least squares estimation of nonlinear parameter. *J Soc Indust Appl Math* 1963; **11:** 431–41.

Radiol Oncol 1995; 29: 248–9.

European Code Against Cancer

Peter Boyle,[1] Maja Primic-Žakelj[2]

[1] *Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy*
[2] *Epidemiology Unit, Institute of Oncology, Slovenia*

Introduction

Cancer is an important public health problem in European Community, as well as in Central and Eastern Europe. In the frame of the Europe Against Cancer Programme in the European Community, the European Code Against Cancer – ten recommendations to reduce cancer incidence and mortality – has been developed. The European Cancer Week in October this year will be devoted to the propagation of the message of the revised Code. Herewith it is presented to the readers of this Journal.

European Code Against Cancer

Certain cancers may be avoided and general health improved if you adopt a healthier lifestyle.

1. Do not smoke. Smokers, stop smoking as quickly as possible and do not smoke in the presence of others. If you do not smoke, do not experiment with tobacco.
2. If you drink alcohol, whether beer, wine or spirits, moderate your consumption.
3. Increase your daily intake of vegetables and fresh fruits. Eat cereals with a high fibre content frequently.
4. Avoid becoming overweight, increase physical activity and limit intake of fatty foods.
5. Avoid excessive exposure to the sun and avoid sunburn, especially in childhood.
6. Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances which may cause cancer.

More cancers may be cured if detected early.

7. See a doctor if you notice a lump, a sore which does not heal (including in the mouth), a mole which changes in shape, size or colour, or any abnormal bleeding.
8. See a doctor if you have persistent problems, such as a persistent cough, persistent hoarseness, a change in bowel or urinary habits or an unexplained weight loss.

For women:

9. Have a cervical smear regularly. Participate in organised screening programmes for cervical cancer.
10. Check your breasts regularly. Participate in organised mammographic screening programmes if you are over 50.

Discussion

The purpose of the European Code Against Cancer is to provide guidance for the general population whose adoption would serve to re-

Corrpodence to: Maja Primic-Žakelj M.D., Ph.D., Epidemiology Unit, Institute of Oncology, Zaloška 2, 61105 Ljubljana, Slovenia. Tel.: +386 61 13 22 316; fax: +386 61 131 41 80.

duce incidence and mortality from cancer as well as other diseases. While other items were considered by the experts who revised the code, these ten recommendations were all scientific evidence could support at present (1, 2). Respecting these recommendations should lead to a minimum of a 40 % reduction in cancer incidence and a greater proportionate reduction in mortality, as smoking-related cancer of the lung, oesophagus and pancreas have a notoriously poor prognosis. In addition to these recommendations, it is important to continue to search for advances in the outcome of therapy resulting in survival gain or improvement in quality of life. Progress in cancer control will come from the continued combined efforts of the primary, secondary and tertiary prevention. However, it is evident that the greatest potential for improvements lies in the general public: every individual is responsible for adoption of a healthier lifestyle.

References

1. Boyle P, Veronesi U, Tubiana M et al. European code against cancer. Eur J Cancer 1995 – in press.
2. Boyle P, Primic Žakelj M. Evropski kodeks proti raku. *Zdrav Vestn* 1995; **64:** 447–52.

Radiol Oncol 1995; 29: 250–2.

Report from the ESO training course on tumor biology

The European School of Oncology (ESO) in collaboration with Hacettepe University Institute of Oncology, Ankara, Turkey, organised a Tumor Biology training course. The course was held in Side, Antalya, Turkey, from 17 to 21 April 1995. Fifty-six physicians, biologists and chemists from five countries attended the course. The lecturers came from Turkey, Greece, Italy, Israel, United Kingdom and France.

The program of the course was focused on the following specific areas of tumor biology:

- *Genome structure, cell cycle and its control.* As an introduction to the course M. Özgüç held a lecture about the structure of DNA, genome organization, DNA replication, chromosome and chromatin structure, and genes and their expression. The role of cyclins, cyclin dependent protein kinases (Cdk's) and cyclin dependent inhibitory protein (CKI) in the control of cell cycle, and their involvement in the formation of cancer were also presented. The cyclins and Cdk's act like oncogenes, in other words, contribute positively to the formation of cancer, whereas newly isolated CKI's act as tumor suppressors leading to cancer in the case of their inactivation.
- *Hybridisation techniques and PCR technology* with special focus on the use of these techniques in diagnosis and monitoring of the efficacy of antitumor therapy. An example of monitoring the efficacy of the therapy is bone-marrow transplantation in leukemia. If the disease causing mutation is known, a direct PCR assay aiming to detect the mutation is employed to look for the presence of malignant cells (T. Özçelik).
- *Mechanisms of carcinogenesis.* Carcinogens fall generally into three categories: chemical carcinogens, radiation and oncogenic viruses. Chemical carcinogens are extremely varied in composition and structure. Most of them act by binding to DNA directly or after metabolic activation step. Ultraviolet radiation and ionising radiation are a well-known cause of experimental and clinical cancer. They have different radiobiological effects; ultraviolet radiation produces pyrimidine dimers on the same strand of DNA, while the effects of ionising radiation on cellular DNA are single and double strand breaks. The exact cellular mechanisms of viral carcinogenesis are not known for every virus. Viral products may interfere with cellular tumor suppressor mechanisms, may influence cell growth and apoptosis and may activate oncogenes, growth factors and their receptors (S. Ruacan, S.D. Kottaridis).
- *Oncogenes and tumor suppressor genes.* First, definition and classification of oncogenes and tumor suppressor genes were presented by two lecturers, W.E. Criss and M. Öztürk. In addition, they presented several examples of oncogenes and tumor suppressor genes involvement in cancer formation.
- *Membrane alterations in tumor cells.* The lecture presented by K. Emerk was focused on sfingomiyelin cycle, which is a sfingolipid signalling pathway. Activation of the sfingomyelin cycle in a responsive cell turns on one or more of three anti-proliferative pathways: inhibition of cell growth, induction of differentiation or apoptosis.
- *Cell death.* The lecture given by L. Sachs was focused on regulation of cell viability, growth and differentiation. In his lecture he also compared the control of programmed cell death (apoptosis) in normal and leukemic cells.
- *Tumor antigens and tumor markers* with an

emphasis on the use of tumor markers in diagnosis, prediction of prognosis, determination of risk and detection of early relapse. Also, a definition of sensitivity, specificity, prevalence and positive predictive value were given by E. Kansu, one of the course chairpersons.

- *Cancer immunotherapy.* Different strategies for cancer immunotherapy; monoclonal antibodies, bispecific monoclonal antibodies, biological response modifiers, recombinant cytokines, lymphokine-activated killer cells, tumor infiltrating lymphocytes, tumor vaccines, and cytokine gene transfer into tumor cells were presented by M. Papamicail.
- *Cytogenetic abnormalities in hematological malignancies and solid tumors.* It is well known that chromosomal aberrations in tumor cells are associated with specific types of cancer. The lectures given by A. Turker and Y. Özisik dealt with the cytogenetic analyses of tumors, which are very important for the determination of diagnosis, classification, prognosis and management of tumor.
- *Minimal residual disease.* The lecture of A. Biondi dealt with the problems associated with the detection of the minimal residual disease. These problems are due to the limitation of techniques used for identifying minimal residual disease. He presented a PCR approach for the evaluation of minimal residual disease in acute leukemia.
- *Biology of metastasis.* In her lecture A. Ayhan described the events occurring during metastasic dissemination. A special part of her lecture was devoted to the molecular genetics of metastasis, specifically to the role of some oncogenes *(ras, src, mos, fus)* in enhancement of metastatic potential of tumor cells and the role of nm23 gene which is a metastasis-specific suppressor gene.
- *Tumor growth kinetics.* The J.V. Watson's lecture was divided into two parts: in the first part the mathematical calculations of tumor growth with respect to the rate constant for cell production and the rate constant for cell loss were explained. The second part of his very interesting lecture was devoted to flow cytometry and its use for the determination of cell cycle duration.
- *Mechanisms of anticancer drugs.* The lecture presented by A. Larsen dealt with the cytotoxic action of anticancer drugs at a cellular level. Factors involved in the cytotoxic action were divided into the following sections: pretarget events, interaction with target, and post target events. The factors that play a role in pretarget events, i.e. how much active drug reaches the target, are membrane proteins (P-glycoprotein, MRP-protein), drug metabolising enzymes located in the endoplasmic reticulum (cytochrom P-450 monooxygenase) and cytoplasmic enzymes (glutathion-S-transferases). According to the mechanism of action, anticancer drugs are divided into antimetabolites, alkylating agents, topoisomerase inhibitors, mitotic spindle inhibitors and hormones. After drug-target interaction, additional factors are involved in biological consequences of the induced lesions. These include repair enzymes, macromolecular synthesis and proteins involved in the apoptotic pathway of cell death.
- *Multidrug resistance(MDR) in cancer chemotherapy.* This topic presented by M. Tezer Kutluk was devoted to four major types of MDR: P-glycoprotein mediated drug resistance (classical MDR), atypical MDR (topoisomerase II related drug resistance), MDR protein (MRP) mediated resistance and glutathione transferases mediated resistance.
- *Biochemical modulation* covers the efforts to enhance the antitumor activity of a cytostatic agent by a second drug with little or no antiproliferative activity or little intrinsic toxicity. The lecture of A. Kars' was focused on 5-flouro uracil modulations with leucovorin, levamisole, PALA, dipyridamole and interferons.
- *Gene therapy of cancer.* W. E. Criss presented a short overview of several approaches to developing gene therapy including: (a) use of single stranded complementary DNA to form triple stranded oligonucleotide structures; (b) DNA mutation region binding

with complementary DNA or RNA; (c) tying-up the altered mRNA with anti mRNA messages; (d) modification of nucleic acid structures so that they can enter cells easier without being degraded by plasma or intracellular nucleases; (e) replacement of DNA regions (e.g. exons) where they are missing; (f) replacement of entire genomes with stabilised DNA or mRNA; (g) stimulation of H-RNAase.

At the beginning of the course all participants received the book of lectures presented. The lectures were very well prepared, and covered the latest knowledge in each particular area. Every section of the course ended with a quiz and discussion. At the end of this very fruitful course the participants were asked to complete a course evaluation form in order to give the organisers some feedback information about the success of this course.

Maja Čemažar
Department of Tumor Biology
Institute of Oncology
Zaloška 2
61000 Ljubljana
Slovenia

Notices

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

Gynaecology

The course "8th Annual Techniques in Gynecologic Surgery" will be offered in Scottsdale, Ariz., USA, *November 2–4, 1995.*

Contact Trish Geann MCS, 13400 E. Shea Blvd, Scottsdale, AZ 82529, USA; or call + 1 602 301 7447.

Information systems

The seminar "Information Systems for Managed Care and Integrated Delivery Networks" will be held in Boston, USA, *November 6–9, 1995.*

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

Gynaecology

The symposium "Pregnancy, Sex and the Liver" will be offered in Santiago, Chile, *November 10–11, 1995.*

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

Radiological accidents

The conference "Health Consequences of Chernobyl and Other Radiological Accidents" will be offered in Geneva, Switzerland, *November 20–23, 1995.*

Contact Office of Global and Integrated Environmental Health, WHO, 1211 Geneva 27, Switzerland; or call + 41 22 791 3756.

Data management in cancer clinical trials

The course will take place in Leuven, Belgium, *November 27–December 1, 1995.*

Contact European School of Oncology, Via Ripamonti 66, 20141 Milan, Italy; or call + 39 2 5730 5416; Fax: + 39 2 5730 7143.

Head and neck tumours

The advanced course on head and neck tumours, Part I: Thyroid cancer, will be offered in Milan, Italy, *November 29–December 2, 1995.*

Contact European School of Oncology, Via Ripamonti 66, 20141 Milan, Italy; or call + 39 2 5730 5416; Fax: + 39 2 5730 7143; or contact ESO Vienna, c/o Arztekammer für Wien, Fortbildungsreferat, Weihburggasse 10–12, 1010 Vienna; or call + 43 1 51501293; Fax: + 43 1 51501240.

Haematology

The meeting of American Society of Haematology will take place in Seattle, USA, *December 1–15, 1995.*

Contact American Society of Haematology, 1101 Connecticut Ave NW, 7th Floor, Washington DC, USA, Fax: + 1 202 857 1164.

Gastroenterology

The "6th Joint Meeting of Surgeons and Gastroenterologists", entitled "International Gastro-Surgical Club 1995" will be offered in Bangkok, Thailand, *December 3–6, 1995.*

Contact Secretary General, Organising Committee, Dept. of Surgery, Pramongkutklao Hosp., Rajavithi RD., Bangkok 10400, Thailand; or call + 66 2 246 1400 28.

Information systems

The seminar "Healthcare Information Systems Management" will be held in Boston, USA, *December 4–7, 1995.*

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

Brachytherapy

The "Annual Mid-Winter Meeting" will be held in Scottsdale, Ariz., USA, *December 10–13, 1995.*

Contact ABS, 1101 Market St., Suite 1400, Philadelphia, PA 19107, USA; or call + 1 215 574 3158.

Clinical Services

The "Program for Chiefs of Clinical Services" will be held in Boston, USA. *January 14–26, 1996.*

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

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

KLINIČNI SEMINAR

STRATEGIES ON MECHANICAL VENTILATION IN NEWBORNS AND INFANTS

Vsebina: predavanja in praktično delo z respiratorji in modeli pljuč,
patofiziološke osnove diagnostike,
algoritmi uporabe mehanske ventilacije pri novorojencih in majhnih otrocih

ORGANIZACIJA:
Bogdany K., Budimpešta, Madžarska, in Simbruner G., München, Nemčija

---

Predavatelji:
Simbruner G., Ludwig-Marximilians Univ., München, Nemčija
Frantz I., Tufts University, Boston, ZDA
Greenough A., University of London, Anglija
Schulze A., Technical University, Dresden, Nemčija

Ciljna skupina: neonatologi, anesteziologi in drugi zdravniki, ki želijo poglobiti znanje v intenzivni medicini otrok

Število udeležencev omejeno: 30

Datum: **Marec 25.–28., 1996, pričetek ob 9.00**

Mesto tečaja: **Budapest, Leisure & Youth Center in Csilleberg, Konkoly-Thege M. Srt. 21, Hungary**

Kotizacija: 300 USA $

Certifikati: **Diploma IPOKRaTES** za seminar: Strategies on Mechanical Ventilation in Newborn and Infants

Informacije/Prijava/Registracija:
IPOKRaTES, Scientific Academy of Lower Austria,
Dr. Karel Dorrek Str. 35, A-3500 Krems/D, Austria
Tel. + 43 (0) 2732 70545-302, Fax: + 43 (0) 2732 70545-305
Registracija velja samo ob plačilu kotizacije na **IPOKRaTES** bank account pri:
BANK AUSTRIA 20151, Acount. Nr. 466 007 515

FONDACIJA "DOCENT DR. J. CHOLEWA"
JE NEPROFITNO, NEINSTITUCIONALNO IN NESTRANKARSKO
ZDRUŽENJE POSAMEZNIKOV, USTANOV IN ORGANIZACIJ, KI ŽELIJO
MATERIALNO SPODBUJATI IN POGLABLJATI RAZISKOVALNO
DEJAVNOST V ONKOLOGIJI.

MESESNELOVA 9
61000 LJUBLJANA
TEL 061 15 91 277
FAKS 061 21 81 13

ŽR: 50100-620-133-05-1033115-214779

NAMENI IN CILJI

Namen Fondacije "Docent dr. J. Cholewa" je materialno podpirati slovenske raziskovalce pri proučevanju rakastih bolezni. Raziskovanje je zahtevno, zapleteno in natančno intelektualno delo, ki poleg radovednosti, inovativnosti, vztrajnosti, znanja in izkušenosti raziskovalca zahteva tudi veliko denarja. Marsikatera dobra zamisel ne more biti uresničena zaradi pomanjkanja finančnih sredstev.

Namen Fondacije je pomagati, da bo v raziskovanju rakastih bolezni tudi Slovenija enakovredna drugim po svetu. Raziskovalni rezultati slovenskih znanstvenikov prav s področja biomedicine niso zanemarljivi tudi zunaj meja Slovenije, vendar zaradi pomanjkanja finančnih sredstev niso pravi odraz raziskovalnih sposobnosti.

Število rakastih obolenj v Sloveniji narašča iz leta v leto. Da bi bili pri zdravljenju bolnikov še bolj učinkoviti, se morajo naši zdravniki neprestano izobraževati in vključevati v raziskave, ki pomagajo odkrivati neznanke bolezni in nove načine zdravljenja.

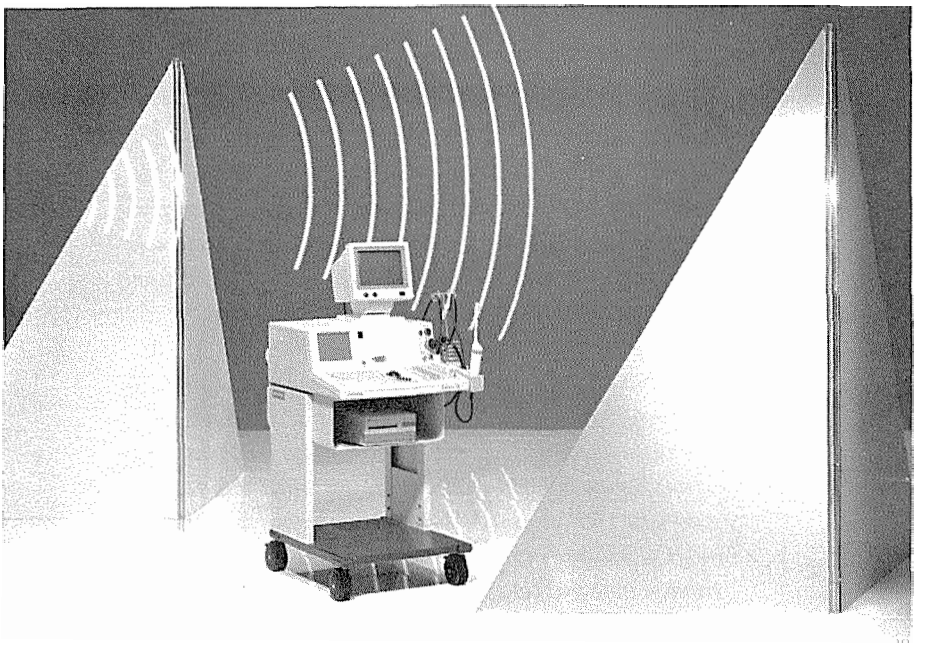
Že od leta 1957 slovenski zdravniki aktivno z mnogimi ustanovami po svetu, ki zdravijo in raziskujejo rakaste bolezni. Leta 1991 se je Slovenija pridružila evropskemu programu boja proti raku, njegov cilj je do leta 2000 zmanjšati umrljivost za rakom za 15 odstotkov. Temu cilju se je mogoče približati samo z neprestanim izobraževanjem in raziskovalnim delom, kajti le raziskovanje prinaša nova vedenja in vodi k boljšemu razumevanju rakastih bolezni ter pomaga pri preprečevanju, zgodnjem ugotavljanju bolezni in učinkovitem zdravljenju.

S Fondacijo "Docent dr. J. Cholewa" želimo zato pomagati sposobnim raziskovalcem dopolnjevati znanje in udejanjati lastne ideje ter s tem pospeševati njihova prizadevanja pri premagovanju te hude bolezni. Da bomo lahko izkoristili naš znanstveno-raziskovalni potencial in obogatili zakladnico znanja o rakastih boleznih, vas pozivamo, da s svojimi prispevki omogočite Fondaciji uresničevanje njenega poslanstva.

Akademik
prof. dr. Vinko Kambič

SIEMENS

Vaš partner v ultrazvočni diagnostiki:



SIEMENS * SONOLINE SL-1

* **Možnost priključka sektorskega, linearnega, endo-p in endo-v aplikatorja**
* **Izredno ugodna cena (možnost kredita ali leasing-a)**
* **Servis v Sloveniji z zagotovljenimi rezervnimi deli in garancijo**
* **Izobraževanje za uporabnike**

SIEMENS D.O.O.
Dunajska 47, Ljubljana
Tel. 324-670
Fax. 132-4281

SANDOZ

je koncern z dolgoletno zgodovino. Ustanovljen je bil leta 1886 v Baslu kot kemijska tovarna, ki je izdelovala sintetične barve. Leta 1917 je bil ustanovljen farmacevtski oddelek in že leto za tem (1918), so v raziskovalnih laboratorijih izolirali iz rženih rožičkov alkaloid ergotamin, nato pa še kardiotonične glikozide, kar je bil revolucionaren napredek v zdravljenju žilnih bolezni. V teh pionirskih časih so uspeli tudi poskusi zamenjave do tedaj uporabljanih soli kalcija z lažje prenosljivimi in Ca - Sandoz je postal pojem za nekaj nadaljnih let.

Na slovenskem tržišču je Sandoz Pharma prisotna od leta 1952. Sodeluje s slovensko farmacevtsko industrijo in tovarno zdravil Krka, ki proizvaja 7 zdravil po licenčni pogodbi s Sandozom. Tudi za zdravila, ki se uvažajo, so narejene klinične študije v Sloveniji, ki potrjujejo in zagotavljajo kakovost.

V Sloveniji so na voljo registrirana zdravila:

Lamisil® (terbinafin)
- nov pristop k zdravljenju glivičnih infekcij kaže, nohtov in lasišča
- prvi fungicidni antimikotik za oralno in lokalno uporabo

Leponex® (klazapin)
- antipsihotik za bolnike s shizofrenijo, ki se ne odzivajo na klasične nevroleptike

Lescol® (fluvastatin)
- sintetični inhibitor reduktaze HMG-CoA
- učinkovito in varno zniža holesterol v krvi tudi pri rizičnih skupinah bolnikov

Leucomax® (molgramostim)
- rekombinantni humani dejavnik, ki pospešuje nastanek kolonij granulocitov in makrofagov
- normalizira število belih krvnič in makrofagov pri bolnikih z zmanjšano imunsko odpornostjo

Melleril® (tioridazin)
- anksiolitik v nizkih dozah, nevraleptik v visokih dozah
- ne povzroča ekstrapiramidnih sopojavov

Miacalcic® (kalcitonin)
- hormon, ki regulira metabolizem kosti in mineralov
- za zdravljenje pomenopavzalne in senilne osteoporoze, Pagetove bolezni, Sudeckove distrofije

Navoban® (tropisetron)
- antagonist receptorjev 5-HT_3
- visokoselektivni antiemetik pri emetogeni kemoterapiji, radioterapiji in pooperativnem bruhanju

Sandimmun Neoral® (ciklosporin)
- imunosupresiv, ki preprečuje zavrnitveno reakcijo pri transplantacijah,
- učinkovit pri avtoimunih boleznih in boleznih, kjer je udeleženo avtoimuno komponenta, kot so psoriazo, revmatoidni artritis, atopični dermatitis in endogeni uveitis

Sandostatin® (oktreotid)
- sintetični oktapeptidni derivat somatostatina
- pomemben v gastroenterologiji, endokrinologiji in intenzivni medicini

Sirdalud® (tizanidin)
- mišični relaksant s centralnim delovanjem
- za zdravljenje bolečine v križu, mišičnih spazmov in spastičnosti

Syntocinon® (oksitocin)
- sintetični oksitocin za spodbujanje materničnih kontrakcij
- Syntocinon - nosni spray za spodbujonje izločanja mleka

Tavegyl® (klemastin)
- introvenski antihistaminik prvega izbora

SANDOZ

vaš partner pri zdravljenju

Informacije in literatura so na voljo pri SANDOZ PHARMA Ltd.
Basel, Predstavništvo za Slovenijo, Dunajska 107, 61113 Ljubljana, tel. 061/168 14 22, faks 061/34 00 96.

Instructions to authors

The journal **Radiology and Oncology** publishes original scientific papers, professional papers, review articles, case reports and varia (reviews, short communications, professional information, ect.) pertinent to diagnostic and interventional radiology, computerised tomography, magnetic resonance, nuclear medicine, radiotherapy, clinical and experimental oncology, radiobiology, radiophysics and radiation protection.

Submission of manuscript to Editorial Board implies that the paper has not been published or submitted for publication elsewhere: the authors are responsible for all statements in their papers. Accepted articles become the property of the journal and therefore cannot be published elsewhere without written permission from the Editorial Board.

Manuscripts written in English should be sent to the Editorial Office: Radiology and Oncology, Institute of Oncology, Vrazov trg 4, 61000 Ljubljana, Slovenia; Phone: +38661320068, Fax: +38661314180.

Radiology and Oncology will consider manuscripts prepared according to the Vancouver Agreement (N Engl J Med 1991; 324: 424-8.; BMJ 1991; 302: 6772.).

All articles are subjected to editorial review and review by two independent referees selected by the Editorial Board. Manuscripts which do not comply with the technical requirements stated here will be returned to the authors for correction before the review of the referees. Rejected manuscripts are generally returned to authors, however, the journal cannot be held responsible for their loss. The Editorial Board reserves the right to require from the authors to make appropriate changes in the content as well as grammatical and stylistic corrections when necessary. The expenses of additional editorial work and requests for reprints will be charged to the authors.

General instructions: 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. Authors are encouraged to submit their contributions besides three typewritten copies also on diskettes (5 1/4") in standard ASCII format.

First page:

– name and family name of all authors,

– a brief and specific title avoiding abbreviations and colloquialisms,

– complete address of institution for each author,

– in the abstract of not more than 200 words cover the main factual points of the article, and illustrate them with the most relevant data, so that the reader may quickly obtain a general view of the material.

Introduction is a brief and concise section stating the purpose of the article in relation to other already published papers on the same subjects. Do not present extensive reviews of the literature.

Material and methods should provide enough information to enable experiments to be repeated.

Write the **Results** clearly and concisely and avoid repeating the data in the tables and figures.

Discussion should explain the results, and not simply repeat them, interpret their significance and draw conclusions.

Graphic material (figures and tables). Each item should be sent in triplicate, one of them marked original for publication. Only high-contrast glossy prints will be accepted. Line drawings, graphs and charts should be done professionally in Indian ink. All lettering must be legible after reduction to column size. In photographs mask the identities of patients. Label the figures in pencil on the back indicating author's name, the first few words of the title and figure number: indicate the top with and arrow. Write legend to figures and illustrations on a separate sheet of paper. Omit vertical lines in tables and write the next to tables overhead. Label the tables on their reverse side.

References should be taped in accordance with Vancouver style, double spaced on a separate sheet of paper. Number the references in the order in which they appear in the text and quote their corresponding numbers in the text. Following are some examples of references from articles, books and book chapters:

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

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

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

Kodak systems provide dependable performance for advanced diagnostic imaging. Our quality components are made to work together from exposure to viewbox.

Kodak X-Omat processors are the most respected in the field. Kodak X-Omatic cassettes are known the world over for unexcelled screen-film contact and durability. Kodak multiloaders have earned an enviable reputation for reliability. The Kodak Ektascan laser printer is changing the look of digital imaging. The list goes on. There are quality Kodak products throughout the imaging chain.

Equally important, they are made to work together to achieve remarkable performance and diagnostic quality. Contact your Kodak representative for more information.

ADVANCED DIAGNOSTIC IMAGING SYSTEMS. KODAK

Quality imaging worldwide

Kodak

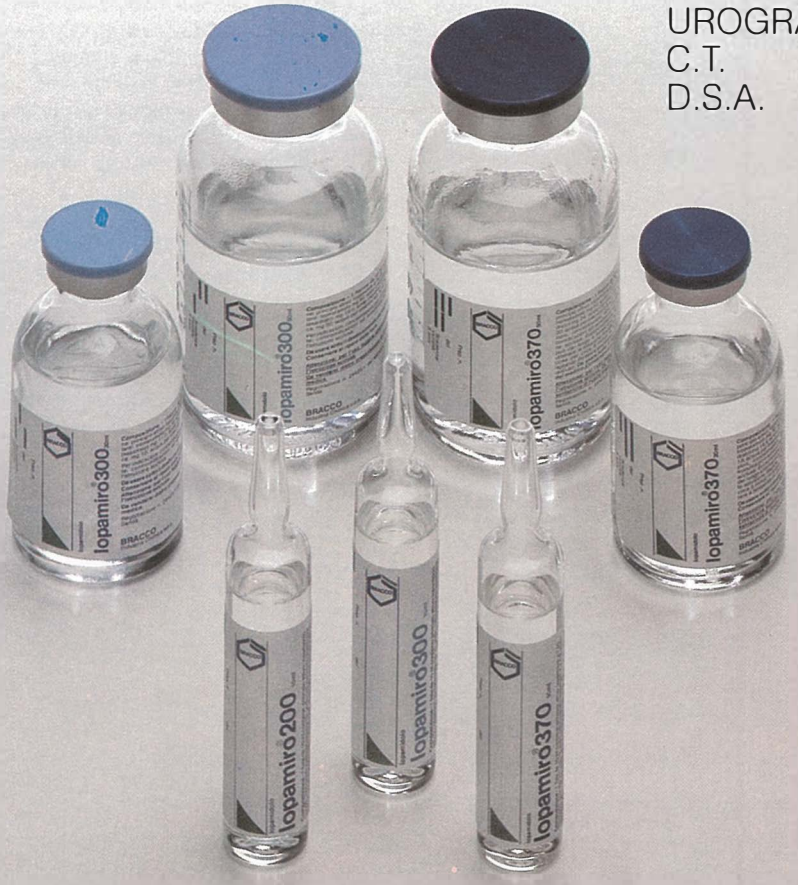
Iopamiro®

Iopamidol

150 - 200 - 300 - 370 mgI/ml

FOR ALL RADIOLOGICAL EXAMINATIONS

MYELOGRAPHY
ANGIOGRAPHY
UROGRAPHY
C.T.
D.S.A.



THE FIRST WATER SOLUBLE READY TO USE NON-IONIC CONTRAST MEDIUM

anufacturer:

racco s.p.a.
a E. Folli, 50
0134 - Milan - (I)
ax: (02) 26410678
elex: 311185 Bracco I
none: (02) 21771

BRACCO

Distributor:

Agorest s.r.l.
Via S. Michele, 334
34170 - Gorizia - (I)
Fax: (0481) 20719
Telex: 460690 AF-GO I
Phone: (0481) 21711

Nepotrebno je, da bolezen spremlja bolečina

TADOL®

kapsule, kapljice, svečke, injekcije

tramadol

Moč opioidnega analgetika brez opioidnih stranskih učinkov

- **centralno delujoči analgetik za lajšanje zmernih in hudih bolečin**
- **učinkovit ob sorazmerno malo stranskih učinkih**

Indikacije: Srednje močne do močne akutne ali kronične bolečine. *Po tristopenjski shemi Svetovne zdravstvene organizacije za lajšanje bolečin pri bolnikih z rakavim obolenjem tramadol odpravlja srednje hudo bolečino ali bolečino druge stopnje.* **Kontraindikacije:** Zdravila ne smemo dajati otrokom, mlajšim od 1 leta. Tramadola ne smemo uporabljati pri akutni zastrupitvi z alkoholom, uspavali, analgetiki in drugimi zdravili, ki delujejo na osrednje živčevje. Med nosečnostjo predpišemo tramadol le pri nujni indikaciji. Pri zdravljenju med dojenjem moramo upoštevati, da 0,1 % zdravila prehaja v materino mleko. Pri bolnikih z zvečano občutljivostjo za opiate moramo tramadol uporabljati zelo previdno. Bolnike s krči centralnega izvora moramo med zdravljenjem skrbno nadzorovati. **Interakcije:** Tramadola ne smemo uporabljati skupaj z inhibitorji MAO. Pri sočasni uporabi zdravil, ki delujejo na osrednje živčevje, je možno sinergistično delovanje v obliki povečane sedacije, pa tudi ugodnejšega analgetičnega delovanja. ●**pozorila:** Pri predoziranju lahko pride do depresije dihanja. Previdnost je potrebna pri bolnikih, ki so preobčutljivi za opiate, pri starejših osebah, pri miksedemu in hipotiroidizmu. Pri okvari jeter in ledvic je potrebno odmerek zmanjšati. Bolniki med zdravljenjem ne smejo upravljati strojev in motornih vozil. **Doziranje in način uporabe:** *Odrasli in otroci, starejši od 14 let:* Injekcije: 50 do 100 mg i.v.,i.m.,s.c.; intravensko injiciramo počasi ali infundiramo razredčeno v infuzijski raztopini. Kapsule: 1 kapsula z malo tekočine. Kapljice: 20 kapljic z malo tekočine ali na kocki sladkorja; če ni zadovoljivega učinka, dozo ponovimo čez 30 do 60 minut. Svečke: 1 svečka; če ni učinka, dozo ponovimo po 3 do 5 urah. *Otroci od 1 do 14 let:* 1 do 2 mg na kg telesne mase. Dnevna doza pri vseh oblikah ne bi smela biti višja od 400 mg. **Stranski učinki:** Znojenje, vrtoglavica, slabost, bruhanje, suha usta in utrujenost. Redko lahko pride do palpitacij, ortostatske hipotenzije ali kardiovaskularnega kolapsa. Izjemoma se lahko pojavijo konvulzije. ●**prema:** 5 ampul po 1 ml (50 mg/ml), **5 ampul po 2 ml (100 mg/2 ml)**, 10 ml raztopine (100 mg/ml), 20 kapsul po 50 mg, 5 svečk po 100 mg.

Podrobnejše informacije so na voljo pri proizvajalcu.

KRKA
SLOVENIJA