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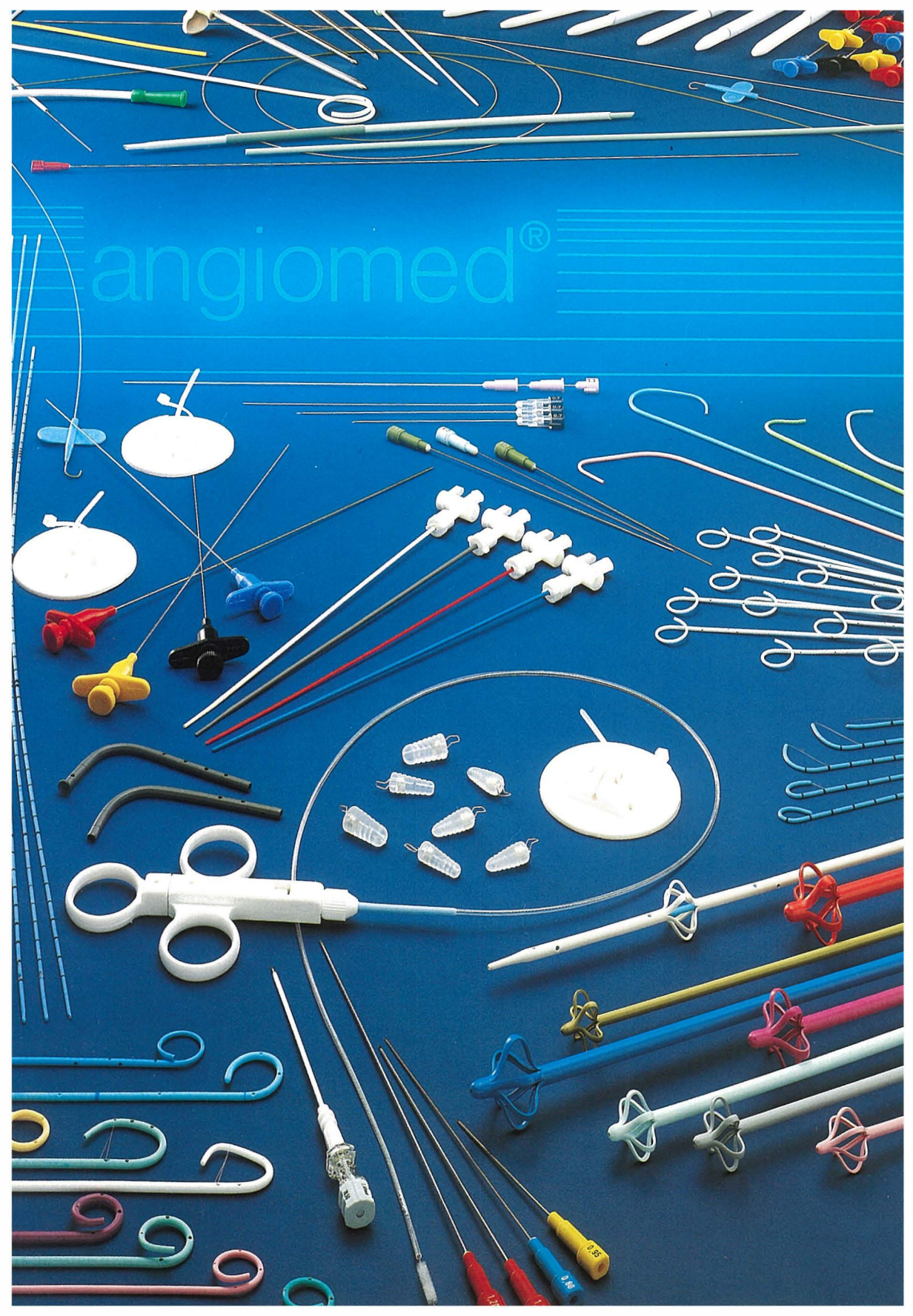
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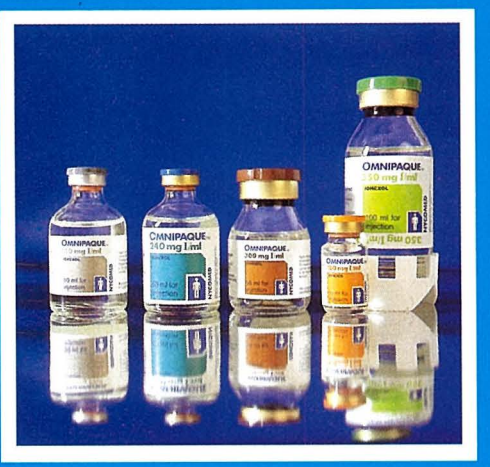

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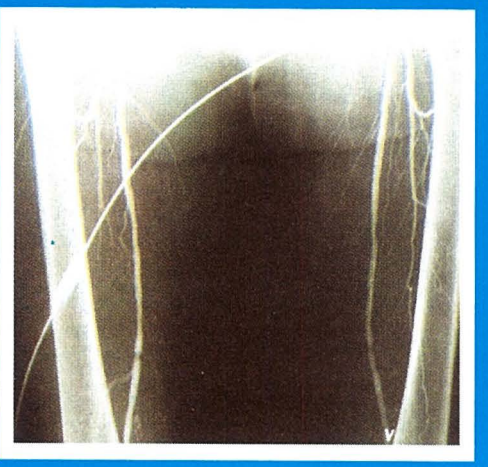

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DEAR AUTHORS AND COWORKERS,

I am pleased to inform all of you who are, or will be, in one way or the other participating in our jubilee issue, that the editorial work on this publication is being carried out as planned. The members of our editorial board has had several meetings with the editors of individual chapters in order to determine the most efficient way of collaboration between the authors, editors and redaction. It has been agreed that the authors should be asked to submit their manuscript on diskettes whenever possible.

Starting with our jubilee issue, we plan to change the design and format of our journal in order to up-to-date its outlook and rationalize technical procedures at print.

By the help of several medical institutions in the country and abroad, as well as by means of sponsors and advertisements in other journals we shall try to increase the number of participating authors as well as readers of RADIOLOGIA IUGOSLAVICA.

Finally, I wish to remind the authors that the deadline for submission of their manuscripts for jubilee issue is June 30. 1991.

And, to point out again, all institutions related to radiology, nuclear medicine and oncology in Yugoslavia are most welcome to take part in this relevant publication.

Tomaž Benulič, MD,
Editor –in–Chief

RADIOLOGIA IUGOSLAVICA, The Institute of Oncology Zaloška 2, 61105 Ljubljana, Slovenia / Yugoslavia; Tel.: +38 61 327 955; Fax: +38 61 329 177

SODELAVCEM!

Vsem, ki bodo sodelovali v naši jubilejni publikaciji, sporočamo, da vsa pripravljalna dela potekajo po zastavljenem načrtu. Do sedaj smo se redaktorji večkrat sestali z uredniki posameznih poglavij in se dogovorili o sodelovanju med avtorji, uredniki in redakcijo.

Avtorje naprošamo, da nam, v kolikor je le možno, pošljejo prispevke pisane na disketi.

Z jubilejno publikacijo uvajamo namesto tega novo zunanjo in notranjo ureditev, ki jo bomo uporabljali pri vseh nadaljnjih izdajah naše revije, z namenom da posodobimo njen izgled in racionaliziramo tiskarski postopek.

S pomočjo številnih medicinskih ustanov doma in tujini, sponzorjev izdaje in z objavo oglasov v drugih revijah bomo skušali za našo jubilejno izdajo, kot tudi za redne številke, pridobiti nove sodelavce in naročnike revije.

Ob koncu tega sporočila še obvestilo avtorjem: rok za dostavo rokopisov je 30. junij 1991.

K sodelovanju pri izdaji publikacije vabimo vse radiološke, nuklearnomedicinske in onkološke ustanove v Jugoslaviji.

Dr. Tomaž Benulič
glavni in odgovorni urednik

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ANGIOGRAFSKA ANALIZA PATOLOŠKIH PROMJENA VERTEBRALNIH ARTERIJA U DIJAGNOSTICI ISHEMIJE MOZGA

ANGIOGRAPHIC ANALYSIS OF PATHOLOGICAL CHANGES OF VERTEBRAL ARTERIES IN THE DIAGNOSIS OF CEREBRAL ISCHAEMIA

Gaćina M, Hebrang A, Boschi S, Praprotnik T, Gaćina P

Abstract – The aim of this work was to prove angiographically the frequency of changes on the vertebral artery, subclavian artery and brachiocephalic trunk in patients with symptoms of cerebral ischaemia, to compare the results with the changes on the same arteries in patients without symptoms, and to find a correlation with pathological changes on the carotid artery. The examinations have been done by means of angiograms analysis in a hundred patients who underwent consecutive angiography of the aortic arch because of cerebrovascular ischaemia symptoms. The control group consisted of 30 patients without cerebrovascular ischaemia symptoms. The results have shown that pathological changes of vertebral arteries were 3.3 times more frequent in the examined than in the control group of patients. The greatest number of changes have been found in the examined group with milder degree of stenosis, as well as in kinking and hypoplasia of the vertebral arteries. Pathological changes of brachiocephalic trunk have been frequent too in the examined group (50%), and twice as frequent in subclavian artery. Opposite to this, pathological changes have been equally frequent in the control and examined groups.

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Key words: cerebral ischaemia, vertebral artery–radiography

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Radiol Iugosl 1991; 25:97-101

Uvod – Patološke promjene na vratnim arterijama mogu predstavljati hemodinamsku zapreku protoka krvi ili su izvor embolija u distalne intrakranijalne ogranke. Točnim prikazom mjesta, rasprostranjenosti i vrste patološkog procesa na arterijama kao i pružanjem uvida u kolateralnu cirkulaciju, angiografija je stvorila dobre uvjete za planiranje operativnog liječenja stenotičko–obliterativnih promjena arterija.

Među najčešćim uzrocima ishemije mozga su patološke promjene na vratnim arterijama. U dijagnostici ishemije mozga pažnja je vrlo često usmjerena patološkim promjenama arterije karotis i njezinih ogranaka. U angiografskom prikazu u ovih bolesnika nerijetko nedostaje područje vertebralnih arterija. Iz iskustva je poznato, a na anatomskim studijima i potvrđeno, da doprinos i udio vertebralnih arterija u opskrbi mozga može biti znatan. Pri tome treba misliti i na arterije koje dovode krv do vertebralnih arterija, a to su trunkus brahiocefalikus i arterija supklavija.

U dosadašnjoj literaturi postoje oskudni podaci o patološkim promjenama vertebralne arterije, ali bez usporedne analize s kontrolnom skupinom bolesnika koji ne boluju od ishemije mozga. Zato su ti nalazi manjkavi, jer ne ukazuju na ovisnost moždane ishemije o promjenama vertebralnih arterija. U stranoj literaturi nalazimo radove u kojima su patološke promjene vertebralnih arterija analizirane u sklopu analize luka aorte (1,2). U našoj literaturi nalazimo također analitičke radove o promjenama na ograncima luka aorte, također bez usporedbe s bolesnicima bez simptoma moždane ishemije (3). Iz ovog obrazloženja proizlazi, da će ispitivanje učestalosti patoloških promjena vertebralnih arterija u bolesnika s ishemijom mozga, uz usporedbu nalaza s angiogramima bolesnika bez ishemije mozga, prestavljati novi doprinos spoznaji o uzrocima cerebrovaskularne insuficijencije.

Materijal i metode – Ispitivanu skupinu sačinjavaju bolesnici sa simptomima ishemije mozga. Kontrolna skupina su bolesnici bez simptoma takve ishemije.

Received: January 21, 1991 – Accepted: February 19, 1991

Metoda proučavanja je usporedna analiza učestalosti, stupnja i vrste patološke promjene ekstrakranijalnih dijelova moždanih arterija kod ispitivane i kontrolne skupine bolesnika.

Ispitivanje obuhvaća 100 bolesnika uzastopno upućenih na angiografiju luka aorte zbog simptoma ishemije mozga. Od tog broja su 74 muškarca, a 26 žene. Najstariji bolesnik ima 75 godina, a najmlađi 32 godine (tabela 1).

Tabela 1 – Dob i spol bolesnika ispitivane skupine

Table 1 – Age and sex of the patients in examined group

Dob Age	Muškarci Male	Žene Female
20 – 30	0	0
31 – 40	5	5
41 – 50	23	10
51 – 60	32	7
61 – 70	9	3
71 – 80	5	1
UKUPNO TOTAL	74	26

Kontrolna skupina obuhvaća analizu angiograma 30 bolesnika bez simptoma ishemije mozga. Od tog broja 21 je muškarac, a 9 žena. Najstariji pacijent ima 74 godine, a najmlađi 29 godina. Broj je znatno manji nego kod ispitivane skupine radi toga, jer je broj indikacija za angiografiju luka aorte kod takvih bolesnika neuporedivo manji. Uputna dijagnoza pacijenata je: stanje nakon traume, kongenitalne anomalije luka aorte, otkrivanje tumora, sumnja na aneurizmu aorte (tabela 2).

Tabela 2 – Dob i spol bolesnika kontrolne skupine

Table 2 – Age and sex of the patients in controlled group

Dob Age	Muškarci Male	Žene Female
20 – 30	0	1
31 – 40	2	0
41 – 50	8	3
51 – 60	6	4
61 – 70	4	1
71 – 80	1	0
UKUPNO TOTAL	21	9

Rezultati – Rezultati rada prikazani su tabelarno u apsolutnim brojevima i u postocima.

Broj promjena na trunkus brahiocefalikus u ispitivanoj skupini nađen je u 15 (15%), a u kontrolnoj skupini u 3 (10%) bolesnika (tabela 3).

Tabela 3 – Usporedni rezultati promjena na trunkus brahiocefalikus ispitivane i kontrolne skupine

Table 3 – Compared results of examined and controlled groups changes on brachiocephalic trunk

		Ispitivana skupina Examined group	Kontrolna skupina Controlled group
Obliteracija Obliteration		0	0
Stupanj stenoze	30%	12 (12%)	3 (10%)
	50%	3 (3%)	0
Degree of stenosis	90%	0	0
»Kinking« Kinking		0	0
Hipoplazija Hypoplasia		0	0
UKUPNO TOTAL		15 (15%)	3 (10%)

Kod arterije supklavije broj patoloških promjena u ispitivanoj skupini je u 48 (48%), a u kontrolnoj u 7 (23,3%) bolesnika (tabela 4).

Obliteracija arterije vertebralis neznatno je češća u kontrolnoj u odnosu na ispitivanu skupinu ((16,6:11%) ali je izrazita razlika u svim oblicima stenoza u korist ispitivane skupine. Nalazimo ih u 36 slučajeva (36%) u ispitivanoj, a samo 2 (3,3%) u kontrolnoj skupini. Razlika učestalosti «kinkinga» je isto upadljiva: 14 (14%) u ispitivanoj skupini, a 1 (3,3%) u kontrolnoj skupini. Još veću razliku nalazimo kod hipoplazija: 16 (16%) u ispitivanoj, a niti jedan slučaj u kontrolnoj skupini. Razlika učestalosti hipoplazija i stenoza vertebralnih arterija između ispitivane i kontrolne skupine je najveća razlika koju smo našli u našem ispitivanju. Učestalost broja svih patoloških promjena arterije vertebralis između ispitivane i kontrolne skupine je 3,3 puta veća u korist ispitivane skupine (77% :23,3%) (tabela 5).

Kod arterije karotis komunis ukupan broj svih patoloških promjena je u ispitivanoj skupini 27 (27%), a u kontrolnoj 7 (23,3%) (tabela 6). Kod arterije karotis interne ukupan broj patoloških

Tabela 4 – Usporedni rezultati promjena na arteriji supklaviji ispitivane i kontrolne skupine

Table 4 – Compared results of examined and controlled groups changes on subclavian artery

			Ispitivana skupina Examined group	Kontrolna skupina Controlled group
Obliteracija		D		
		R	1 (1%)	0
Obliteration		L		
		L	3 (3%)	1 (3,3%)
		D		
		R	16 (16%)	1 (3,3%)
	30%	L		
		L	18 (18%)	2 (6,6%)
Stupanj stenoze		D		
		R	1 (1%)	1 (3,3%)
	50%	L		
Degree of stenosis		L	4 (4%)	1 (3,3%)
		D		
		R	1 (1%)	1 (3,3%)
	90%	L		
		L	1 (1%)	0
»Kinking«		D		
		R	3 (3%)	0
Kinking		L		
		L	0	0
Hipoplazija		D		
		R	0	0
Hypoplasia		L		
		L	0	0
UKUPNO TOTAL			48 (48%)	7 (23,3%)

Tabela 5 – Usporedni rezultati promjena na arteriji vertebralis ispitivane i kontrolne skupine

Table 5 – Compared results of examined and controlled groups changes on vertebral artery

			Ispitivana skupina Examined group	Kontrolna skupina Controlled group
Obliteracija		D		
		R	3 (3%)	3 (10%)
Obliteration		L		
		L	8 (8%)	2 (6,6%)
		D		
		R	15 (15%)	0
	30%	L		
		L	9 (9%)	0
Stupanj stenoze		D		
		R	4 (4%)	0
	50%	L		
Degree of stenosis		L	4 (4%)	0
		D		
		R	4 (4%)	1 (3,3%)
	90%	L		
		L	0	0
»Kinking«		D		
		R	7 (7%)	0
Kinking		L		
		L	7 (7%)	1 (3,3%)
Hipoplazija		D		
		R	10 (10%)	0
Hypoplasia		L		
		L	6 (6%)	0
UKUPNO TOTAL			77 (77%)	7 (23,3%)

promjena je u ispitivanoj skupini 39 (39%), a u kontrolnoj 12 (40%) (tabela 7).

Rasprava – U našim istraživanjima obuhvatili smo različita patološka stanja na arterijama koja mozgu dovode krv, a koje mogu uzrokovati cerebrovaskularnu ishemiju. U interpretaciji rezultata treba uzeti u obzir da postoje i drugi razlozi kao što su metabolički poremećaji, hipertonija (4), hipotenzija (5), promjene kalibra (6). Za nastanak bolesti važna su i druga patološka stanja koja smanjuju priliv krvi u mozgu, kao arteriovenske fistule ili vazodilatacija ekstracerebralnih kao i intracerebralnih žila.

Uz navedene uzroke ishemije mozga svakako da priliv krvi u mozak znatno otežavaju stenotičko-obliterativne promjene ekstra i intrakranijalnih arterija. Među uzrocima ovih promjena po učestalosti na prvom mjestu je arterioskleroza. Pri tome je stupanj arterioskleroze samo od relativnog značaja. Djelomično to pokazuje preraspodjela po dobnim skupinama u naših ispitanika. Najveći je broj u srednjoj dobnoj skupini (40–50 godina života).

Kod proučavanja patologije vertebralnog arterijskog sliva moramo osim arterioskleroze uzeti u obzir i druge moguće uzroke opstrukcije. Neki od njih nisu još dovoljno poznati. Najbolje nam to ilustriraju obliteracije moždanih arterija u djece od 9–14 godina (7,8,9). Kao najčešći uzrok kompresije arterije vertebralis navode rebro, »kinking« ili zavojiti tok arterije, što može zbog narušavanja hemodinamike dovesti do tromboze.

Tabela 6 – Usporedni rezultati promjena na arteriji karotis komunis ispitivane i kontrolne skupine

Table 6 – Compared results of examined and controlled groups changes on artery common carotid

			Ispitivana skupina Examined group	Kontrolna skupina Controlled group
Obliteracija Obliteration		D R L L	2 (2%) 1 (1%)	0 0
Stupanj stenoze Degree of stenosis	30%	D R L L	11 (11%) 11 (11%)	0 4 (13,3%)
	50%	D R L L	2 (2%) 0	1 (3,3%) 1 (3,3%)
	90%	D R L L	0 0	0 1 (3,3%)
»Kinking« Kinking		D R L L	0 0	0 0
Hipoplazija Hypoplasia		D R L L	0 0	0 0
UKUPNO TOTAL			27 (27%)	7 (23%)

Tabela 7 – Usporedni rezultati promjena na arteriji karotis interni ispitivane i kontrolne skupine

Table 7 – Compared results of examined and controlled groups changes on artery internal carotid

			Ispitivana skupina Examined group	Kontrolna skupina Controlled group
Obliteracija Obliteration		D R L L	2 (2%) 1 (1%)	1 (3,3%) 1 (3,3%)
Stupanj stenoze Degree of stenosis	30%	D R L L	10 (10%) 14 (14%)	2 (6,6%) 2 (6,6%)
	50%	D R L L	4 (4%) 2 (2%)	3 (10%) 2 (6,6%)
	90%	D R L L	2 (2%) 4 (4%)	0 1 (3,3%)
»Kinking« Kinking		D R L L	0 0	0 0
Hipoplazija Hypoplasia		D R L L	0 0	0 0
UKUPNO TOTAL			39 (39%)	12 (40%)

Sličan mehanizam nalazimo kod obliteracije vertebralnih arterija zbog prekomjernih pokreta vratne kralježnice (10,11,12). Nalazimo opise tromboze područja vertebrobazilarnog sustava bez vidljivih uzroka pa je autori nazivaju idiopatskom (13). Dok se većina autora slaže da je arterioskleroza glavni etiopatološki mehanizam stenotičko-obliterativnih promjena u području arterije karotis, iz navedenih primjera vidimo da su uzroci ishemije vertebrobazilarnog područja još nedovoljno razjašnjeni. U našim rezultatima našli smo znatno veću učestalost patoloških promjena na arterijama vertebrobazilarnog sustava nego li na arterijama karotidnog sustava. Ovaj nalaz još više naglašava važnost vertebrobazilarne cirkulacije u etiopatogenezi moždane ishemije.

Najznačajniji naš nalaz je podjednaka učestalost patoloških promjena na arteriji karotis u bolesnika sa simptomima ishemije mozga kao i bez tih simptoma, odnosno sasvim suprotno onom kod vertebralnih arterija. U literaturi nema podataka o angiografski dokazanim stenotičko-obliterativnim promjenama u bolesnika bez moždane ishemije i to radi toga jer takvi bolesnici rijetko dolaze na angiografiju. U analizi broja moždanih udara u bolesnika s ishemijom u području arterije karotis i onih s ishemijom u području arterije vertebralis postoje različiti podaci. Prema nekim autorima bolesnici s vertebrobazilarnom insuficijencijom rjeđe doživljavaju moždani udar (14,15). Drugi autori navode pak podjednaku učestalost moždanih udara kod bolesnika s ishe-

mijom karotidnog kao i u bolesnika s ishemijom vertebrobazilarnog područja (16).

Zaključak – Stenotičko-obliterativne promjene u ispitivanoj i kontrolnoj skupini jednako su česte na arteriji karotis komunis i arteriji karotis interni.

Stenotičko-obliterativne promjene u području arterije vertebralis tri puta su češće u ispitivanoj skupini. Samo obliteracije u području arterije vertebralis čak su nešto veće u kontrolnoj nego u ispitivanoj skupini. »Kinking« i hipoplazija arterije vertebralis znatno su češće u ispitivanoj nego u kontrolnoj skupini, što ukazuje na uzročnu povezanost ovih promjena sa simptomima ishemije mozga.

Sažetak

Cilj ispitivanja ovog rada bio je angiografski utvrditi učestalost promjena na arteriji vertebralis, supklaviji i trunkus brahiocefalikusu kod bolesnika sa simptomima ishemije mozga, usporediti nalaze s promjenama istih arterija kod bolesnika bez simptoma, te pronaći korelaciju s patološkim promjenama na arteriji karotis.

Ispitivanja su obavljena analizom angiograma 100 bolesnika koji su uzastopno upućeni na angiografiju luka aorte zbog simptoma cerebrovaskularne ishemije. Kontrolnu skupinu sačinjava 30 bolesnika bez simptoma cerebrovaskularne ishemije. Rezultati su pokazali da su patološke promjene arterije vertebralis 3,3 puta češće u ispitivanoj, nego u kontrolnoj skupini. Najveće razlike u korist ispitivane skupine našli smo kod blažeg stupnja stenoze, zatim kod »kinkinga« i hipoplazije arterije vertebralis. Patološke promjene trunkus brahiocefalikusa bile su također češće u ispitivanoj skupini (za 50%), a kod arterije supkalvije dvostruko češće. Suprotno tome, stenotičko-obliterativne promjene ekstrakranijalnih dijelova arterije karotis našli smo jednako često u kontrolnoj i ispitivanoj skupini.

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ANOMALIES OF INTESTINAL ROTATION AND FIXATION IN RADIOLOGICAL FINDINGS

Frković M, Šimunić S, Mandić A, Bradić I, Kačić M, Vučković R, Dujšin M

Abstract – The term malrotation of the bowel loops includes anomalies of all stages of embryonal development and all onthogenically different bowel segments. To recognize these anomalies it is necessary to know the onthogenic and embryonal stages of bowel development, the anatomic changes and pathophysiology which occurs as a result of the abnormal development. During the 7-year period (1981–1987) the gastrointestinal tract was x-rayed in 14 364 patients. Malrotation of the bowel loops was found in 1 017 (7.1 %) patients of which 555 (54.6 %) were males and 462 (45.4 %) females, (ratio 1.2 : 1). With regard to onthogenetic development the most frequent anomalies were the anomalies of the midgut, umbilical loop, respectively – 590 (58 %). With regard to embryologic stages of development, the most frequent were anomalies of the IIIrd embryologic stage or intestinal fixation – 896 (88.1 %). Anomalies of intestinal rotation and fixation were most frequently noted in adults – 707 (69.5 %).

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Key words: intenstines-abnormalities, gastrointestinal system-radiography

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Introduction – In many patients who underwent gastrointestinal examination we found that the etiological cause of their disturbances was the presence of anomalies of rotation and fixation of the bowel. Since this pathology was mainly analysed in pediatric and surgical journals, and all radiologic findings, although important and indispensable part of diagnostico-therapeutical treatment, were usually only occasionally mentioned, we felt the need to demonstrate this problem from radiological point of view.

Insufficient understanding of embryonal development and pathologic changes that result from the deviation from the usual course of development we consider partly, the cause of inadequate clinico-radiological treatment, which we specially stress in this study.

Malrotation is the term (etymologically malus, MALUM – L. ill–disease, rotatio – rotation) that includes a great number of various types of incomplete or abnormal bowel rotation around arteria mesenterica superior and failure of bowel fixation to the posterior abdominal wall, although it is mainly used for special types of anomalies. We think that the term «anomalies of rotation and fixation of the bowel» is more adequate because it includes the anomalies of all embryonal stages of development and all ontogenetically different bowel segments.

Etiologically, these anomalies, as the anomalies in general, are results of mosaic impressions of endogenetic and exogenic teratogenetic factors without the possibility of determining the participation of any of them. The mechanism of their acting is to delay the development, due to which at the certain point the course of development takes different direction.

Ontogenetically, the duodenum develops from the foregut in its proximal part. From the midgut, umbilical cord, develops the aboral part of duodenum, jejunum and ileum, cecum and ascending colon and the proximal part of the transverse colon. The hindgut is the base of the aboral part of the transverse colon, descending colon, sigmoid, rectum, the upper part of the anal canal and one part of the urogenital system.

The first stage of embryonal development is characterized by the change of form and position of the stomach and umbilical cord – they move from sagital to frontal plane.

In further development, characterized by quicker growth in length of bowel loops than the growth of abdominal cavity (1,2,3) the bowel develops in the celom of the umbilical cord, so

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we speak about physiological umbilical hernia (3,4).

The second stage of development is characterized by »the rotation of the bowel in more narrow sense« and it refers to the changes of position of the bowel, derivative of umbilical cord (5,6,7), although it includes complete alimentary tract (8,9). At the same time there is proximally induced rotation of the duodenojejunal segment, and distally of the cecocolic segment of the umbilical cord, around arteria mesenterica superior as the axis of rotation, for 270° in counter clockwise direction »steering wheel shape« (8) (Fig. 1). The hindgut is thus, together with its mesentery, pushed to the left, therefore not being particularly involved in the process of rotation (9).

In the third stage of embryonal development a unique dorsal mesentery differentiates and attaches to the posterior abdominal wall, thus forming 3 fields of secondary peritoneum. Radix of mesentery has the oblique grip which extends from the doudenojejunal flexure to the ileocecal junction.

In pathologic anatomy it is generally important to make distinction between anomalies of rotation and fixation of gastroduodenal and umbilical cord examination during developmental stages, and they are often found in combination.

Anomalies of rotation and fixation of gastroduodenal loops present as inverse rotation of gastroduodenal loops, or an the error in fixation of the duodenum to the posterior wall, in which case mobile duodenum persists (10).

By incomplete growth and elongation of the ascending part of the duodenum a mixed form of duodenal anomaly will develop (10,11,12) so it is possible to speak about this form as an anomaly of rotation of the umbilical cord.

Anomalies with complete absence of rotation of the umbilical cord will not be found in viable children.

Malformations in form of persisting greater or lesser omphalocele or remaining omphalomesenteric ductus (in the form of Meckel's diverticulum, yolk cord with umbilical sinus, yolk cyst or yolk fistula (13)) can remain from the first stage of embryional development of the bowel.

If the process of rotation of either duodenojejunal or cecocolic segment or both develops in some other direction and stops at some other stage, various forms of malrotation can develop. Therefore, inevitably and often in the cases in which the rotation was in normal direction and complete, fixation of the bowel to the posterior abdominal wall fails. Thus volvulus can develop as an acute or chronic condition, as well as abnormal connections with consequential extraluminal bowel compression, and more or less obvious signs of obstruction in passage. These conditions are the cause of intraabdominal hernias (14,15). For diaphrampatic hernias, whether protrusion of abdominal viscera through physiological orifices in the diaphragm or through the patologic congenital or posttraumatic orifices, it is important that, as precondition, there is accentuated mobility of abdominal organs which become the content of hernia.

Pathologic physiology: the anomalies of rotation and fixation of the bowel do not cause the disturbances of physiological functions until complications and volvulus develop.

In acute volvulus by mechanical occlusion of blood vessels, the primary venous drainage is compromised and afterwards also lymphatic and arterial circulation and innervation (16,17).

The resulting ischaemic lesions lead to bowel necrosis with all further complications (bleeding, perforation).

In chronic volvulus the process of torsion repeats or progressively advances and causes gradual lesion of circulation and innervation, which damages the absorbtion function of bowel mucosa, which then results in the disturbances in clinical status of patients (18).

Patients and methods – We retrospectively reviewed 14 364 patients which underwent examination of the during 7-year period (1981–1987) gastrointestinal tract. Among them were 2268 children (15,7%) in the age of 15 years, of which 132 (0,9%) were up to 1 year old. In the examined group there were 1017 (7,8%) patients with the finding of anomalies of rotation and fixation of the bowel.

Since the age range is markedly wide, from the moment of birth until the very old age, and owing to the specific pathology examined, it was not possible to define the age of patients with equidistal stages. For that reason we divided the examined patients in age groups characterized by the well known specific biophysical parameters, among which is calender duration of certain period of time. Thus we divided the patients into 4 age groups.

1. neonatal period – from the birth until 28 days of life
2. infantile period – until 1 year of age
3. childhood period – until 15 years of age
4. adolescent period – until 20 years of age

5. adult period – more than 20 years of age at the time of radiologic examinations.

We divided the findings of anomalies according to embryonal stages using Grob's schematic demonstration of anomalies (19), and according to ontogenetic development. We also examined the distribution of anomalies with regard to the age and sex of patients.

In all patients, the diagnosis of anomalies was made on the basis of classical radiologic imaging of the gastrointestinal tract.

Plain radiograph of the abdomen was made in supine and upright position of patients, depending on their condition.

For gastroduodenal examinations and barium enema studies we mostly used a suspension of barium sulfate, 100–300 ml, and exceptionally we used watersoluble contrast medium, 10–30 ml.

Irrigoscopy was performed by applying double contrast enema.

The examinations were performed on Garantix 1000 Siemens and Super 100 Philips units.

We applied the usual electrical conditions suited to the constitution of patients.

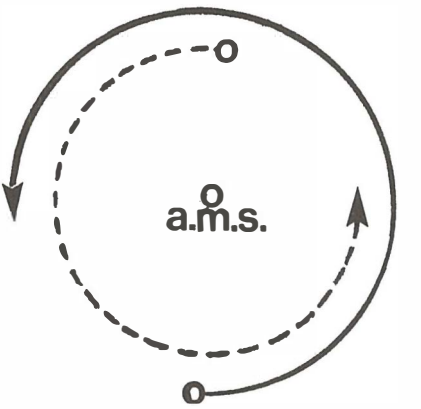
Results – According to embryional stages and in relation to the age of patients, the findings of anomalies of rotation and fixation of the bowel are shown in Table 1.

According to ontogenetic development in relation to age and sex of patients the distribution of anomalies is presented in Tables 2 and 3.

It is obvious that from the total number of found anomalies of rotation and fixation of the bowel the greatest number of anomalies refer to bowel segments of the umbilical cord. In proportion, this type of anomaly was mostly found in all age groups (Table 2) and in neonatal age with the greatest relative value, 84.6%, (calculated by method of vertical 100 – the method of relative number). Mode for all 3 types of anomalies is in adult age.

In relation to the sex of patients (table 3) the result CHI square test is 22157 with 2 degrees of freedom and confidence limits P = 0.01 which indicates that there is a relationship between sex and types of anomalies. However, according to the results obtained by methods of association (Joul FI = 0.148, contingency coefficient C = 0.146), the existing relationship is not of great intensity.

Discussion – By defining the bowel as etiological, embryological, topographic and functional



0_ _ _ _ _ _ _ = direction of rotation of duodenojejunal loops
0 _____ = direction of rotation of cecocolonal loops

Fig. 1 – »Steering–wheel shape«

unity of alimentary tract, we inevitably, with the most frequently treated anomalies of the umbilical cord as derivative of midgut, examined the anomalies of position and fixation of the duodenum in the proximal segment of derivative of foregut, and the anomalies of aboral part of the colon, the derivative of hindgut.

Based on our own experience we believe that schematic presentation of physiological process of rotation of the bowel as »steering wheel shape« (8) is simple, clear and adequate for the explanation of topographic relationships of the bowel noted in radiologic findings. The finding of anomaly of rotation and fixation of the bowel is sometimes difficult to define exactly and to include in any of the given schematic frames (5,20,21) on direct surgical examination. It is understandable therefore, that it is a far greater problem in radiologic treatment where indirect methods are applied. Indeed, we think it is not necessary, because excessive bowel mobility due to the absence of fixation offers many possibilities for change – from normal bowel position to volvulus and complete obstruction of bowel lumen between 2 radiologic treatments and even during a single radiologic treatment.

In total, anomalies of rotation and fixation of the bowel are more often found in men than in women, which is demonstrated in relation 1.2:1 and it correlates with well known facts about the incidence of these anomalies in relation to sex. However, the data from literature about the incidence in general population (1–2%) (22,23,24) differ a great deal from our results (7.1%). These results, partly from the fact that in many patients

Table 1 – Embryonal stage and type of anomalies in relation to the age of patients (N=1017)

Embryonal stage	Anomalies	1.	2.	3.	4.	5.	Total	%
I. N'=18(1,77%)	Omphalocele	11					11	1,1
	Ductus omphalomesentericus persistens		1	2		1	4	0,4
	Meckel's diverticulum			1		2	3	0,3
II. N''=103(10,13%)	Malrotation (type I and II, non-rotation, reversed rotation)	24	10	6	13	26	79	7,8
	Intrinsic herniae					2	2	0,2
	Congenital diaphragmal herniae	2	7	13			22	2,1
III. N'''=896(88%)	Duodenum mobilae	7	9	10	13	349	388	38,2
	Coecum mobilae	2	16	29	44	160	251	24,7
	Anomalies of growth of mesentery and bowel fixation	5	1	12	53	147	218	21,4
	Anomalies of hindgut rotation and fixation	1	2	6	10	20	39	3,8
TOTAL	52	46	79	133	707	1017	100	

Explanation: 1. – neonatal period
2. – infantile period
3. – childhood period
4. – adolescence period
5. – adulthood period

N'= number of anomalies in the Ist embryonal stage
N''= number of anomalies in the IInd embryonal stage
N'''=number of anomalies in the IIIrd embryonal stage

Table 2 – Demonstration of anomalies of intestinal rotation and fixation according to ontogenetic development in relation to the age of patients (N=1017)

Anomalies	1.	2.	3.	4.	5.	Total	%
A.	7	9	10	13	349	388	38,2
B.	44	35	63	110	338	590	58
C.	1	2	6	10	20	39	3,8
TOTAL	52	46	79	133	707	1017	100

Explanation: 1. – neonatal period
2. – infantile period
3. – childhood period
4. – adolescence period
5. – adulthood period

A. – anomalies of duodenum, segment of foregut
B. – anomalies of umbilical loops, of midgut
C. – anomalies of hindgut

(14364) we found anomalies of rotation and fixation of the bowel of all ontogenetically different bowel segments and from all embryonal stages of bowel development. We think that more important cause of this difference is also in the fact that the interpretations of radiologic findings are part of pediatric and surgical studies (4,5,8,19,20,21,23–31) and their treated patients are strictly specific. For pediatrics these patients are children with chronic recurrent abodminal pain often characterized as psychogenesis. For pediatric surgeons that is as a rule a small group of patients in which these anomalies are manifested with complications of high ileus or acute volvulus, where a surgical intervention of pathologic condition was necessary. In adult patients along with anomalies there are often another pathologic substrates which is of greater importance in clinical picture without defining their eventual cause-effect relationship. Since the aut-

Table 3 – Demonstration of anomalies if intestinal rotation and fixation according to ontogenetic development, in relation to the sex of patients (N=1017)

Sex	A.	B.	C.	TOTAL	%
male	176	358	21	555	54,6
female	212	232	18	462	45,4
TOTAL	388	590	39	1017	100
Ratio m:f	1:1,2	1,5:1	1,2:1	1,2:1	

Explanation: A. – anomalies of duodenum, of foregut
B. – anomalies of umbilical loops, of midgut
C. – anomalies of hindgut

hors used radiologic files and didn't have informations about the methods used and interpretations of examinations, the explanations of findings are insufficient and errors are inevitable.

The data according to which chronic volvulus is considered to be an etiological cause of disturbances in 25% of the patients from the total number of patients hospitalized due to pain in the abdomen, and in 10% of children who were hospitalized due to the problem (34), confirm our statement that these anomalies are not rare findings and are not without importance as it is often believed.

Above mentioned facts can serve as an explanation for the differences in data about age of patients with anomalies. Namely, Snyder (4,8), El Gahari (25) et al. (32,33,34) report that 50–70% of these anomalies are manifest even in neonatal period and only 20% are diagnosed after first year of life (25,35–38). We have found nearly 70% of these anomalies in adults, which correlates with a number of examined patients, and with importance, range and expressiveness of anomalies in clinico-radiological picture.

The number of radiologic studies dealing with this problem is relatively small, and the demonstration of anomalies is fragmentary (36,39-44). Thus, for our sample of found pathology, which to some extent can present the sample of population in general, we could neither find nor form otherwise indespensable control group of patients. That is because in the literature we have not found a similar demonstration, and here we have exact problems in population with added risk linked with x-ray.

There are various data about accuracy of radiologic diagnoses (25,37) and they are mainly based on the analysis of a small group of patients in preoperative treatment of examined patients. Such data do not provide the exact insight into the frequency of these anomalies in general population, or perhaps in a more specifically defined pattern of population with abdominal, gastrointestinal disturbances, and similar disorders.

Sažetak

ANOMALIJE ROTACIJE I FIKSACIJE CRIJEVA U RADIOLOŠKOJ SLICI

Termin anomalije rotacije i fiksacije crijeva, ili malrotacija u najširem smislu, obuhvaća anomalije svih stadija embrionalnog razvoja i svih, ontogenetski različitih, segmenata crijeva.

Za prepoznavanje ovih anomalija u radiološkom nalazu neophodno je poznavanje embrionalnog razvoja crijeva, patoanatomskih i patofizioloških promjena koje nastaju kao posljedica odstupanja od normalnog razvoja.

U sedmogodišnjem periodu (1981–1987) pri radiološkom pregledu gastrointestinalnog trakta 14 364 bolesnika, našli smo 1 017 (7.1 %) bolesnika s anomalijama rotacije i fiksacije crijeva, od čega 555 (54.6 %) muških i 462 (45.4 %) ženskih, odnosno u omjeru 1.2 : 1.

S obzirom na ontogenetski razvoj utvrdili smo da su najbrojnije anomalije srednjeg crijeva, pupčane petlje – 590 (58 %).

S obzirom na embrionalne stadije najbrojnije su anomalije III. embrionalnog stadija, anomalije fiksacije crijeva – 896 (88.1 %).

Anomalije rotacije i fiksacije crijeva evidentirali smo u najvećem broju u odraslih bolesnika – 707 (69.5 %).

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MINOR DEFORMACIJE I ARTROZA KUKA

MINOR DEFORMITIES AND OSTEOARTHRITIS OF THE HIP JOINT

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Abstract – In order to assess the presence of any minor deformities responsible for the incongruity of the hip joint and consequential degenerative changes, the radiographies of the hips in 332 normal adults were examined. The deformities comprised imperfect acetabular development – acetabular dysplasia, and the tilt deformity of the femoral head as a residual condition of epiphyseolysis in adolescence. Using Wiberg's CE–angle, acetabular dysplasia was found in 13.8% of cases; the tilt deformity, using the technique by Murray, was confirmed in 9.8%. It is considered that these minor anatomical abnormalities can be recognized by more accurate examination of pelvic radiographs and that their presence should indicate joint incongruity and potential osteoarthritic changes. Earlier recognition of these deformities enables earlier and simple treatment and arrest of the hip joint decline.

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Key words: hip joint–radiography; osteoarthritis, hip

Profess paper

Radiol Iugosl 1991; 25:109-13.

Uvod – Artroza kuka je česti uzrok fizičke nesposobnosti koja se u različito teškim oblicima javlja u srednjim i kasnijim godinama života. Na važnost ovoga problema mogu najviše ukazati epidemiološke analize kretanja artroze kuka u populaciji. One su u našoj sredini manjkave.

Artroze kuka se obično dijele na primarne i sekundarne. Kod primarnih se artroza nastanak pripisuje određenim unutarnjim degenerativnim procesima zglobne hrskavice, a kod sekundarnih prethodno nastala bolest deformira zglob na način koji vodi lokaliziranom degenerativnom propadanju zglobne hrskavice. Kao najčešći uzroci sekundarne artroze navodi se prirođeno iščašenje kuka, Perthesova bolest, aseptička nekroza glave femura i epifizeoliza. U nizu izvještaja pojedinih autora vidljivo je da kod gotovo polovine bolesnika sa artrozom kuka nije utvrđen primarni uzrok nastanka bolesti (1, 2, 3) . Takovi su slučajevi opisani kao »primarni«, »idiopatski« ili nepoznati.

Po Murray–u (4) slučajevi primarne artroze vrlo su često rezultat manjih defromacija kuka. Ovakove manje promjene autor nalazi kod epifizeolize glave femura i acetabularne displazije, a koje su dovoljne da remete kongruentnu funkciju zgloba i time oštećuju globnu hrskavicu. U radiološkoj studiji na 200 slučajeva primarne artroze kuka isti autor uspijeva potvrditi određene deformacije u 65% slučajeva. To ga je potaklo da postavi zahtjev revizije podjele artroza. Rad Solomona (5) daljnje je nastojanje na novoj koncepciji. Njegova studija obuhvaća 327 slučajeva artroze kuka gdje autor klinički i radiološki nalaz veže na pato–anatomske promjene tkiva dobivenih kod operacije na zglobovima. Displastičnu čašicu nalazi u 20% slučajeva, a blaže oblike epifizeolize u 18% slučajeva. Samo u 27 slučajeva ne uspijeva utvrditi prethodne primarne promjene zgloba.

Materijal i metode – Želeći ispitati koliko su manje anatomske deformacije, a koje mogu biti značajne u razvoju artroza, prisutne u populaciji odraslih osoba, provedena je obrada kukova u 210 žena i 122 muškaraca. Za tu svrhu korišten je materijal istraživačkog rada koji obuhvaća razvoj kukova djece rođene u rodilištu Kliničke bolnice »Dr M.Stojanović« u Zagrebu. Kod roditelja djece sa kliničkim normalnim kukovima izvršen je pregled kukova koji uključuje radiografiju u antero–posteriornoj projekciji. Na ovim kukovima ispitana je prisutnost minor deformacija sa posebnim naglaskom na acetabularnu displaziju

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i epifizeolizu glave femura. Starosna dob ispitanika kretala se od 18 do 47 godina.

Acetabularna displazija

Displastički razvoj acetabuluma najčešće je vezan na prirodno iščašenje kuka. U znatno manjoj mjeri susreće se kod osteohondritisa i različitih oblika klijenuti gdje u osnovi manjka potreban stimulans razvoja čašice. Međutim, plitku čašicu većeg ili manjeg stupnja može se naći i kod odraslih osoba bez utvrđenih poremećaja u razvoju zgloba. Preciznije razlikovanje težih od lakših stupnjeva displazija, te razvoj acetabuluma praktički se utvrđuje pomoću linearnih i kutnih mjera. Geometrijski postupak utvrđivanja displatičnog acetabuluma opisao je Wiberg (6) u poznatoj monografiji. Po tome CE–kut, koga tvori središte glave femura i vanjski rub acetabuluma biva prihvaćen kao primjereno mjerilo stupnja razvoja acetabuluma. Na osnovu brojnih analiza Wiberg utvrđuje da vrijednosti CE–kuta veće od 25° predstavljaju normalne kukove odraslih osoba, da se granične vrijednosti kreću između 25-20°, dok su one sa 20° i niže patološke i indikativne za acetabularnu displaziju. Te su podatke kasnije potvrdili i drugi autori (7, 8).

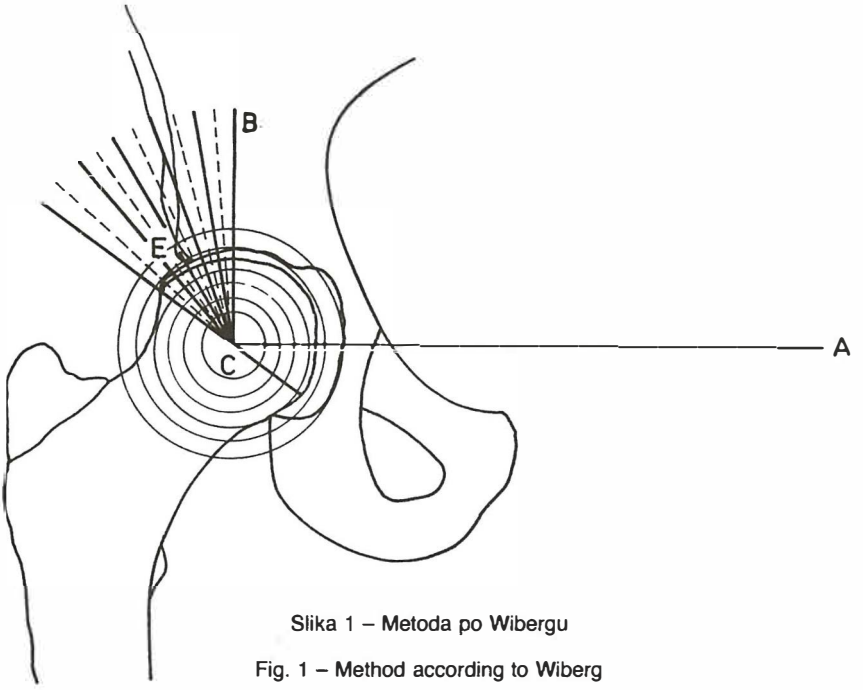
U našem radu korištena je metoda Wiberga. Ce–kut čini vertikalna linija koja presjeca sjedište glave femura sa linijom koja povezuje sjedište glave sa vanjskim rubom acetabuluma (slika 1). Središte glave femura očitava se pomoću koncentričnih krugova na transparentnoj foliji coxometra. Mjerenja je vršila jedna osoba, a pri ponovljenom očitavanju potvrđena je sigurnost mjerenja u razlici od 1°.

Epifizeoliza glave femura

Epifizeoliza je bolest vezana na intenzivni rast u adolescentno doba. Patološke se promjene svode na odvajanje ploče rasta pri čemu epifiza klizi straga i medijalno. Bolesnici se tuže na šepanje i bolove u kuku i koljenu koji mogu duže potrajati. Često poteškoće nastaju postepeno, a šepanje bez prisutne boli može biti jedini znak epifizeolize.

Radiološki nalaz kod epifizeolize ukazuje na traumatsko porijeklo što je zaključiti iz nastupa pregradnje metafize koja se tako prilagođuje kliznuću epifize glave femura. Slijedi koštana resorpcija na vanjskoj strani metafize, dok se sa unutarnje strane javlja apozicijski rast. Takvo oblikovanje stvara sliku deformacije nagiba glave femura kakova se otkriva kod artroza pretežno muških bolesnika. Uz varus nagib glave femura dolazi i do skraćenja vrata femura zbog oštećenja rasta u tom području.

Za potrebe statističke avaulacije ove deformacije korisna je metoda koju je opisao Murray (4). Svrha je mjerenja da se usporede dijelovi



Slika 1 – Metoda po Wibergu

Fig. 1 – Method according to Wiberg

glave femura sa svake strane linije povučene sredinom vrata femura, a time i brojčano izrazi stupanj kliznuća epifize. Najprije se utvrdi središnja točka udaljenosti lateralnog ruba velikog trohantera i medijalnog ruba malog trohantera. Na isti se način označi središnja točka udaljenosti najužeg dijela vrata femura. Obje se središnje točke povezuju linijom koja se produži u područje glave femura. Na kraju se utvrde izbočena mjesta glave femura, te spoje crtom koja presjeca navedenu središnju liniju. Sada se izmjere udaljenosti rubova glave do središnje linije, dobiveni iznos lateralne strane podijeli sa onim medijalne i tako dobije koeficient glave femura. Primjena ove metode prikazana je na slici 2.

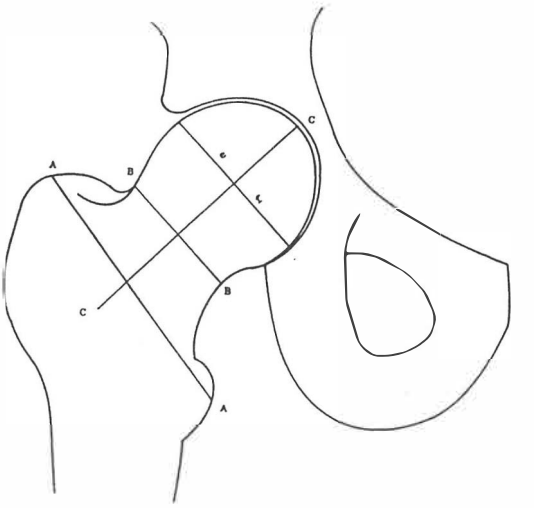
Rezultati – Acetabularna diplazija

Obrada kukova po Wibergu pokazala je stalnu prisutnu razliku između muških i ženskih kukova, kao i između desne i lijeve strane. Tako je srednja vrijednost CE–kuta kod ženskog spola iznosila za desni kuk 32,9°–5,5°, a za lijevi kuk 31,6°–5,4°. Kod muškog spola srednja vrijednost CE–kuta za desni kuk iznosila je 35,9°–5,7°, a za lijevi kuk 33,9°–5,6°. Od ukupno 337 ispitanika granične su vrijednosti CE–kuta od 25 – 20°nađene u 19 slučajeva (5,6%), a patološke vrijednosti od 20° na niže potvrđene u 10 ispitanika (2,9%). Odnos je spola za obje skupine bio 25 F : 5 M. U jednom slučaju nađene su patološke vrijednosti CE–kuta obostrano, a u 5 slučajeva na desnom, dok su 4 na lijevom kuku. Kontralateralni kukovi sadržavali su većinom vrijednosti manje od 25°.

Epifizeoliza glave femura

Značajno je da je epifizeoliza potvrđena u ispitnom materijalu isključivo kod muškog spola. Od 122 ispitanika deformacija nagiba glave femura nađena je u 12 slučajeva (9,8%). Koeficient glave femura kao mjerilo stupnja deformacije mjeren je na oba kuka, a iz njihova zbira izračunata je srednja vrijednost koeficienta koja se kretala od maksimalne 1,72 do minimalne 0,73 sa prosječnom vrijednošću 1,16. Za pretpostaviti je da kukovi sa većim vrijednostima koeficienta glave femura podliježu artrotičnim promjenama. U jednom jedinom slučaju nađena je deformirana glava femura sa varus deformacijom vrata kao posljedica preboljelog Perthesa u dječjoj dobi.

Rasprava – Radovi publicirani zadnjih godina uvjerljivo potvrđuju da je znatan dio artroza kuka sekundarne naravi, te da se u stvari nadovezuje na već prisutne deformacije zglobnih tijela (4, 5). Posebno je značajno da u adolescenata nala-



Linija AA – spojnica vanjskog ruba velikog trohantera i unutarnjeg ruba malog trohantera

Line AA – line connecting the outer margin of trochanter major and the inner margin of trochanter minor

Linija BB – spojnica najužeg dijela vrata femura

Line BB – line connecting the narrowest part of the femoral neck

Linija CC – spojnica središnjih dijelova linija AA i BB

Line CC – line connecting midportions of lines AA and BB

e – spojnica vanjskog dijela glave s linijom CC

e – line connecting the outer part of the femoral head with line CC

f – spojnica unutarnjeg dijela glave s linijom CC

f – line connecting the inner part of the femoral head with line CC

e/f = koeficijent glave femura

e/f = coefficient of the femoral head

Slika 2 – Metoda po Murray–u

Fig. 2 – Method according to Murray

zimo ovakove etablirane morfološke promjene na zglobu kuka, a kao posljedicu razvoja displastičkog zgloba kuka ili epifizeolize (9, 10, 11). Rezultati ovog rada potvrđuju značajnu prisutnost minor deformacija na kukovima populacije odraslih osoba. Treba naglasiti da se u najvećem broju radi o asimptomatskim kukovima. Korištenjem Wibergova kriterija nađene su vrijednosti CE–kuta niže od 25° u 29 slučajeva (13,8%) i to u 24 žene i 5 muškaraca. Ovdje je odnos pola gotovo identičan onom kod prirođenog iščašenja kuka.

Epifizeoliza u slici deformacije nagiba glave femura potvrđena je u 12 slučajeva (9,8%) i to isključivo u muškog spola. Ovdje odnos spolova odudara od onog kod klasične epifizeolize u korist ženskog spola.

Podaci o incidenciji displastičnog acetabula u zdravoj populaciji su u literaturi dosta oskudni. Murray (4) nalazi CE–kut manji od 25° u 3% brojčano male populacije. Wynne Davies (8) navodi identičnu incidenciju u skupini od 159 radiografija kukova.

U tumačenju razvoja displastičnog acetabula više autora (8, 12) smatraju odgovornim nasljedne faktore. Osnovnu smetnju u razvoju zgloba čine labavost periartikuliranih tkiva koja je često prisutna među članovima obitelji. Labava zglobna čahura i ligamenti ometaju kongruentnost zglobnih tijela, a rezultat takovih smetnji je manjkavo formirani acetabulum. Nalaz displastičnog acetabula provlači se nezapaženo i nakon završenog razvoja zgloba do javljanja simptoma u odrasloj dobi.

Radiološki je displastični acetabulum uočen već jednostavnim gledanjem. Promjene su obično izražene obostrano s predominacijom jedne strane. Kongruencija zglobnih tijela biva sačuvana, a nerijetko je prisutna i povećana anteverzija vrata femura. Tako se javlja prekomjerno lateralno opterećenje zgloba pa je očekivati u daljnjem toku propadanje zglobne hrskavice u području gdje se glava femura sudara s vanjskim dijelom acetabula. Dolazi do suženja zglobne pukotine, dok u rasterećenom dijelu glave zglobna hrskavica je sposobna za proliferaciju sa stvaranjem osteofita.

Elmslie (13) je među prvima koji izvještava o ranim artrotskim promjenama na prethodno nastalim deformacijama kuka nakon epifizeolize glave femura. Law (14) zastupa mišljenje da su brojne artroze kod muškog spola rezultat epifizeolize manjeg stupnja koja nije stvarala posebnih teškoća u adolescenciji. Noviji radovi dovode ovu pojavu u vezu sa povećanom fizičkom aktivnošću u adolescentno doba (11, 15).

Deformacija nagiba glave femura po epifizeolizi radiološki je prepoznatljiva i lako se uočava na antero–posteriornoj slici. Glava femura nije kuglasta, više je čunjastog oblika i asimetrično namještena na vrat femura te se izbočuje nad donjom stranom vrata femura. Daljnji, gotovo stalni znak je zadebljanje medijalnog kortikalisa femura očito zbog novostvorene periostalne kosti. Klizanjem epifize prema straga i dolje prednji dio glave femura biva pojačano izložen opterećenju. Stoga pokazuje oštećenje zglobne hrskavice, dok je hrskavica u stražnjem dijelu očuvana te postepeno hipertrofira i stvara osteofite.

Kliničku evaluaciju ovakovih radioloških nalaza trebaju ubuduće intenzivnije obrađivati ortopedi. Sa radiološkog gledišta minor deformacije vode ka inkongruenciji zgloba koja će ubrzati degenerativno propadanje zgloba. Otkrivanje ovakovih deformacija u pristustvu minimalnih kliničkih simptoma ili u njihovoj odsutnosti ne znači da će se bezuvjetno razviti artroza, ali da treba shvatiti kao upozorenje da je takav zglob sklon lošem razvoju. Bolesnika treba uputiti u mogući fizički hendikep kako bi shvatio potrebu ranog aktivnog liječenja i zaustavio daljnje nepovoljne promjene na zglobu.

Sažetak

Analizirani su radiogrami kukova 133 odrasle osobe kako bi se utvrdila prisutnost minor deformacija zglobnih tijela koja dovode do gubitka kongruencije zgloba kuka i dalje do degenerativnih promjena. Svaki je kuk analiziran na prisutnost displastičnog acetabula i deformacije nagiba glave femura koju uzrokuje epifizeoliza u adolescenciji. Stupnjevanje acetabularne displazije vršeno je pomoću Wibergova CE–kuta. Veličina nagiba glave femura izračunata je koeficientom glave femura po Murray–u. Incidencija vrijednosti CE–kuta manjeg od 25°iznosila je 13,8% slučajeva, a deformacije nagiba glave nađene su u 9,8% pregledanih kukova.

Vidljivo je da se ove minor deformacije mogu otkriti detaljnim pregledom radiografija kukova i da njihova prisutnost govori za inkongruentnost zgloba i potencijalne promjene u smislu artroze. Rano otkrivanje ovakovih deformacija omogućuje ranije liječenje kao i usporavanje odnosno prekid propadanja zglobne hrskavice.

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OMNIPAQUE (IOHEXOL) 140 FOR SELECTIVE RENAL INTRAARTERIAL DIGITAL SUBTRACTION ANGIOGRAPHY

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Abstract – New technological inventions in the last two decades, based on digital techniques, have spurred great changes and improvements in diagnostical radiology. One of them is also digital subtraction angiography (DSA). Continuous research activities resulted in the analysis of new radiological diagnostic contrast media and in their quality improvements. One of such media is also Omnipaque (Iohexol), manufactured by NYCOMED, Oslo, Norway. Authors are showing the values of two of these findings on 60 patients. Research was aimed at the possibility to spare patients from their reaction to the quantity and the concentration of contrast media in a selective renal arteries angiography using the iaDSA. With the application of iaDSA it is possible to obtain diagnostically good angiograms with a smaller quantity of a lower contrast medium concentration which is less endangering and exerting for a patient and at the same time provides an economical effect with a cost decrease.

UDC: 616.7-073.755

Key words: renal artery-radiography, iohexol

Profess paper

Radiol Iugosl 1991; 25:115-8.

Introduction – DSA was originally conceived for the intravenous application of contrast medium (ivDSA) with the purpose to display the arterial system. Using this method, it was possible to avoid the arterial punction and catheterization, to simplify and shorten the procedure and to diminish the invasiveness of the angiography itself.

In most cases (depending on blood circulation speed, the patient age and renal function), this method provides a satisfactory display of a higher volume aorta or arteries. For a detailed display, specially for arteries of a smaller volume, the intraarterial application of a contrast medium (iaDSA) is required (1-4).

Conventional contrast media are well known for many undesirable effects. Some of them are pain and burning effect caused by a strong peripheral vasodilatation that appears with hyperosmolality in relation to the blood osmolality. The synthesis of low-osmolal new contrast media provided higher safety and comfort for the patient. One of these is also Omnipaque (Iohexol), manufactured by NYCOMED, Oslo, Norway. It is a three-iodine, water soluble, stable, low-osmolal and non-ionic contrast medium of the second generation. After a thorough experimental and clinical verification, it has been introduced for clinical application in 1980.

There are numerous data in the domestic (5-14) and foreign literature (15-25) about the application and characteristics of Omnipaque and also about the contrast medium usage in DSA comparing to the conventional media (23-37).

Material and methods – The research was performed on 60 patients 26 – 62 years of age (average 40.5); of these 46 (76.7%) were men and 14 (23.3%) women. All patients were directed to the angiographic procedure under a clinical diagnosis of renovascular arterial hypertension.

Angiographies were performed according to Seldinger's technique of percutaneous punction and a catheterization through the femoral artery, of which 56 (93.3%) through the right and 4 (6.5%) through the left femoral artery.

Catheters 4F or 5F for selective renal angiography were used, manufactured by ANGIOMED (Karlsruhe, Germany). Contrast medium Omnipaque 140 was injected in the quantity of 3-5 ml/sec, a total of 7-8 ml, depending on the patient's constitution, the renal artery volume und

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the kidney dimension. The aorto-renovasography survey was performed previously with Omnipaque 300 in the quantity of 5-7 ml/sec, a total of 15-21 ml.

A serial X-raying of 3-4 frames/sec was done on a DIGITRON 2 equipment (with a basic system of Polydoros 100, Angioscope, Coordinate-Angio), manufactured by SIEMENS, Erlangen, Germany.

Results – Research has shown that good quality diagnostic selective angiograms can be obtained with Omnipaque 140 in the iaDSA. The main trunk with segmental branches proved to be particularly accessible to the analysis comparing to tiny intrarenal branches. The intensity of renal parenchyma opacity was also good. Depending on the patient's constitution, renal artery volume and the kidney dimension, Omnipaque 140 was injected in the quantity of 3-5 ml/sec, total 7-8 ml.

For patients with a more delicate constitution and smaller kidneys 3 ml/sec was sufficient (total 7 ml) to obtain diagnostically acceptable angiogram (Fig. 1).

For patients with a stronger constitution and bigger kidneys, 5 ml/sec (total 8 ml) was required (Fig. 2).

Combined results of a selective iaDSA in relation to its diagnostical quality are shown in table 1.

Discussion – DSA appeared as a result of several highly developped technologies, such as the electronic intensifier, videocamera, the transfer of analogical signals into digital ones and the computer processing of a digital picture. By means of electronic substraction, such a system can intensify even slight differences of opacity densities before and after the application of a contrast medium in the same part that is being

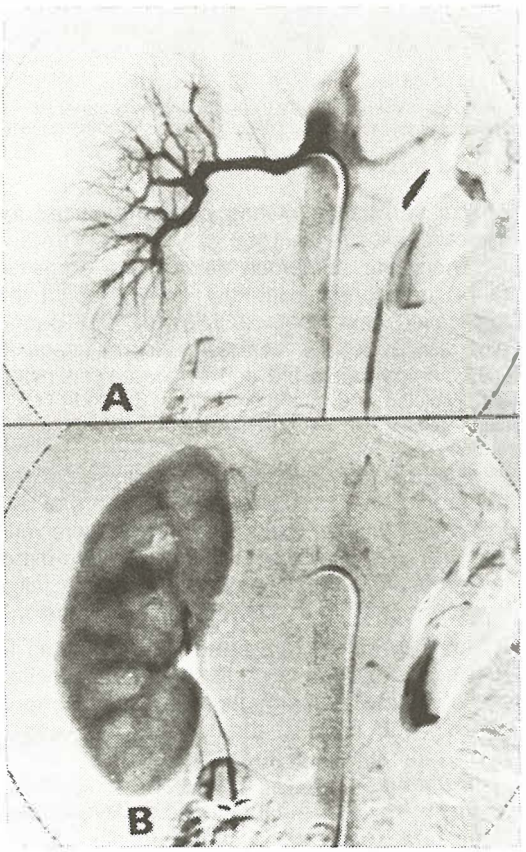

Fig. 1 – Selective renal angiogram (iaDSA) (A) arterial phase, (B) nephrological phase 4/7 ml Omnipaque 140

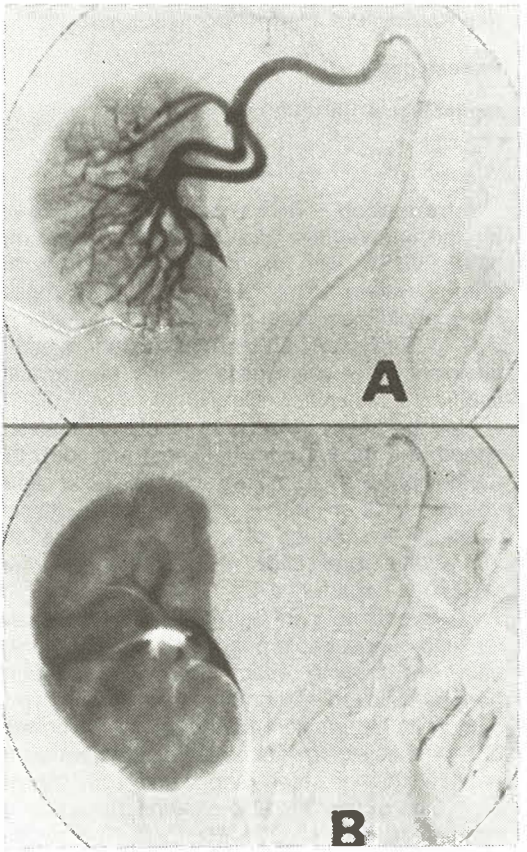

Fig. 2 – Selective renal angiogram (iaDSA) (A) arterial phase, (B) nephrological phase 3/6 ml Omnipaque 140

Table 1 – Diagnostic quality evaluation of selective renal angiograms at iaDSA

Diagnostical quality of angiogram	Quantity of contrast medium	
	3-5/5-7 ml	4-5 /7-8 ml
GOOD (+++)	15	31
SATISFACTORY (++)	3	9
POOR (+)	2	0
TOTAL	20	40

examined. It provides a display of the contrast medium in a concentration of only 2% comparing to the conventional technique requiring a concentration of 40-50%. A picture signal is logarithmically intensified and transformed into a digital form to be then transferred into the computer memory. Memory data can be transferred to the disc for a short-term application or to a tape for a long storage. Signals are monitored on a TV monitor and using a multiformat camera the substraction angiograms are then transferred to a single-layered classical X-ray film for a detailed analysis and lasting storage.

Until now, DSA has not met the expectations to replace peripheral intravenous application of a contrast medium with an intraarterial method. However, good aorta and big arteries display can be obtained by central application of a contrast medium into the vene cava superior or inferior. In these cases, (ivDSA) the performance of angiography is simplified and shortened and feasible also in out-patients. At the same time, it replaces the intraarterial punction and/or catheterization when these are not possible for some reason. For smaller arteries and a detailed analysis, the intraarterial method with catheterization (iaDSA) is till required. Comparing to the conventional method, the advantage is, among other things, that a considerably smaller quantity of a lower concentration contrast medium is sufficient (1-4, 28-31, 34-37).

Conventional contrast media, owing to their hypertonicity and chemotoxicity, can cause various adverse effects. In the attempt to diminish the side effects as much as possible, the research laboratories are continously trying to improve media characteristics. One of their results is also the synthesis of a modern contrast medium called Omnipaque (Iohexol), manufactured by the factory NYCOMED, Oslo, Norway. It is a threeiodine, water soluble, stable, low-osmotic non-ionic contrast medium of the second generation. After several years of experimental and clinical research, the medium appeared in clinical application in 1980. Due to its low osmotic values, small chemotoxicity and high tolerance, it has proved to be suitable for all vascular, subarachnoid and other applications on a large scale of concentration. Beside its low osmotic values and low viscosity when warmed to the body temperature, it is bound to the proteins in human plasma with only 1.5%. It releases only 10% of disposable histamine, it causes less damages to the endothelium, it affects the cardiovascular system less as well the central nervous system. It is eliminated through the urine and extracted entirely within 24 hours. Comparing to the conventional contrast media, it is less risky for patients with renal insufficiency and also suitable for children (3.5-13, 15-26).

Our research has confirmed well known facts that a considerably smaller quantity of lower-concentrated Omnipaque is sufficient for the iaDSA and a selective display of renal arteries.

Conclusion – The intraarterial application of the contrast medium and the X-ray equipment for DSA have contributed to good quality diagnostic angiograms with a considerably lower concentration of contrast medium.

The synthesis of contemporary highly tolerant non-ionic, low-osmotic contrast media improved the safety and comfort of patients. The usage of a high-flow thin-wall catheter 4F or 5F should not be disregarded.

Omnipaque (Iohexol) 140 has proved to be suitable for good quality diagnostic selective renal angiograms at iaDSA. It improves the comfort and safety of the patient and reduces the procedure costs.

Sažetak

OMNIPAQUE (IOHEXOL) 140 ZA SELEKTIVNU RENALNU INTRAARTERIJSKU DIGITALNU SUPTRAKCIJSKU ANGIOGRAFIJU (iaDSA)

Pronalascima novih tehnologija baziranih na digitalnim tehnikama u posljednja dva desetljeća došlo je do velikih promjena i poboljšanja u dijagnostičkoj radiologiji. Jedno od njih je i pronalazak digitalne suptrakcijske angiografije (DSA).

Neprekidan istraživački rad rezultirao je sintezom novih radioloških dijagnostičkih kontrastnih sredstava i poboljšanjem njihovih svojstava. Jedan od tih pronalazaka je i Omnipaque (Iohexol) tvrtke Nycomed, Oslo, Norveška.

Autori prikazuju vrijednosti ovih dvaju pronalazaka na 60 bolesnika. Ispitivanja se odnose na mogućnost poštede bolesnika s obzirom na količinu i koncentraciju kontrastnog sredstva za selektivnu angiografiju renalnih arterija koristeći iaDSA.

Primjenom iaDSA moguće je s manjom količinom slabije koncentriranog kontrastnog sredstva dobiti dijagnostički dobre angiograme, bolesnika manje opteretiti i ugroziti, i istovremeno postići značajni ekonomski efekt smanjenjem troškova.

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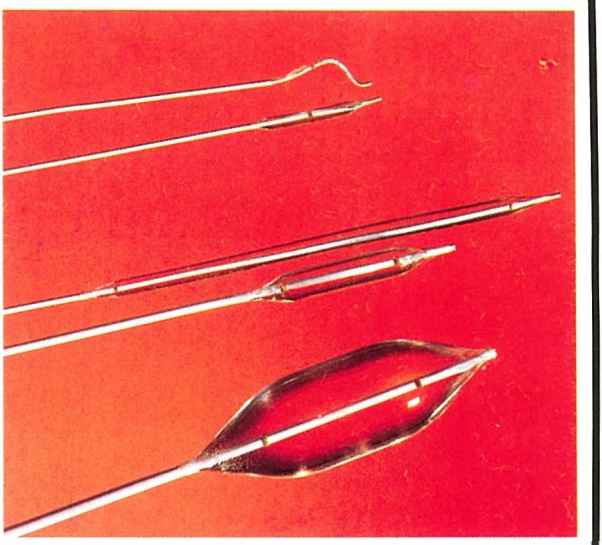

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VOJNA BOLNICA ZAGREB, RADIOLOŠKO ODJELJENJE

FLEBOGRAFIJA VENA ZDJELICE METODOM DIGITALNE SUBTRAKCIJE

PHLEBOGRAPHY OF THE PELVIC VEINS BY METHOD OF DIGITAL SUBTRACTION

Borković Z

Abstract – The tehnique of phlebography of the pelvic veins by means of digital subtraction is described. This examination method was applied in 26 patients with clinical signs of acute and chronic vein obstruction with development of collateral veins, and also in patients with pulmonary embolism in searching the emboli origin. For the opacification of vein blood contrast medium lohexol (Omnipaque 350) in the quantity of 20-30 ml was used. This method provides a lot of information about morphology and patological conditions of the vein system. Advantage of this method is in a large number of images which can be produced later by using a digital tehnique, as well as teduced quantity of contrast medium and decreased exposure to radiation.

UDC: 616.147-073.75

Key words: pelvic veins, phlebography; subtraction technic

Profess paper

Radiol Iugosl 1991; 25:119-21.

Uvod – Tromboza zdjeličnih vena je vrlo česta lokalizacija venske tromboze. Lokalizacija venske tromboze u ilijačnom i ilijo-femoralnom segmentu je često ishodište embolusa, od kojih nastaje embolija plućnih arterija sa teškim kliničkim stanjima, a moguć je fatalni ishod masivnije plućne embolije. Zbog položaja zdjeličnih vena treba izabrati dijagnostički postupak, koji nam daje najviše relevantnih podataka, na temelju kojih donosimo dijagnostičke zaključke.

Na raspolaganju nam stoji više dijagnostičkih postupaka, koji nam mogu dati određene dijagnostički korisne podatke. Najčešće se primjenjuje u dijagnostici venske tromboze pletizmografija, radiofibrinogen test, Doppler, UZ, Duplex, izotopna flebografija, flebografija i digitalna subtrakcijska flebografija (1,2,3,4,5,6,7).

Razvojem računara i njegove primjene u angiografiji razvila se metoda digitalne subtrakcijske angiografije (DSA). Primjenom iste metode u postupku prikaza vena razvila se vrlo jednostavna metoda digitalne subtrakcijske flebografije, kojom su postignute znatne prednosti u odnosu na klasičnu flebografiju (2).

Osim prikaza zdjeličnih vena ovom metodom, nastojimo u istom aktu prikazati distalni dio donje šuplje vene i ilio-femoralni segment, jer često postoji i descendirajući tok tromboze s progresivnim rastom tromba u femoralnu venu.

Materijal i metode – U toku 1989. i 1990. godine metodom digitalne subtrakcijske flebografije zdjeličnih vena obrađeno je 26 bolesnika, kod kojih je postojala sumnja na akutnu vensku trombozu zdjeličnih vena, kod pacijenata sa znacima plućne embolije, kod kojih se tražilo izvorište embolusa, kontrola nakon provedene fibrinolitičke terapije i pacijenti kod kojih se željelo prikazati razvitak kolateralnog venskog toka nakon preboljele tromboze ilijačnih vena.

U navedenom razdoblju metodom digitalne subtrakcije pregledano je 26 bolesnika, od kojih je bilo četiri muškarca u dobi od 54 do 61 godine i 22 žene u dobi od 21 do 57 godina. Svi pacijenti su pregledani na aparatu Philips DVI-CV s elektronskim pojačivačem veličine 14 in. Prilikom svake serije snimaka brzina snimanja je bila 1 snimka u sekundi – ukupno 20 snimaka.

U toku izvođenja pretrage bolesnik leži na leđima u horizontalnom položaju. Donji ekstremiteti su podignuti od ravnine stola 30-45 stupnjeva, da bi se time znatno ubrzao dotok venske krvi i bitno smanjila potrebna apnoična faza.

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Punktira se jedna od vena dorzuma stopala tankom leptirastom iglom od 18-20 gauge i u tom položaju se vrši aplikacija kontrasta.

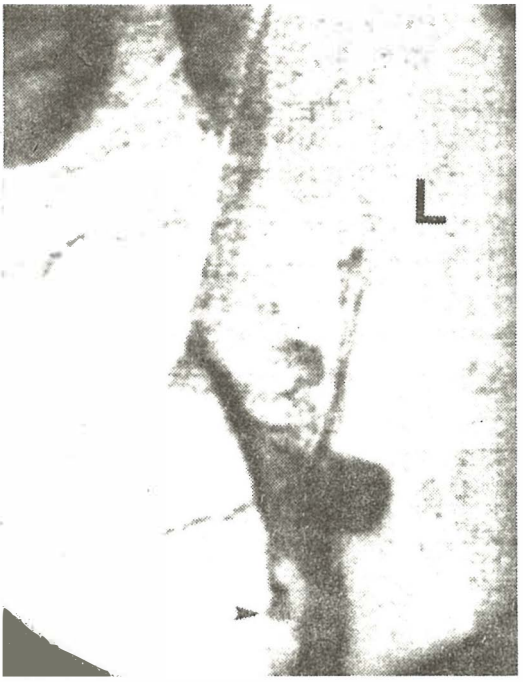
Prije snimanja i. v. se aplicira 1 mg Glukagona ili 40 mg Buscopana u svrhu umirivanja crijevne peristaltike. Za svaku seriju snimaka potrebno je aplicirati 20-30 ccm kontrastnog sredstva s brzinom aplikacije od oko 5 ccm/sek.

U principu, kontrastno sredstvo se aplicira ručno. Kod svih bolesnika korišteno je niskoosmolarno nejonsko kontrastno sredstvo lohexol (Omnipaque 350).

Snimanje počinje 4 sekunde iza početka aplikacije kontrastnog sredstva.

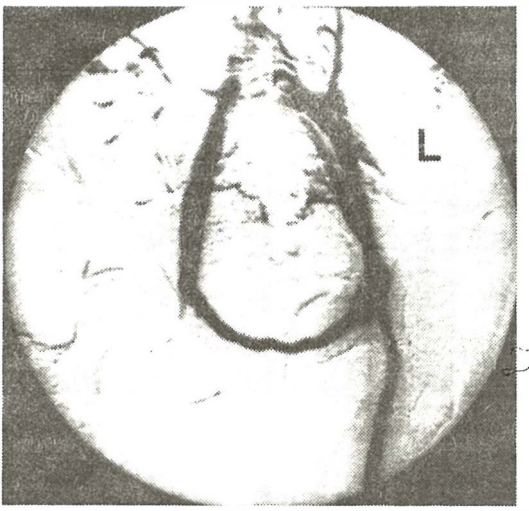
Rezultati – Metodom digitalne subtrakcijske flebografije od ukupno 26 pregledanih bolesnika nađena je akutna okluzija lijeve ilijačne vene kod 5 bolesnika.

Kod jedne bolesnice bio je prisutan descendirajući oblik sa okluzijom lijeve femoralne vene i stvaranjem flotirajućeg tromba (slika 1).



Slika 1 – Tromboza lijeve ilijačne vene i prikaz flotirajućeg tromba u femoralnoj veni

Fig. 1 – Thrombosis of the left iliac vein and survey of the flotation thromb in the femoral vein



Slika 2 – Okluzija lijeve ilijačne vene i razvoj kolaterala.

Fig. 2 – Occlusion of the left iliac vein and development of the collateral veins

Kod 7 bolesnika nadena je okluzija lijeve ilijačne vene i razvijene kolaterale prema desnoj ilijačnoj veni, a i prema lumbalnim venama (slika 2).

Kod ostalih 14 pregledanih pacijenata, na prikazanim zdjeličnim venama, nije se našlo vidljivih patoloških promjena. U našem materijalu sve okluzije su se nalazile u proksimalnom dijelu lijeve ilijačne vene, što je i razumljivo, s obzirom na anatomske odnose u tom području.

Diskusija – Flebografija metodom digitalne subtrakcije se pokazala kao sigurna metoda u dijagnostici patološkog stanja venske cirkulacije i znatno je poboljšanje u odnosu na metodu klasične flebografije (2).

Primjenom ove metode bitno je smanjena količina potrebnog kontrastnog sredstva za prikaz vena, a time je smanjen i rizik od ekstravazacije kontrasta prilikom aplikacije, jer za ovu metodu nije potrebna brza aplikacija kontrastnog sredstva u većoj količini i u što kraćem vremenu, kao kod metode klasične flebografije (2, 4, 5).

Ovom metodom je bitno skraćeno vrijeme pretrage, znatno je smanjena izloženost bolesnika ionizantnom zračenju, trauma zbog punkcije i aplikacije kontrasta je minimalna, a što nije nebitno i cijena pretrage u odnosu na metodu klasične flebografije je smanjena.

Primjenom nejonskog kontrastnog sredstva lohexol (Omnipaque 350) za flebografiju metodom digitalne subtrakcije u malim količinama dobiven je vrlo dobar prikaz vena kod svih pregledanih bolesnika.

Aplikacijom kontrasta periferno u području dorzuma stopala dobiva se dobro miješanje kontrasta i krvi, tako da se time izbjegnu lažno-pozitivni defekti unutar lumena vene. Primjenjujući malu količinu nejonskog kontrastnog sredstva nije se javljala bol na mjestu aplikacije, koja često nastaje zbog podražaja intime vene kod aplikacije koncentriranih jonskih kontrastnih sredstava, a nisu registrirane opće reakcije na primjenjeno kontrastno sredstvo (7, 8, 9). Za ovu metodu pretrage neophodna je potpuna suradnja bolesnika, tj. potrebno je potpuno mirovanje i prestanak disanja za vrijeme uzimanja maske i tokom snimanja u trajanju od oko 25 sek.

Kod nekooperabilnih bolesnika tu pretragu ne treba izvoditi, jer je to jedan od limita primjene ove metode. Treba naglasiti da je često otežana pretraga kod bolesnika sa plućnom embolijom, jer oni vrlo teško podnose prestanak disanja i mirovanje na duže vrijeme i kod pretrage kod takvih bolesnika neophodno je izvršiti veću elevaciju ekstremiteta da bi time ubrzali tok venske krvi i znatno skratili vrijeme apnoe. Aplicirajući uobičajene doze Glukagona od 1 mg ili Buscopana od 40 mg za umirivanje crijevne peristaltike nije bilo nikakvih štetnih nus pojava.

Sažetak

Opisana je tehnika flebografije vena zdjelice metodom digitalne subtrakcije. Ova metoda pretrage vena zdjelice primjenjena je kod 26 bolesnika sa znacima akutne i kronične venske opstrukcije zdjeličnih vena, razvoja kolaterala i kod pacijenata sa plućnom embolijom u traganju za izvorom embolusa.

Za opacifikaciju venske krvi korišteno je nejonsko kontrastno sredstvo lohexol (Omnipaque 350) u količini od 20-30 ml. Primjenom ove metode dobije se mnoštvo podataka o morfologiji i patološkim stanjima venskog sistema.

Prednost ove metode je veliki broj snimaka, koji se naknadno mogu digitalnom tehnikom obrađivati, manja količina kontrastnog sredstva i manja izloženost zračenju.

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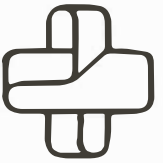
Adresa autora: Dr. Zdravko Borković, radiolog, Vojna bolnica Zagreb - Odjel za radiologiju, Aleja izviđača bb, 41000 Zagreb



TOSAMA

Proizvaja in nudi kvalitetne izdelke:

Komprese vseh vrst
Gazo sterilno in nesterilno
Elastične ovoje
Virfix mrežo
Micropore obliže
Obliže vseh vrst
Gypsona in mavčene ovoje
Sanitetno vato PhJ III
Zdravniške maske in kape
Sanitetne torbice in omarice
Avtomobilske apoteke

FROM PRACTICE FOR PRACTICE

CARDIOVASCULAR SYSTEM
Case 2

What is this investigation and what does it show? How was it performed? What are the possible causes of this condition?

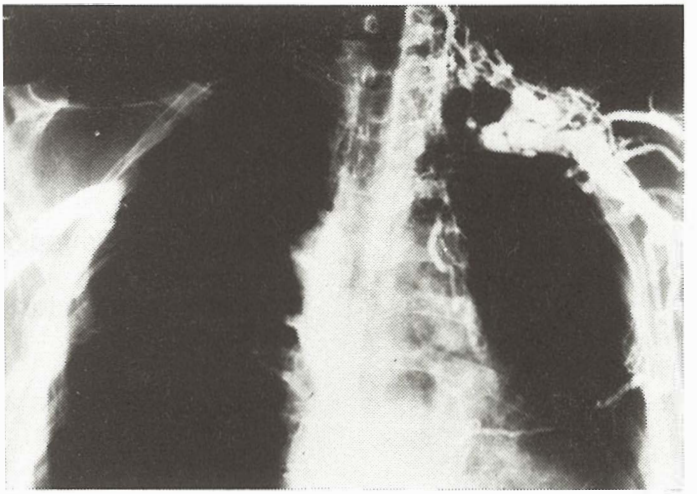


Fig. 1

(For answers see page 148)

Laserski žarki u medicinski praksi

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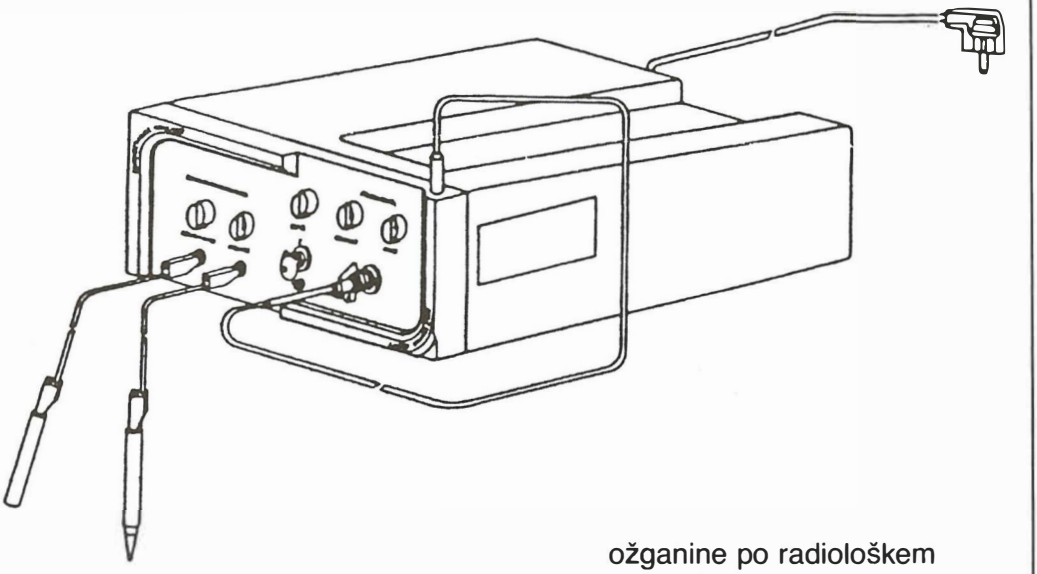

Tip: LSA–02

Za osvetljevanje:
- obzobnih tkiv
- herpesa labialis
- aft
- oteklin
- ulcus cruris, decubitus
- ožganine po radiološkem obsevanju
- rane zaradi sladkorne bolezni
- optopunktura

Prednosti laserske akupunkture:
- ne boli, ni strahu
- ni okužb
- kratki terapijski časi

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Jugoslavija
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Stegne 7, p.p. 59
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Telex: 31687 iskceo yu
Fax: (061) 575-985

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SONOGRAPHIC PRESENTATION OF ADVANCED STAGES OF COLORECTAL CANCER

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Abstract – The paper deals with the importance of ultrasound in the everyday practice of gastrointestinal tract disease diagnostics. Attention is called to the efficiency of detecting malignant disorders of the colon in 5750 ultrasound examinations. Fifteen such patients were verified, practically all of them in advanced stage of the disease. Regardless of these findings, precise diagnosis is made by means of more selective tests such as colonoscopy and pathohistological analysis of the tumor sample. The basic ultrasound characteristics of these malignant disorders are presented on the basis of experience gained from the examinations described in the paper. It is clearly evident that in combintion with the complete diagnostic procedure this noninvasive method helps towards planning the subsequent therapeutic procedure.

UDC: 616.348-006.6-073:616.351-006.6-073

Key words: colorectal neoplasms; ultrasonic diagnosis

Profess paper

Radiol Iugosl 1991; 25:125-8.

Introduction – Contemporary gastroenterological research reveals a steady increase in the incidence rate of colorectal cancer in the past 50 years. In civilized countries this disease occurs in 0.7% of the population (1). Among the causes of death from malignant diseases, colorectal cancer accounts for 12.6% of males in Europe and 14.7% in the USA, just next in order after bronchial cancer (2). In Croatia it comes third according to its incidence in the group of malignant disorders (3). In Slovenia the five-year survival rate after colorectal cancer is 18% with 40% of operable patients (4). As to the etiology of these diseases, it can safely be stated that there are high risk factors for their occurrence, including polyposis of the intestine. Precancerous growths include also colon and rectal polyps, especially adenomatous ones, as well as some inflammatory conditions of the colon. A more frequent occurrence of these disorders has also been observed in some families (5). External factors that may cause malignant diseases of the colon are dietary habits and kind of food, consumption of alcohol and nicotine. The most frequent site of this disease is the rectosigmoid area (50% to 60% (1,5). Pathohistologically they are more often than not adenocarcinomas (96%), but also other forms may occur, such as mucinous, planocellular and nondifferentiated ones (6). The Dukes classification of pathohistological invasion of this disease, being most useful for the treatment and prognosis of the disease, is also important (6).

Besides basic symptomatology, the diagnostics comprises also digitorectal examination, flexible recto sigmoidoscopy or colonoscopy as well as the possibility of cytological and histological analysis, or removal of entire precancerous lesions, i.e. polypectomy (7,8). Irrigography as a radiological method has also its diagnostic importance. In addition to the basic laboratory parameters, the CEA levels are determined as well, which may later on be important for the subsequent follow-up of the patient (9). Today ultrasound occupies a very important place in the work up of patients with colorectal cancer. First of all it is used as a method of screening for spread of the basic disease to adjacent and other organs. In addition, endosonography aims at providing a local scan of the tumor and its spread through the intestinal wall. Its great assistance in determining the curative treatment is evident (10-15).

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Material and methods – In daily work ultrasound is used as a routine method for diagnosis of a number of gastrointestinal tract complaints. The wide use of this simple and noninvasive method enables us to detect in some patients an expansive formation in the abdomen which can be with certain precision determined as belonging to a part of the large bowel. It is clearly evident that what follows is a ciliary diagnostic procedure as mentioned above. In most cases with these patients it is a question of the Dukes C stage, usually confirmed by other methods, and it is also of importance for the subsequent therapy. In this work Hitachi EUB 410 unit with linear probes of 3.5 and 5.0 MHZ has been used. The examinations are carried out according to the conventional technique described by many authors (11,15,16).

Results – An analysis has been made of 5750 ultrasound examinations performed during the period between January 1, 1988 and December 31, 1988. In 15 patients from this group these examinations revealed substantial evidence of colorectal cancer. In 14 of them subsequent diagnostic procedures, colonoscopy and pathohistological tests confirmed this suspicion. Only one of the patients had lymphoma infiltrating the intestine. In seven patients the site was the rectosigmoid area, in three the transversal colon, and in two of them the process was localized in the cecum. In one patient the localization was in the descending colon and in another one in the hepatic flexure. Each of these ultrasound changes was differentiated from adjacent structures, and on the basis of characteristic sonographic scans the working diagnosis of the colon disorder was made (Fig. 1.2.3.4.5.6.7).

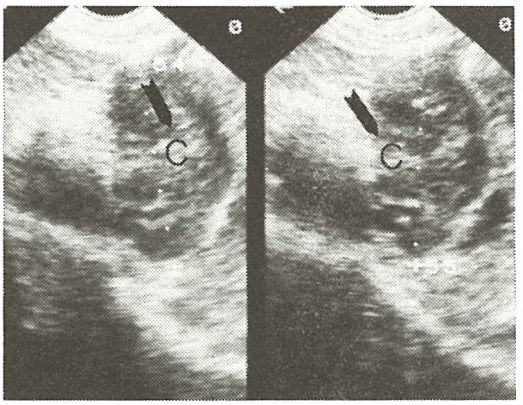

Fig. 1 – Sonographic scan of transverse colon cancer (C)

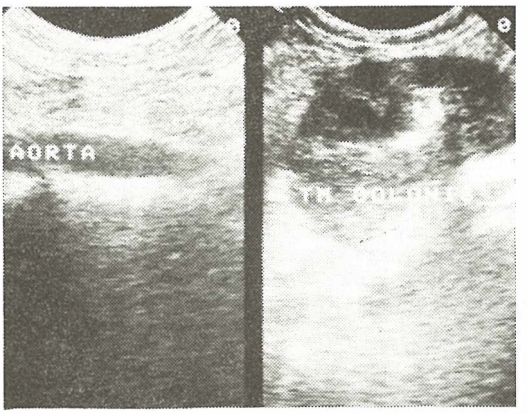

Fig. 2 – Sonographic scan of stenotic cancer of the ascending colon

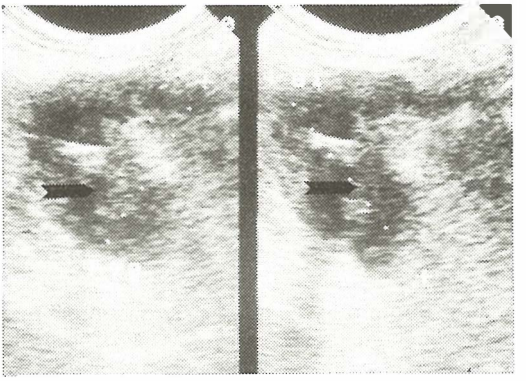

Fig. 3 – Cross-section of ultrasound scan of cecum cancer (arrows)

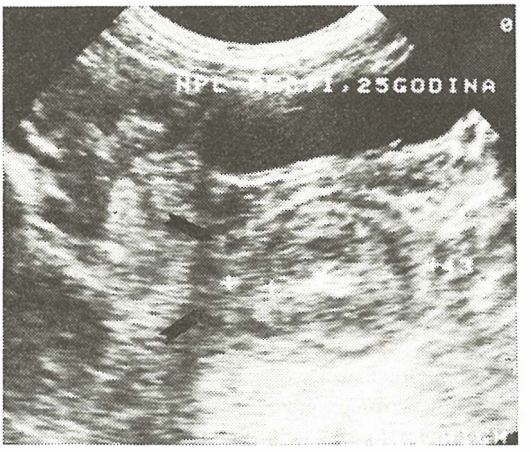

Fig. 4 – Sonographic scan of the pelvis with a malignant lesion of the rectum penetrating the wall (arrow)

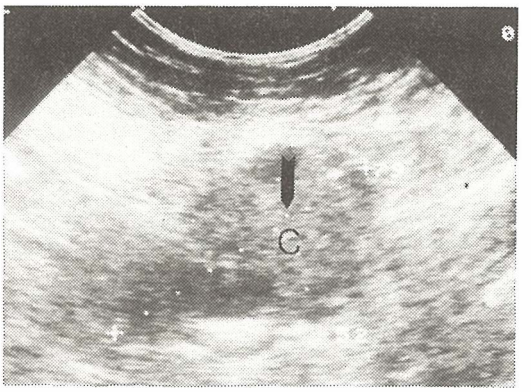

Fig. 5 – Sonographic scan of a relapse of sigmoid cancer (C)

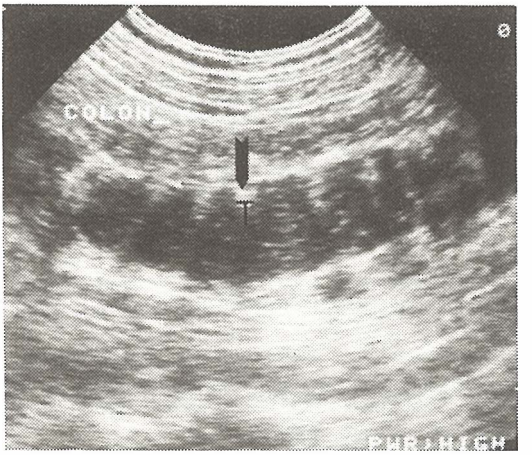

Fig. 6 – Sonographic scan of typically distended large bowel in cancer proximity (T)

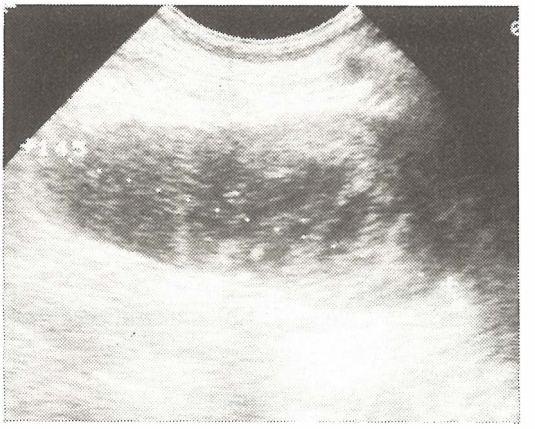

Fig. 7 – Sonographic scan of abdominal non-Hodgkin lymphoma. Differential diagnosis according to colon cancer.

Discussion – At present, ultrasound is a widely used method in the diagnostics of a great number of gastrointestinal complaints, suitable also for assessing the spread of known diseases such as colorectal tumors (8,10,11,12). Thus, it is not surprising that the wide use of this noninvasive method may lead to the discovery of colorectal cancers, which however, are usually in an advanced stage. These 5750 ultrasound examinations of the abdomen revealed 15 patients in whom this disease was suspected. This ultrasound-based diagnosis had to be confirmed by further more exact methods such as colonoscopy and pathohistological tests of scraps of the tumor or whole lesions (7). One of the ultrasound techniques recently in frequent use is endosonography which also provides valuable data on the penetration of the tumor trough the intestinal wall (13,14). The use of conventional ultrasound makes it possible to establish suspicion of a malignant colorectal disease on the basis of sonographic characteristics and the examiner's experience.

– The tumor mass is clearly interperitoneally localized, often separated from other organs, although sometimes cases where it has grown into adjacent structures also occur (e.g. into the liver).

– The tumor mass has irregular edges in all the shown sections.

– Sonographically it is a mixed formation consisting of a number of anechogenic, hypoechogenic, and hyperechogenic areas.

– Often orally of the tumor mass distended convolutions occur, a reliable indication that the tumor mass adheres to the colon.

– The scan of the tumor mass often presents metastatic changes of the liver, extended paraaortal and paracaval lymph nodes, or pyelocaliectasis as additional findings.

It is self-evident that these ultrasound scans depend on the possession of highly efficient apparatus, possibly color dopplers. The human factor also plays a certain part, as the work calls for a trained specialist prepared to carry out long and detailed examinations of the whole abdomen. The conclusion to be drawn from all this is that today ultrasound is only an auxiliary method in the diagnostics of malignant colon disorders. But, regarding its wide application, it is not surprising that it is sometimes the first method directing attention to this disease, as can be seen also from the experience described in this paper (11,15).

Sažetak

SONOGRAFSKI PRIKAZ UZNAPREDOVALIH STADIJA KOLOREKTALNOG KARCINOMA

U radu je prikazana važnost ultrazvuka u dijagnostici bolesti gastrointestinalnoga trakta u svakodnevnom radu. Ističe se uspješnost u otkrivanju malignih bolesti kolona na 5750 učinjenih pretraga gdje smo verificirali 15 bolesnika s kolorektalnim karcinomom ali praktički svi već u uznapredovalom stadiju. Bez obzira na ovaj nalaz točna dijagnoza se postavlja selektivnijim pretragama kao što su kolonoskopija i patohistološka analiza uzorka tumora. Prikazane su osnovne ultrazvučne karakteristike ovih malignih bolesti na osnovu vlastitih iskustava. Jasno da u sklopu cijeloga dijagnostičkoga postupka i ova neinvazivna metoda doprinosi u planiranju daljega terapijskoga postupka.

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SONOGRAPHY OF GIANT RETROPERITONEAL GANGLIONEUROMA IN THE ADULT

Kauzlarić D[1], Barmeir E[2], Donati D[1], Schustar N[1]

Abstract – Ganglioneuroma is a well-circumscribed fully differentiated tumor with fibrous capsule. The tumor grows slowly commonly along the paravertebral line. Clinically this tumors are present as large masses in the retroperitoneum or posterior mediastinum. Biologically, ganglioneuromas are benign tumors mostly diagnosed in patients older than 10 years. Malignant change is uncommon, but does occur.

UDC: 616-006.486-073:534-8

Key words: ganglioneuroma; ultrasonic diagnosis; retroperitoneal neoplasms

Case report

Radiol Iugosl 1991; 25:129-32.

Introduction – Ganglioneuroma is a rare, benign neoplasm occuring mainly in infants and children. The sonographic apearance of ganglioneuroma in children has been described (1-6). In this report we describe the sonographic features of ganglioneuroma in an adult. To our knowledge, the sonographic features of this entity in the adult have not been described yet.

These features include, in addition to a low echogeneity mass characteristic of this lesion, the following findings:

a) lobulation and septation of the tumor, represented by multiple highly echogenic linear bands.

b) extension of the mass across midline, causing displacement of the great vessels.

The sonographic features of this entity are correlated with angiographic and computed tomography (C. T.) findings.

Case report – A 19-year-old man was referred for evaluation of a firm, non-tender right and mid-abdominal mass. The patient complained of intermittent abdominal pain during the past six months. His past medical history was unremarkable.

Sonographic examination revealed a large, well circumscribed retroperitoneal mass (Fig. 1a).

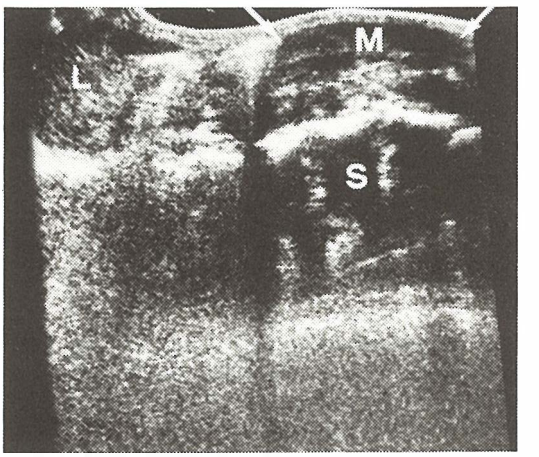

Fig. 1a – Real – Time ultrasound: longitudinal scan at mid-abdomen demonstrating mixed echogeneity mass (M) extending from the liver (L) to the pelvis. The mass is anterior to the spine (S).

This hypoechoic tumor had a multinodular pattern, represented by lobulated contours and multiple radiating highly echogenic bands dividing the mass into nodules (Fig. 1b). The mass extended anteriorly, displacing the aorta to the left (Fig. 1c).

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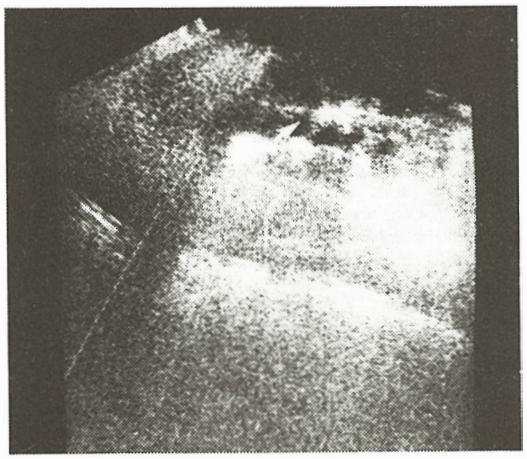

Fig. 1 b – Real – time ultrasound: high echogeneity fibrous septa (arrow) are noted.

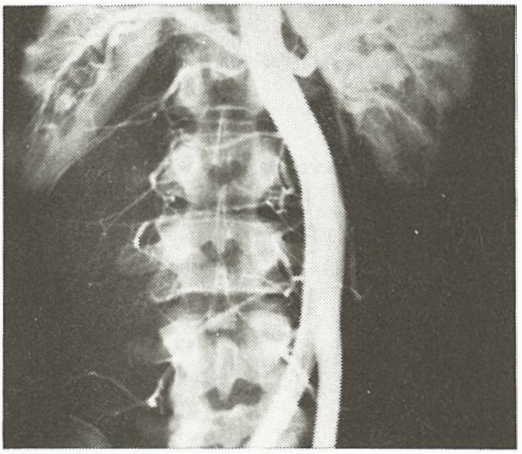

Fig. 2a – Aortogram demonstrating lateral displacement of the aorta by a huge mass.

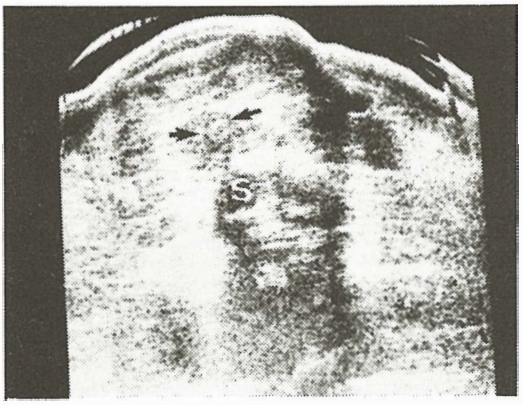

Fig. 1c – Transverse scan at mid-abdomen shows displacement of the aorta (arrow) and I. V. C. (arrows).

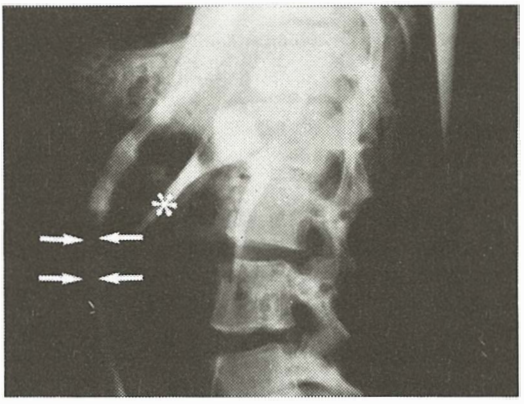

Fig. 2b – Cavogram in right lateral decubitus demonstrating anterior displacement of I. V. C. (arrows) and right ureter (*)

Angiography confirmed a huge mass, with pathological vessels causing lateral displacement of the aorta, celiac axis and mesenteric vessels, as well as superior displacement of the right renal artery (Fig. 2a).

Cavography showed anterior displacement of the IVC and right ureter (Fig. 2b).

Computed tomography (CT) confirmed the findings of a huge septated retroperitoneal soft tissue mass displacing the aorta, ureters and bowel loops (Fig. 3).

On operation a large lobulated mass was removed (Fig. 4). The tumor involved multiple nerve trunks along the para-vertebral gutter on the right.

Pathologic examination established the diagnosis of a benign ganglioneuroma.

The patient's postoperative recovery was rapid and he was discharged 5 days after surgery.

Clinical, laboratory and sonographic follow-up examinations over an 18-month period showed no sign of recurrence.

Discussion – Primary retroperitoneal tumors, either benign or malignant, are rare.

In the past, the retroperitoneum had been a hidden area, extremely difficult to image by conventional radiological means. With the advent of new imaging modalities, i. e. ultrasound, CT and magnetic resonance (MR) the diagnosis of retro-

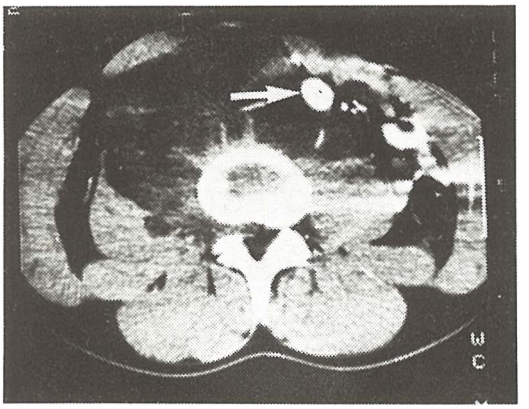

Fig. 3 – C. T. scan with contrast shows a large low density lobulated mass with multiple septa. The aorta and ureter are displaced anteriorly.

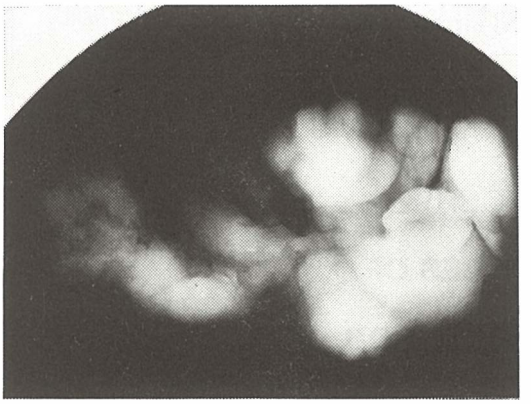

Fig. 4 – Radiograph of the pathologic specimen showing multinodular appearance.

peritoneal masses has been much facilitated. Ultrasound, being rapid, non-invasive and easy to perform is often used as the first screening modality.

Neurogenic tumors represent 2% of all benign retroperitoneal tumors (2, 4). Neuroblastoma, ganglioneuroblastoma and ganglioneuroma are all derived from primordial neural creast cells of the developing spinal cord, and are usually found in the sympathetic ganglia and adrenal medulla.

Neuroblastoma, which is the least differentiated of these tumors, is made of primitive neuroblasts. Ganglioneuroma, being a fully differentiated tumor is characterized by Schwann cells and ganglion cells and it has considered a benign tumor (2).

Ganglioneuroma is found in patients less than 20 years old in 60% of cases (3) with a slight female predominance (6). 43% of ganglioneuromas are found in the mediastinum, 32% in the abdomen and 8% in the neck (1, 4). Ganglioneuroma seldom causes symptoms and is usually discovered incidentally.

An abdominal mass is usually palpable in the midline, with variable cranio-caudal extension.

Ultrasound provides information about the size and shape of the tumor as well as its intrinsic pattern (Fig. 1). In addition, invasion of adjacent organs and relashionship to vascular structures can be established. This information is important in determining the operability of the mass and in planning the surgery. Angiography is essential pre-operatively to determine tumor vascularity and relations to the great vessels (Fig. 2).

CT can define density of the tumor, its extent and the presence of calcifications. In our case, the tumor showed low density with enhancing septa and capsule (Fig. 3). The performance of CT myelogram may determine para-spinal and intraspinal tumor extent.

Conclusion – Ganglioneuroma, although uncommon, should enter the differential diagnosis of posterior mediastinal and retroperitoneal masses in children and adults. On ultrasound this tumor shows low level echogenicity with irradiating septa and lobulated borders. The tumor mass may cross the mid-line and displace the large vessels.

Sažetak

ULTRAZVUČNI PRIKAZ RETROPERITONEALNOG GANGLIONEUROMA

Ganglioneurom je visoko diferencirani, oštro ograničeni tumor okružen fibroznom kapsulom. Raste vrlo sporo uzduž paravertebralne linije. Klinički se radi o opsežnoj masi u retroperitoneumu ili stražnjem medijastinumu. Biološki, ganglioneurom je benigni tumor najčešće dijagnosticiran u pacijenata starijih od 10 godina. Izuzetno može doći do maligne alteracije.

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AUTOANTITIJELA NA TRIJODTIRONIN I TIROKSIN HIPERTIREOZI

AUTOANTIBODIES TO TRIIODOTHYRONINE AND THYROXINE IN HYPERTHYREOSIS

Biuković M[1], Musafija A[2], Skrobić M[1], Golubović N[1], Zubović I[1]

Abstract – The role of autoantibodies against triiodothyronine (T3) and Thyroxine (T4) hormones in thyroid gland disease is still unknown. Earlier results on the presence of those autoantibodies in patients with hyperthyreosis are fairly cotradictory. We have estimated atuoantibodies against T3 and T4 in 40 patients with hyperthyreosis. Positive autoantibodies against T3 and T4 were found in 17.5% patients. Statistically significant diference was found with reference to control group. The control group consisted of 50 healthy subjects with no such antibodies found. The antibodies were also tested in the course of thyreostatic therapy, and the results were found positive in 15% of patients, which was not statistically significant compared to the pretherapeutic state. The role of autoantibodies against T3 and T4 hormones in hyperthyreosis is unknown. The number of patients with such autoantibodies present in the course of tyreostatic therapy remains unchanged.

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Key words: hyperthyroidism; autoantibodies, triiododothyronine; thyroxine

Profess paper

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Uvod – Autoimuna oboljenja štitne žlijezde niz godina služe kao modeli za proučavanje autoagresije (1). Uloga većine autoantitijela u nastanku i toku ovih bolesti je manje ili više razjašnjena. Za razliku od ostalih, autoantitijela na hormone trijodtironin (T3) i tiroksin (T4) još nisu našla svoje pravo mjesto u kompleksnom mehanizmu autoimunih poremećaja štitne žlijezde. Najčešće se na ova antitijela obraćala pažnja kada su ona dovodila do lažno pozitivnih ili lažno negativnih rezultata hormona T3 ili T4 (2).

U hipertireozi ova antitijela su malo proučavana i rezultati su veoma oprečni. Desai (3) od 101 bolesnika sa hipertireozom nalazi kod jednog bolesnika antitijela na T4 a Nakamura (4) nalazi u 20% bolesnika sa hipertireozom pozitivna autoantitijela na T3 i T4.

Cilj rada je bio ispitati autoantitijela na T3 i T4 u bolesnika sa hipertireozom prije terapije i odrediti njihovu promjenljivost u toku tireostatske terapije.

Ispitanici i metod rada – Ispitali smo 40 bolesnika sa hipertireozom. Žena je bilo 35 a muškaraca 5. Bolesnici su bili životne dobi 15-74 godina. Bolesnici su ispitani prije tireostatske terapije i 1-8 mjeseci od započinjanja tireostatske terapije. U tireostatskoj tarapiji upotrebljavani su tiamazol i propranolol. Bolesnici kod kojih su korišteni kortikosteroidi nisu uključivani u ispitivanje.

U kontrolnoj grupi ispitano je 50 zdravih osoba koje su bile životne dobi 19-82 godina. Žena je bilo 29 a muškaraca 21.

Autoantitijela na T3 i T4 određivali smo modifikovanom metodom Sakate (5). Metod uključuje zakiseljavanje seruma sa ciljem da se odvoje antitijela koja su vezana u kompleksu hormon – antitijelo i vezivanje oslobođenog hormona na dekstran čarkoal (6).

Postupak određivanja antitijela na hormone štitne žlijezde smo provodili na slijedeći način:

0,1 ml ispitivanog seruma
+
04 ml – 0,05 M glicin – HCl pufer, pH 2,2 dekstran čarkoal

Inkubacija 1^h na 4^oC, centrifugiranje 20 min. na 4^oC

0,2 ml supernatanta
+
0,7 ml 0,06 M barbital pufera, pH 8,6. sa 8-ANSA
+

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0,1 ml ^{125} J–T3 ili ^{125}J–T4, inkubacija 20^{h} na 4°C
+

Taloženje humanim antiserumom (finalna koncentracija 10 mg/ml)
Centrifugiranje 20 min. na 4°C.

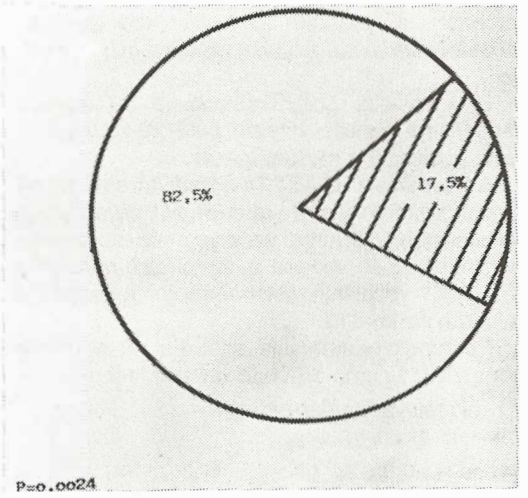
Mjerenje aktivnosti taloga u gama brojaču.

Rezultati se izračunavaju u procentima specifičnog vezivanja. Ukoliko je više od 50% aktivnosti vezano u istaloženom dijelu rezultat je pozitivan.

Detekcija autoantitijela vršena je i elektroforezom. Postupak je identičan prethodnom ali se umjesto taloženja vrši elektroforeza na celuloznom acetatu. Trake od elektroforeze se sijeku na pojedine frakcije i vrši se mjerenje radioaktivnosti pojedinih frakcija.

Prisustvo više od 50% aktivnosti u gama frakciji upućuje na prisustvo autoantitijela na hormone T3 ili T4 (7). U statističkoj obradi podataka korišten je χ^2 – test i Fišerov test (8).

Rezultati – Od 40 bolesnika sa hipertireozom koji su ispitani prije uvođenja tireostatske terapije, autoantitijela na T3 ili T4 našli smo u 7 bolesnika ili 17,5%. 6 bolesnika su imali autoantitijela na T3 a 3 bolesnika istovremeno i na T3 i T4 a 1 bolesnik samo na T4 (Slika 1).

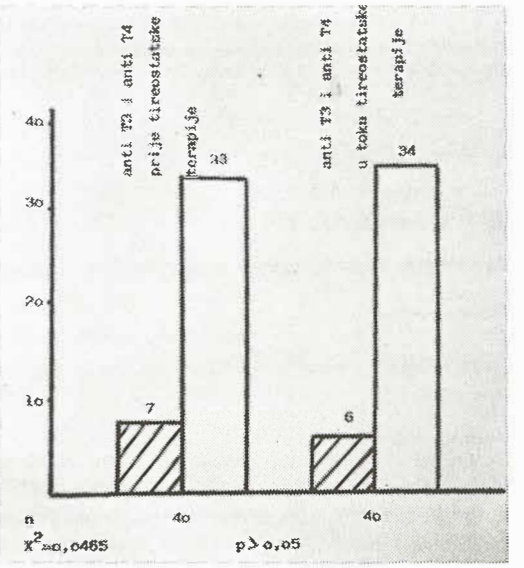


Slika 1 – Grafički prikaz rezultata autoantitijela na trijodtironin i tiroksin u bolesnika sa hipertireozom. Šrafirano polje pokazuje bolesnike sa pozitivnim antitijelima.

Fig. 1 – Graph showing the results of autoantibodies against triiodothyronine and thyroxine in patients with hyperthyreosis; cross–hatched bars represent the patients with positive antibodies.

U kontrolnoj grupi je ispitano 50 osoba bez oboljenja štitne žlijezde i kod njih nisu nađena autoantitijela na T3 ili T4. Statistički postoji značajna razlika između kontrolne grupe i grupe bolesnika sa hipertireozom.

U ispitivanjima urađenim u toku tireostatske terapije autoantitijela na T3 ili T4 su dokazana u 6 bolesnika ili 15%. Statistički ne postoji razlika u odnosu na ispitivanje prije tireostatske terapije (Slika 2)



Slika 2 – Grafički prikaz rezultata autoantitijela na trijodtironin i tiroksin u bolesnika sa hipertireozom prije i u toku terapije

Fig. 2 – Graph showing the results of autoantibodies against triiodothironine and thyroxine in patients with hyperthyreosis prior to and in the course of thyreostatic therapy. Cross–hatched bars represent the patients with positive antibodies.

Diskusija – U autoimunim oboljenjima štitne žlijezde javlja se više autoantitijela čija međusobna povezanost i uloga često ostaje nerasvijetljena. Autoantitijela na hormon T4 je prvi opisao Robins (5). Zbog male molekularne težine T3 i T4 ne mogu djelovati antigeno već su vjerojatno vezana za tireoglobulin koji je jako imunogena supstanca (9). Uloga ovih antitijela je nejasna. Wu i Green tvrde da antitijela na T3 i T4 usporavaju metaboličke efekte ovih hormona, Geola smatra da nemaju ulogu u metaboličkim funkcijama a Inada da autoantitijela na T3 i T4 pospješuju metaboličke efekte ovih hormona (5).

Oprečni rezultati su dobiveni kod bolesnika sa hipertireozom. Nakamura (4) nalazi više od 20% bolesnika sa hipertireozom kod kojih su pozitivna antitijela na T3 i T4 a Desai (3) nalazi manje od 1%. Nakamura nalazi da u toku tireostatske terapije dolazi do smanjenja broja bolesnika sa pozitivnim autoantitijelima na T3 i T4.

U našim ispitivanjima našli smo u bolesnika sa hipertireozom 17,5% koji imaju pozitivna autoantitijela na T3 ili T4. Češće se javljaju autoantitijela na T3. Kod zdravih osoba nismo našli prisustvo antitijela na hormone T3 ili T4. U toku tireostatske terapije nije se bitnije mijenjao broj bolesnika sa autoantitijelima na T3 ili T4.

Sažetak

Uloga autoantitijela na hormone trijodtironin (T3) i tiroksin (T4) u oboljenjima štitne žlijezde još nije razjašnjena. Ranije objavljivani rezultati o prisutnosti ovih autoantitijela u bolesnika sa hipertireozom su veoma oprečni.

Ispitali smo autoantitijela na T3 i T4 u 40 bolesnika sa hipertireozom. Pozitivna autoantitijela na T3 ili T4 našli smo kod 17,5% bolesnika. Statistički postoji značajna razlika u odnosu na kontrolnu grupu. U kontrolnoj grupi smo ispitali 50 zdravih osoba i nismo našli prisutna ova antitijela.

Ova antitijela smo odredili i u toku tireostatske terapije i našli smo ih pozitivna u 15% bolesnika što statistički nije značajna razlika u odnosu na stanje prije terapije.

Uloga autoantitijela na hormone T3 i T4 u hipertireozi je nepoznata. U toku tireostatske terapije ne mijenja se broj bolesnika kod kojih su prisutna ova autoantitijela.

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EUROPEAN SCHOOL OF ONCOLOGY
The Institute of Oncology and the Faculty of Medicine
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Preliminary Announcement

2nd Rare Tumor Symposium

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For more detailed information please contact:

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THE INSTITUTE OF ONCOLOGY, LJUBLJANA[1]
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TREATMENT OF PARANASAL SINUS MALIGNANCIES AT THE INSTITUTE OF ONCOLOGY IN LJUBLJANA BETWEEN 1979 AND 1984

Budihna M[1], Šmid L[2], Zakotnik B[1]

Abstract – Between 1979 and 1984, 50 patients with malignant tumours of the paranasal sinuses were treated at the Institute of Oncology in Ljubljana. A great majority of tumours were in an advanced stagew of disease. Twenty three patients were operated on and 22 of them had postoperative irradiation. Radiotherapy was the main treatment in 27 patients. Seventeen patients (34%) survived more than 5 years with no evidence of disease. Patients with carcinoma treated by the combination of surgery and postoperative radioatherapy survived significantly better (12/20-60%) than those treated by irradiation as the main treatment (2/25-8%) $p<0.001$.

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Key words: paranasal sinus neoplasms–therapy

Orig sci paper

Radiol Iugosl 1991; 25:137-41.

Introduction – Cancer of the paranasal sinuses is a rare disease. The symptoms are unspecific and are readily mistaken by both, the patient and the primary care physician for upper respiratory infections. Therefore, they are diagnosed late and more often than not are uncontrolled by current methods of treatment.

The aim of this study was to evaluate the treatment of paranasal sinus malignant tumours in Slovenia between 1979 and 1984, and possibily, to find some prognostic factors.

Patients and treatment – In the period 1979 to 1984, at the Institute of Oncology, Ljubljana, 50 patients (25 females and 25 males), aged 40-90 years, were treated for malignant tumours of the paranasal sinuses. Table 1 shows the distribution of tumours by localization and histology.

A majority of tumours were in an advanced stage of disease. The UICC TNM classification (1987) was applicable only for maxillary sinus carcinoma (Table 2).

Four maxillary and one ethmoid carcinoma seeded into regional lymph nodes and so did one malignant lymphoma originating from the ethmoid. One squamous cell carcinoma and one adenocarcinoma metastasized into the bones and lungs, respectively.

Table 1 – The localization and histology of malignant tumours of the paranasal sinuses

Histology	Maxillary	Sinus Ethmoid	Sphenoid	Total
Squamous carcinoma	33	6	1	40
Adeno carcinoma	1	1		2
Adenoid cystic carcinoma	3	1		4
Malignant lymphoma	2	1		3
Fibrosarcoma		1		1
TOTAL	39	10	1	50

Twenty–three patients were primarily operated on, 22 of them were postoperatively irradiated. Twenty–seven patients had irradiation therapy alone because the tumour was inoperable or because the patient's condition was poor.

Partial or total maxillectomy with or without ethmoidectomy was used for tumour removal.

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Table 2 – The distribution of maxillary sinus carcinoma by T (tumour) and N (node)

	N_0	N_1	N_2	N_3	Total
T_1			1		1
T_2	3				3
T_3	10		1		11
T_4	20	2			22
TOTAL	33	2	2		37

Minor operations could not be considered as therapeutic, but rather as dignostic procedures.

The operations were performed at various hospitals throughout Slovenia, but most of them at the University ENT Department in Ljubljana.

All patients were irradiated on a Cobalt–60 unit at the Institute of oncology in Ljubljana. The irradiated volume encompassed the primary tumour and the clinically involved lymph nodes. Patients were treated 5 times weekly, with 1.8 - 2 Gy per fraction, total tumour dose being 60 – 78 Gy when the irradiation was the sole method of treatment. When irradiated postoperatively without residual tumour, 40-60 Gy were given, and up to 72 Gy in the case of residual growth. Some of the patients were treated by split–course irradiation with the rest interval 2-4 weeks.

The cytotoxic drugs applied intravenously were used in 11 patients. In 4 patients the chemotherapy was part of the primary treatment (2 carcinomas and 2 malignant lymphomas), in 7 patients it was used with palliative intent. The cytotoxic drugs Methotrexate, Cyclophosphamide, Platinol, 5-Fluorouracil, Adriamycin, Bleomycin, Vinblastin, and Vincristine were used in various combinations.

S t a t i s t i c a l m e t h o d s – All patients were eligible for a minimum of 5-year follow-up. The survival of patients was calculated from the beginning of treatment. Cumulative survival rates were calculated according to the product–limit method of Kaplan and Meier (1958). Logrank test (Peto et al. 1977) was used for testing the significance in survival difference.

Results – Seventeen out of 50 (34%) patients survived more than 5 years with no evidence of disease (Fig. 1). Two patients died with distant metastases, 5 with local and regional disease and 26 with local disease only.

Five–year survival of patients by localization and tumour histology is shown in Table 3. The differences in survival were non statistically significant.

Table 3 – The 5–year survival by localization and histology

Histology	Sinus Maxillary	Ethmoid	Sphenoid	Total
Squamous carcinoma	9/33	2/6	0/1	11/40
Adeno carcinoma	0/1	1/1	–	1/2
Adenoid cystic carcinoma	1/3	1/1	–	2/4
Malignant lymphoma	2/2	0/1	–	2/3
Fibrosarcoma	–	1/1	–	1/1
TOTAL	12/39 (31%)	5/10 (50%)	0/1 (–)	17/50 (34%)

Females surived better (10/25 – 40%) than males (7/25 – 28%). The difference was not statistically significant.

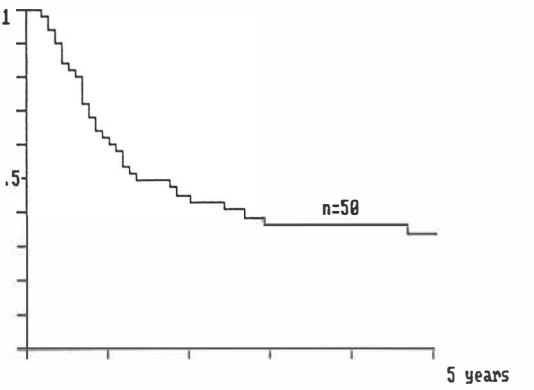

Fig. 1 – Tumours of the paranasal sinuses; 5–year disease free survival of all patients. n = number of patients.

The survival of patients with squamous cell carcinoma aged under 55 years (0/6) was significantly worse than survival of older patients (12/34-35%) ($p<0.05$).

Patients with T_1 and T_2 tumours survived better (4/4) than patients with T_3 (1/11 – 9%) and T_4 tumours (5/22 – 23%), the difference was not statistically significant (Fig. 2).

Patients with carcinoma of the paranasal sinuses with metastases to the regional lymph nodes survived worse (1/5 – 20%) than those without metastases (13/41 – 32%), but he number of patients was too small for statistical significance.

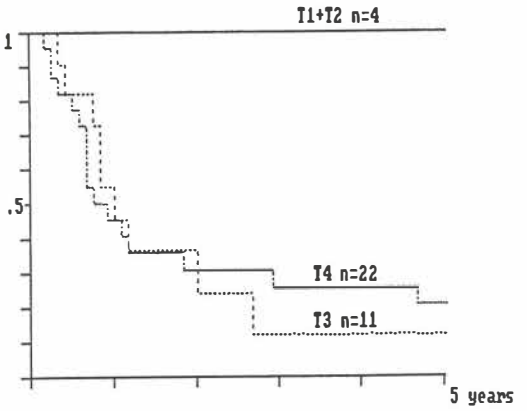

Fig. 2 – Carcinoma of the maxillary sinus. Survival by stage of the primary tumour. T = tumour, n = number of patients

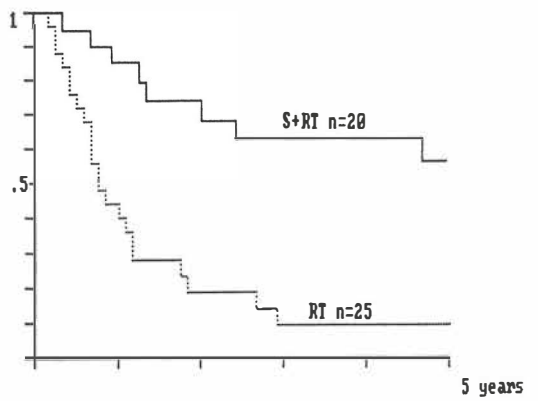

Fig. 3 – Carcinoma of the paranasal sinuses. Survival by main treatment. S = surgery, RT = radiotherapy, n = number of patients.

A better 5–years survival was established in patients with carcinoma treated by a combination of surgery and postoperative radiotherapy (12/20 – 60%) than in patients treated by irradiation alone (2/25 – 8%) (Fig. 3). The difference was statistically significant ($p<0.001$). There was also statistically significant difference in survival between postoperatively irradiated (5/10 – 50%) and only irradiated patients (2/22 – 9%) with T_3 & T_4 tumours ($p<0.025$). (Fig. 3)

The only patient who was operated but did non have postoperative irradiation treatment died with disease.

All patients with total tumour removal survived more than 5 years with no evidence of disease (6/6 – 100%). The rest of the operated patients

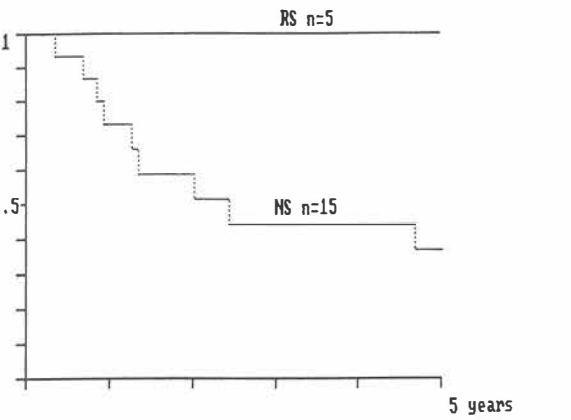

Fig. 4 – Carcinoma of the paranasal sinuses. Survival by radicality of surgery. RS = radical surgery, NS = nonradical surgery, n = number of patients

survived significantly worse (6/15 – 40%), ($p<0.05$) (Fig. 4).

None of 3 nonradically operated patients irradiated postoperatively with less than 50 Gy survived 5 years whereas 6/12 (50%) nonradically operated patients irradiated with a tumour dose >50 Gy survived more than 5 years.

The spread of squamous cell carcinoma of the paranasal sinuses into one of the adjacent regions such as neighbouring sinus, the orbit, oral cavity, retromaxillary space, subcutaneous tissue or intracranially adversely influenced the outcome of treatment in the operated patients. The difference was statistically not significant.

Two patients, one with malignant lymphoma and one with squamous cell carcinoma, in whom chemotherapy was part of the curative treatment, survived 5 years with no evidence of disease. Two patients with chemotherapy as part of the curative treatment and 7 patients with chemotherapy given for treatment of recurrent disease died of cancer.

Discussion – The frequency of occurrence of malignancies of the paranasal sinuses with respect to the site, histology and stage was in our patients similar to that reported by other authors (Moss, 1987; Thiel et al. 1989).

A great majority of patients with carcinoma of the paranasal sinuses who were not cured died with local disease (31/33). This is in agreement with some other reports (Thiel 1989) and it shows the significance that the local treatment has for the patient.

It is almost generally accepted that in carcinoma of the paranasal sinuses the combined

modality treatment is superior to the single modality therapy (Yu–Hua et al. 1982, Weymuller et al. 1980, Tsujii et al. 1986, Thiel and Rettinger 1986). This was confirmed also by our results: patients treated by a combination of surgery and radiotherapy survived significantly better than those treated only by irradiation ($p<0.001$). Statistically significant difference between the results of combined and single modality treatment of maxillary sinus carcinoma in our patients persisted also when early stages were excluded ($p<0.025$).

However, the radicality of operation seems to be important: all 6 radically operated patients were cured, whereas only 6/9 nonradically operated patients survived more than 5 years. The difference was statistically significant ($p<0.05$) (Fig. 3).

The spread of carcinoma beyond the primarily involved sinus was associated with somewhat worse outcome. Among various adjacent regions which were involved by the tumour, the involvement of the retromaxillary space had the worst impact on prognosis (only 1/4 patients with the involvement of the retromaxillary space in comparison to 11/16 patients without retromaxillary involvement survived 5 years with no evidence of disease).

From our series of patients, it was impossible to evaluate the influence of irradiation dose in carcinoma of the paranasal sinuses in patients treated by radiotherapy alone because of the poor survival in this group: only 2 out of 25 patients were cured. But in the group of postoperatively irradiated patients who were not radically operated on all 3 patients irradiated with the tumour dose less then 50 Gy died, and 6/12 irradiated with the tumour dose above 50 Gy were cured. This would indicate, though not with certainty, that the tumour dose could be of importance. This is in agreement with Kondo et al. (1984, 1985), who found less recurrences with the increasing tumour dose.

The survival of patients with early tumours was much better than the survival of patients with tumours in advanced stages, which was in accordance with other reports (Kondo 1985, Thiel 1989), but the number of patients with early tumours was so small that the statistical significance could bot be confirmed.

The small number of patients, heterogeneity of tumour histology and diversity of applied cytotoxic drugs do not permit any conclusions about the value of chemotherapy with cytotoxic drugs in our patients.

It is surprising that patients under 55 years of age survived worse than older patients. The explanation for this phenomenon remains obscure.

Conclusions – The combination of surgery and radiotherapy in the treatment of carcinoma of the paranasal sinuses is superior to radiotherapy alone.

Tumour stage and radicality of operation seem to be important for the outcome of treatment in the patients with paranasal sinus carcinoma.

Povzetek

Med leti 1979 in 1984 je bilo na Onkološkem institutu v Ljubljani zdravljenih 50 bolnikov z malignimi tumorji obnosnih votlin. Velika večina tumorjev je bila v napredovalem stadiju bolezni. Triindvajset bolnikov je bilo operiranih, 22 izmed njih je bilo pooperativno obsevanih. Pri ostalih 27 bolnikih je bilo glavno zdravljenje obsevanje. Sedemnajst bolnikov (34%) je preživelo vec kot 5 let brez bolezni. Bolniki s karcinomom ki so bili operirani in pooperativno obsevani so preživeli bistveno bolje (12/20 – 60%) od bolnikov, ki so bili zdravljeni samo z obsevanjem (2/25 – 8%), p ☎ 0.001).

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TISSUE ABSORBED DOSE RATE FROM IRIDIUM-192 LINE SOURCE

Lokner V

Abstract – A simple model of tissue absorbed dose rate from iridium-192 line source is formulated. Model incorporates corrections for radiation losses as a result selfabsorption, attenuation in source cladding as well as absorption in the tissue. The form of corrections is analyzed. The model is used for calculation of tissue absorbed dose rate for different source lengths (20-150 mm) and a set of distance (up to 75 mm) in central plane of wire source. The calculated absorbed dose rates are in good agreement with previously published results. Theoretical error of our values is of the order of ±6%. Calibration measurement of air kerma rate for 1 cm source sample is used for the normalization of tabulated data to a given set of sources or a wire coil. Uncertainty associated with dosimetric description of clinically set iridium-192 interstitial implant is of the order of ±15%. Normalized absorbed dose rates are intended for use as computer look–up table with Paris dosimetry system.

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Key words: brachytherapy; radiation dosage; iridium radioisotopes

Orig sci paper

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Introduction – Dosimetry of the interstitial brachytherapy implants is generally based on a model of relations between quantity of the used radioactive material and the absorbed dose. Relating the source and the energy delivered to the tissue is rather complicated; apart from the physical properties of radionuclide and radiation in vacuum, the dosimetry model must include description of the path of radiation through different media. One of the ways of model formulation is refining crude implant description (inverse square law model) with the introduction of correction factors and/or effective values of some parameters to reflect the attenuation losses (1).

In the process of model building two problems are pronounced: (a) model verification by measurements is limited; (b) practical use of model strongly depends on the published values of parameters or calibration of sources. As a consequnce, there is no unique way of implant description used in the clinical control of radiotherapy.

There are differences in the way of calculation of tissue absorbed dose for a line iridium-192 source. Traditionally used crossline data (2) and escargot curves (3) were enhanced by the introduction of corrections for radiation losses (4, 5, 6, 7). Disparity is still – 10%, mostly due to the differences in the definition of the effective strength for the sealed source.

This work describes a simple model of dose distribution which is formulated according to the method described by Godden (8). In the explicit form the model uses the value of air kerma rate calibration.

Material and model – Source : We analyze standard iridium-192 source in the form of flexible wire with diameter d = 0.3 mm. The wire is obtained in the form of 500 mm long coils. Prior to use, wire is filled in the plastic tube (outer diameter 0.85 mm) and cut in pieces (linear sources) of suitable length from 20 to 150 mm. The source consists of two parts. Active core (diameter 0.1 mm) is alloy consisting of 25% iridium and 75% platinum. The core is surrounded by 0.1 mm thick cladding which filters beta component of radiation. Iridium-192 sources are cyclotron activated, with high specific activity from 1.11-37 $MBqmm^{-1}$.

Dosimetric model : We start from elementary description of an ideal point source in the vacuum, in order to introduce symbols and units:

$$A\Gamma_6 = \dot{K}_{air}(r)\, r^2 \qquad [1]$$

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r [m] is the distance from the source to a point in space which is surrounded by a very small volume filled with air; energy transfer within small volume of air is described by the air kerma rate $\dot{K}_{air}(r)$ [Gy/h]; A [Bq] is activity of the point source; Γ_6 [$Gyh^{-1}m^2Bq^{-1}$] is the air kerma rate constant for all gamma radiation up to energy δ. It should be stressed that eq.[1] holds only if three conditions are met simultaneously: (a) transfer of energy is limited to a very small volume of air where equilibrium ionization holds; (b) radiation originates strictly from the point source; (c) the space between source and observed small volume of air is vacuous. Description of real iridium-192 source, which is linear and surrounded by the tissues, could be based on eq.[1], but it must reflect the differences from all three conditions. Improvements of eq.[1] will be introduced through (a) concept of tissue absorbed dose, (b) segmentation of the source and (c) introduction of correction parameters to account for the attenuation losses.

Tissue absorbed dose D_{tissue} is traditionally used for the control of brachyradiotherapy effects; instead of air, radiation ionizes equally sized volume of the tissue. If ionization equilibria holds, with bremsstrahlung losses so small that they could be disregarded, $\dot{D}_{tissue}$ is directly proportional to $\dot{K}_{air}(r)$, with k_1 as constant of proportion $\dot{D}_{tissue}$ is tissue absorbed dose rate.

We will approximate the value of $\dot{D}_{tissue}$ in a point of implant from the linear source of the length L [mm] and activity A [Bq] (linear activity ϱ = A/L [$Bqmm^{-1}$]), with the sum of absorbed doses coming from N equally spaced point sources that are placed in the centers of segments of lenght l [mm] (L = N x l). Generally, $\dot{D}_{tissue}$ for the line source could be represented by Sievert integral, but in that case we must regard the source as having one dimension only (d = 0). Nonuniform radial structure of wire prohibits such a simplification. Description of point dependent attenuation losses in the core as well as in the cladding will be numerically more simple in a case of source segmentation than utilizing direct Sievert analytical approach.

We will describe the loss of radiation due to the self-absorption in the core and attenuation in the cladding by the introduction of correction factor $k_2(\theta)$ in eq.[1]. Attenuation and scattering of radiation in a tissue are accounted for by the introduction of $k_3(r,\theta)$. Both factors are angle θ dependent whereas attenuation in medium additionally depends on the distance r (Fig. 1 A).

Respecting all the differences, corrected model will be:

$$\dot{D}_{tissue} = k_1 \varrho l \Gamma_6 \sum_{i=1}^{N} \frac{k_2(\theta_i)}{r_i^2} k_3(r_i,\theta_i) \qquad [2]$$

where i (i = 1, N) denotes i-th segment. The explicit structure of this model will depend on the form of correction factors. Before choosing them, we should point out some problems concerning values of ϱ and Γ_6 constants ϱ is nominal linear activity. Since all iridium-192 wire sources are cyclotron activated, their actual linear activities could significantly differ ($\pm$10%) from nominal values, for each of the activated sources. Like wise, published data for iridium-192 Γ_6 constant show 15–20% difference, mainly because of the conceptual disagreement (definitions of filtered/nonfiltered sources) (1,5,8). The influence of ϱ and Γ_6 uncertainties on the value of $\dot{D}_{tissue}$ could be minimized with source calibration.

Standard calibration of sealed brachytherapy sources is performed in the defined geometry. Measurement is done 1 m from the source, in radial plain of the source. For wire sources measurement is done on 1 cm long samples. We will describe calibration by the same model we use for dosimetry. Radiation coming from a 1 cm sample, placed 1 m from the detector, could be considered as coming from the point source:

$$\dot{K}^c_{air} = \varrho_R L \Gamma_6 \frac{k_4}{r_K^2} k_5(r_K) \qquad [3]$$

$\dot{K}^c$ [μGyh^{-1}] is calibration air kerma rate; ϱ_R [$Bqmm^{-1}$]
is real linear activity; L [mm] is active length of the sample; r_K [m] is distance from the source to the measuring device. The losses in the sample are described by the attenuation factor K_4 (which is free of θ because of a very big r_K), and those in the air that fill the space between the sample and the measuring device with $k_5(r_K)$ (Fig. 1 B). After substitution:

$$\dot{D}_{tissue} = k_1 \dot{K}^c_{air} \frac{l}{L} \sum_{i=1}^{N} \frac{r_K^2}{r_i^2} \frac{k_2(\theta_i)}{k_4} \frac{k_3(r_i,\theta_i)}{k_5(r_K)} \qquad [4]$$

Eq. [4] assumes knowledge of the calibration system geometry. If the calibration could not be done directly, the values supplied by the manufacturer (source certificate) should be used.

Results – Assuming ionization equlibria and very small bremsstrahlung energy losses, k_1 is nearly equal to the ratio of the tissue mass absorption coefficient to the corresponding one

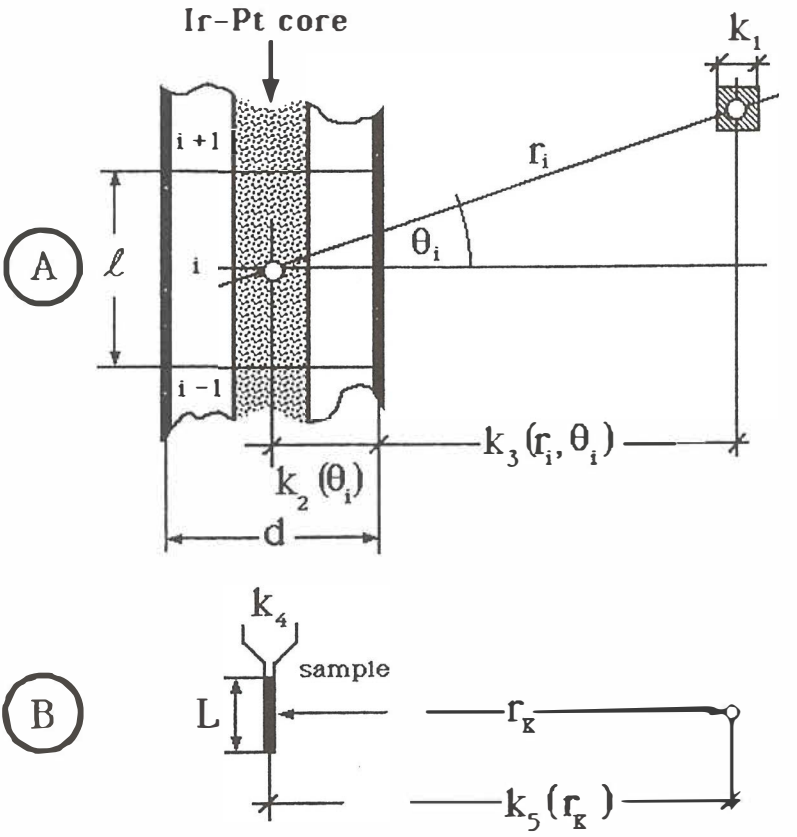

Fig. 1A – Small segment of iridium-192 line source (length l and diametere d) approximately radiates as point source. Absorbed dose rate in a point of interstitial implant is derived from crude model applying three correction factors: k_1 describing the relation between air and tissue kerma rates in small volume in close proximity of observed point; $k_2(\theta_i)$ correcting for radiation losses due to selfabsorption in Ir-Pt wire core and attenuation in the Pt cladding; $k_3(r_{i,\theta i})$ associated with absorption of radiation in the tissue.

Fig. 1B – Calibration measurement of the air kerma rate for a source sampole (length **L**) is described with the same model we use for description of line source radiation distribution. Two correction factors are introduced to describe losses: k_4, attenuation in the wire; $k_5(r_K)$ attenuation in the air.

in the air. k_1 is approximately constant from 200–2000 keV (9) and is independent of the type of absorption medium for ~ 370 keV gamma-photons; for the water $K_{1W} = 1.11$, and for muscular tissue, $k_{1M} = 1.10$ (8,10). Rounded value of $k_1 \approx 1.1$, describes acceptably all iridium-192 interstitial implants.

$k_2(\theta)$ and k_4 were introduced into the model to balance core selfabsorption losses and platinum cladding attenuation of radiation. Selfabsorption could be neglected altogether since it was established that for 1 mm of Ir-Pt absorption material it is only 0.5% (11). Attenuation is described with the standard exponential form. Since dimensions of implant and calibration setting are different ($r_K \gg r_i$), θ dependence of k_4 could be disregarded, therefore:

$$\frac{k_2(\theta_i)}{k_4} = e^{-\frac{\mu d}{2\cos\theta_i} + \frac{\mu d}{2}} \qquad [5]$$

μ is linear absorption coefficient and d is thickness. Eq. [5] is strictly met only for single point in the center of the i-th segment. Some effective values μ_{ef} and d_{ef} could be introduced if all radiation coming from different points of l is to be taken into account. If $r_i \gg l$, then $d_{ef} \approx d$. Different values are published for μ_{ef} [0.43 mm^{-1}

(2,6,12), 0.445 mm^{-1} (13) and 0.5 mm^{-1} (7)]. $\mu_{ef} \approx 0.45$ mm^{-1} suffices practical needs. Rounding error introduced into the model is < 0.5%.

For convenience, source calibrations are done in the air. It was shown that for iridium-192 source, $k_5[r_K] < 1.01$ (13). Taking $k_5[r_K] \approx 1$ in the model, introduces error < 1%.

If the implant is set in such a way that sources are fixed inside metal guides used for implementation, k_3 could be separated:

$$k_3(r_i,\theta_i) = k_{3t}(r_i)\, k_3{}^g(\theta_i) \qquad [6]$$

$k_3{}^t(r_i)$ describes absorption in the tissue; $k_3{}^g(\theta_i)$ compensates absorption in the metal guide. $k_3{}^t(r_i)$ is approximated with the second order polynomial having measured (14) or Monte Carlo simulation study determined coefficients (15). We use:

$$k_3(r_i) = 0.9834 + 1.754 \times 10^{-3} r_i - 2.205 \times 10^{-5} r_i{}^2 \qquad [7]$$

$k_3{}^3(\theta_i)$ is having standard exponential structure with $\mu = 0.54$ cm^{-1} for ~ 370 kwV energy.

The plane perpendicular to long axes of sources, dividing the sources by half, is named central plane (CP). Using explicit form of the model, absorption dose rates in tissue was calculated for the CP of single line source (Table 1). Values are tabulated for different source lengths (20–150 mm) and (nearly exponential) set of distances from the source (1–75 mm). Radiation of the source on the distance > 75 mm could be disregarded. Values of $\dot{D}_{tissue}$ are calculated with $l = 1$ mm and for niminal $\dot{K}^c_{air} = 0.754$ μGyh^{-1} corresponding to 1 m measurement of ideal source with the linear activity of 6.66 $MBqmm^{-1}$. Calculated values do not take into account absorption in metallic guides ($k_3(r_i,\theta_i) \equiv k_3{}^t(r_i)$). Absorption in standard steel metallic guides is not substantial; it is pronounced only for short sources (up to 40 mm) and small distances from the source (for 3 mm distance, dose rate in CP is ~ 1.5% lower). For $r_i > 10$ mm the influence of the metallic guide absorption could be disregarded (< 1%).

Two dosimetric schemes are used for numerical control of iridium-192 implants: Paterson–Parker and Paris system. The last one, formulated exclusively for iridium-192, relates implant geometry with absorbed dose through special rules on spatial distribution of line sources [16]. In Paris system ideal planar implants are formed from straight and parallel sources of the same linear activity, equally distant from nearest neighbors. Volume implants are formed as stacks of planar implants. Table 1. is generated to be used as computer look-up table for fast calculation of Paris implant dosimetry. The density of points is sufficient for simple linear interpolation.

The tables could equally be used for singlepin as well as hairpin sources, when effective length of sources should be taken.

Discussion – Two decimal places used for the tabulated values of $\dot{D}_{tissue}$ are utilized to show how slowly over the observed range the absorbed dose rate changes. Actual accuracy is considerably lower. Main reasons for that are: inherent weakness of the corrections introduced in basis model as well as approximate values for the **k**

Table 1 – The values of $\dot{D}_{tissue}$ [Gyh^{-1}] were calculated for the line source with nominal linear activity of 6.66 $GBqmm^{-1}$ (180 $\mu Cimm^{-1}$). For given linear source, tabulated values should be normalized (multiplied by $f = \dot{K}^c_{air} / 0.754$). If independent calibration of source is not possible, $\dot{K}^c_{air}$ [μGyh^{-1}] from suppliers declaration could be used. Short half-life of iridium-192 requires adequate corrections.

source length [mm]	Central plane distance [mm]																
	1	2	3	4	5	6	7	9	12	15	19	24	30	37	47	59	75
20	2.25	1.08	0.68	0.48	0.36	0.28	0.22	0.15	0.10	0.07	0.04	0.03	0.02	0.01	0.01	0.01	0.00
24	2.26	1.10	0.70	0.50	0.38	0.30	0.24	0.17	0.11	0.08	0.05	0.03	0.02	0.01	0.01	0.01	0.00
28	2.27	1.11	0.71	0.51	0.39	0.31	0.26	0.18	0.12	0.08	0.06	0.04	0.02	0.02	0.01	0.01	0.00
32	2.28	1.12	0.73	0.53	0.41	0.33	0.27	0.19	0.13	0.09	0.06	0.04	0.03	0.02	0.01	0.01	0.01
36	2.28	1.13	0.73	0.54	0.41	0.33	0.28	0.20	0.13	0.10	0.07	0.05	0.03	0.02	0.01	0.01	0.01
42	2.28	1.13	0.74	0.54	0.43	0.34	0.29	0.21	0.14	0.11	0.07	0.05	0.03	0.02	0.02	0.01	0.01
48	2.29	1.14	0.75	0.55	0.43	0.35	0.30	0.22	0.15	0.11	0.08	0.06	0.04	0.03	0.02	0.01	0.01
50	2.29	1.14	0.75	0.56	0.44	0.36	0.30	0.23	0.16	0.12	0.09	0.06	0.04	0.03	0.02	0.01	0.01
60	2.29	1.15	0.76	0.56	0.44	0.37	0.31	0.23	0.16	0.12	0.09	0.06	0.05	0.03	0.02	0.01	0.01
70	2.29	1.15	0.76	0.57	0.45	0.37	0.31	0.24	0.17	0.13	0.10	0.07	0.05	0.04	0.02	0.02	0.01
90	2.29	1.15	0.77	0.57	0.45	0.38	0.32	0.24	0.18	0.14	0.10	0.08	0.06	0.05	0.03	0.02	0.02
120	2.29	1.15	0.77	0.58	0.46	0.38	0.33	0.25	0.18	0.14	0.11	0.08	0.06	0.05	0.03	0.02	0.02
150	2.29	1.15	0.77	0.58	0.46	0.38	0.33	0.25	0.19	0.15	0.11	0.09	0.07	0.05	0.04	0.03	0.02

parameters. It could be estimated through model evaluation that uncertainty associated with the tabulated values of $\dot{D}_{tissue}$ is approximately ± 6% (1). This could be considered as the theoretical error of dosimetry since nominal value of air kerma rate $\dot{K}_{air}$ is assumed in calculations.

Normalization of table 1 to a specific source with measured $\dot{K}^{c}_{air}$ appends considerable practical error to dosimetry. Since $\dot{K}^{c}_{air}$ is established with at least ± 5%, overall uncertainty of $\dot{D}_{tissue}$ is not better than ± 11%. Some additional practical errors could even 'worsen the expected uncertainty. Since iridium-192 wire sources are produced by cyclotron activation, contents of the core could vary significantly (±4–5%) along the single 500 mm coil (17). Therefore, the supplier guaranties only that activity measured with 1 mm window along the source length will not be changing for more than ±5%. Multiple use (bending) of wire thins platinum cladding. Possible local inhomogeneity due to the increase of beta radiation is to be assumed. As a result $\dot{D}_{tissue}$ derived from the tabulated values could not be better than ±15%.

If the implant is complex, consisting of several line sources set in intricate pattern, the uncertainty margins for evaluated dose rate are even wider.

Direct comparison between our results and **cross-line** or **escargot** curves is not possible due to the insufficient normalization data. Values in table 1 are in good agreement with those described by Dutreix et al. (13) showing only 2–3% difference on average. Somewhat bigger disagreement is observed when table 1 is compared with the values obtained by Kline et al. (5). Typical 3–6% difference depends on the source length and the distance from the source.

Relatively small deviation indicates consistent modelling which could not be considerably improved. It should be stressed that clinical utilization of any model of tissue absorbed dose rate from iridium-192 line source strongly depends on practical errors. Therefore, numbers derived from tabulated values of $\dot{D}_{tissue}$ should be understood only as an acceptable estimate of achieved absorbed dose rate.

Sažetak

APSORBIRANA DOZA U TKIVU OKO RAVNOG IRIDIJ-192 IZVORA

Formuliran je jednostavan model brzine apsorbirane doze u tkivu oko ravnog iridij-192 izvora. Model sadrži korekcije zbog gubitka u zračenju zbog samoapsorpcije, atenuacije u ovojnici žice kao i apsorpcije u tkivu. Analizirani su oblici korekcija. Model se koristi za izračunavanje vrijednosti apsorbirane doze za različite duljine izvora (20–150 mm) i skup udaljenosti (do 75 mm) u centralnoj ravnini žičanog izvora. Izračunate brzine apsorbirane doze dobro se slažu sa prije objavljenim rezultatima. Teorijska pogreška naših vrijednosti je reda ±6%. Kalibracijsko mjerenje brzine kerme u zraku za 1 cm dugački uzorak izvora koristi se za normalizaciju podataka za dani skup izvora ili namotaj žice. Netočnost pridružena dozimetrijskom opisu kliničke postave iridij-192 intersticijskog implantata je reda ±15%. Normalizirane brzine apsorbirane doze namjenjene su računarskoj upotrebi gdje se kao *look-up* table koriste u Pariškom dozimetrijskom sustavu.

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FROM PRACTICE FOR PRACTICE

Case 2

Answer: This is a superior vena cavogram which shows that there is no opacification of the superior vena cava. Contrast medium opacifies both distal subclavian veins which drain into dilated collateral veins around the base of the neck and chest wall. There is opacification of the azygos and hemi-azygos veins. The diagnosis is superior vena cava occlusion, which is probably chronic in view of the well developed collateral veins shown on this image.

This investigation is performed by inserting venous cannulae into veins in both arms, preferably a large antecubital vein, and injecting non-ionic contrast medium through both cannulae simultaneously. This allows demonstration of the proximal occlusions on both sides of the chest on the same film.

There are many causes of superior vena cava occlusion, a majority producing thrombosis. These include mediastinal malignancy, radiotherapy, mediastinal sepsis, fibrosing mediastinitis, peripheral or central administration of irritant infusion fluids or cytotoxic drugs, and central venous foreign bodies (such as pacing wires, and central venous canulae).

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ADAPTIVE RESPONSE OF MAMMALIAN CELLS TO IONIZING RADIATION

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Abstract – Human lymphocytes and Chinese hamster cells pretreated with low dose of ionizing radiation either from incorporated ^{3}H-thymidine or x- or gamma rays become less susceptible to the clastogenic effects of a subsequent higher dose. This phenomenon has been termed adaptive response to ionizing radiation. The possibility that adaptation effect involves different cell stage sensitivity to radiation or selective killing of a radiosensitive subpopulation was rejected through the experimental data. The cell preirradiation with low doses induces several proteins (not seen in control cells) which are potential candidates for adaptive response. Poly (ADP-ribose) polymerase seems to be one of them. Several factors may influence the adaptive response: the total adapting dose, the rate at which this dose is given, the phase of the cell-cycle in which the cells are preirradiated, the time interval between adapting and challenge dose, and the variability of the human population in the adaptive response to ionizing radiation. The cells adapted with low doses of x- or gamma rays or low concentrations of ^{3}H-thymidine displayed a cross resistance to mitomycin C, bleomycin and near ultraviolet light, but not to methyl methane sulphonate, ethyl methane sulphonate or cis-dichlorodiammineplatinum (II). In conclusion, adaptive response to ionizing radiation is one of the repair systems that can be induced by DNA damage, like SOS-response, adaptive response to alkylating agents induced domage, the inducible system for reparing oxidizing damage and, perhaps, the heat-shock regulatory network.

UDC: 616-001.28

Key words: dose-response relationship, radiation; radiationtolerance

Review paper

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All living organisms are exposed to numerous deletorious agents. The critical target in the cell for many of them is the DNA molecule. DNA unique sequence of nucleotides encodes the genetic information fundamental to control cellular metabolism and reproduction. Adequate maintenance of the genetic material requires an extremely accurate mechanism for copying DNA sequences once every cell generation and a mechanism for repairing many accidental lesions occurred spontaneously in DNA or due to environmental agents. In terms of DNA repair, there is a number of distinct linear pathways that can help an organism to recover from the introduction of lesions into its DNA (1,2). However, it is important to bear in mind that there are often several choices how a given lesion or repair intermediate can be processed.

Damage in DNA can induce several repair systems to reverse or minimize the effects of DNA damage. The first discovered, SOS response, is the largest, most complex and best understood DNA damage inducible system (3,4). Induced as the response to UV-light exposure and treatment with certain chemicals, it improves the survival but simultaneously increases mutagenesis. The mechanisms of induction and the genes coded for DNA repair proteins are very well characterized in prokaryotes (5). However, the existence of SOS response in eukaryotes is uncertain (1,6).

Another type of DNA-damage-inducible response, adaptive response, is observed for cells treated with alkylating agents (7–9). Due to induction of specific enzymes which remove alkyl groups or alkylated bases (2), the survival of damaged cells increases and the yield or mutations decreases. Again, this repair inducible system is well characterized in prokaryotes (10), but the evidence for its exsistance in eukaryotes are contraversal (1,11).

Thermotolerance to a subsequent hypertermic treatment can be induced by a short exposure to a nonlethal heat treatment. The molecular mechanisms of these changes are not known. Heat stress causes a variety of alterations in cellular physiollogy, including increase in the synthesis of certain proteins (heat shock proteins-hsps). Evidence is accumulating that hsps or their cognates may function in growth and differentiation in some manner as yet not fully understood (12). Heat shock response can be induced also by DNA damage from UV-radiation or nalidixic acid (13). There is, however, little evidence that the induction of heat-shock-re-

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sponse modifies survival or mutagenesis after subsequent DNA damage.

In addition, studies show that E. coli has an inducible system for repairing oxidizing damage. The pretreatment with H_2O_2 induced the repair of lesions induced by peroxide itself and by ionizing radiation (14).

An adaptive response phenomenologically analogous to adaptive response to alkylating agents was discovered for ionizing radiation. It was first reported by Olivieri et al. (15). If human lymphocytes were cultured in a medium containing low concentrations of tritiated thymidine, as a source of low level chronic irradiation, and then exposed to subsequent higher dose of x-rays, the yield of chromatid aberrations was less than the sum of yields of these aberrations induced by ^{3}H-thymidine and x-rays separately. These results have been interpreted as evidence for the induction of an adaptive chromosomal repair process. Shadley and Wolff (16) observed, that a very low acute dose of x-rays (0,01 Gy) can also protect the lymphocytes against the clatogenic effects of a subsequently higher dose. Several reports published since than confirm these results (17–21). Adaptive response to ionizing irradiation was also observed for Chinese hamster cells (22,23), and Vicia faba root tip cells (24).

The decline in chromatid aberrations can be atributed to the selective killing of a radiosensitive subpopulation of cells and the prevention of their progression to mitosis, or to differential stage sensitivity to radiation. To examine the first hypothesis, ^{3}H-thymidine labelled female cells were co-cultured with unlabelled male cells. The proportions of female and male cells were determined at metaphase by analysing the sex chromosome constitution of the scored cells. In control experiments unlabelled female cells were co-cultured with unlabelled male cells. In both cases the same proportion of female to male cells were recovered at metaphase as were initially established in the cultures. In addition, autoradiograms of the metaphase preparations showed that all cells observed at metaphase were labelled, indicating that there was no selection against cells labelled with ^{3}H-thymidine. Consequently, the adaptive response cannot be attributed to selective killing of a radiosensitive population of cells by the incorporated radioisotope, which than would lead to an apparent decrease in aberration yield (17).

It has been documented by Olivieri et al. that differential stage sensitivity does not account for the decline in chromatide aberrations (15). Human lymphocytes cultured with ^{3}H-thymidine and than exposed to 1.5 of x-rays were fixed at different time after irradition (5–11 hours). In all cases, the yield of chromatid breaks was less than the sum of the yield of aberrations induced by ^{3}H-thymidine and x-rays separately, indicating that stage sensitivity coupled with a differential delay in the progression of irradiated cells to metaphase is not an explanation for adaptive response.

The machanism underlying the adaptation to ionizing radiation is not exactly known. The cell preirradiation with low doses of ionizing radiation induces several proteins (not seen in control cells), which are potential candidates for adaptive response (25). Olivieri et al. (15) have postulated that adaptive response is mediated through the induction of the enzyme, involved in chromosomal repair. Poly (ADP-ribose) polymerase is probably one of them. It is required for the efficient repair of chromosomal damage (26). DNA strand breaks, which occur as the common lesion after ionizing radiation, are responsible for stimulating of poly (ADP-ribose) synthesis (27). To test the possibility that poly (ADP-ribosyl)ation might be involved in the adaptive response to ionizing radiation, Wiencke et al. (17) carried out the adaptation studies in the presence of 3-aminobenzamide (3 AB), a potent inhibitor of poly(ADP-ribose) polymerase (28). The addition of 3 AB prevented the adaptive response. In dose-fractionation studies carried out in G_1 lymphocytes with 3 AB present between two doses, 3 AB markedly prolonged the time required for x-ray-induced breaks to become repaired. Therefore, low levels of ^{3}H-thymidine concentrations induced a chromosomal repair mechanism whose activity can be inhibited by an inhibitor of poly (ADP-ribose) polymerase, i.e. poly (ADP-ribose) polymerase is involved in adaptive response.

The specificity of 3 AB as an inhibitor of poly(ADP–ribose) polymerase has been questioned recently because it migh interfere with metabolic reactions other than those mediated by poly(ADP–ribose) polymerase. Whether poly(ADP–ribosyl)ation itself is directly involved, or whether the response is a secondary effect was examined by Wiencke (29). Poly(ADP–ribosyl)ation inhibition can be achieved alternatively by depletion of cellular NAD pools. Exogenous source of nicotinamide is required for NAD synthesis in human lymphocytes. Therefore, nicotinamide–free medium which prevents poly(ADP–ribosyl) ation by depletion of cellular

NAD, was used to study the involvement of poly(ADP–ribosyl) polymerase in adaptive response. It was found that nicotinamide deficiency mimics the effects of 3 AB on both adaptive response and chromosomal repair. These results indicate that poly (ADP–ribose) polymerase activity itself, and not other metabolic processes affected by inhibitors of this enzyme, plays an essential role in the adaptive response.

The importance of cellular NAD concentration and poly(ADP–ribosyl)ation is considred. However, the mechanisms by which these factors affect chromosomal repair are not exactly known. Poly(ADP–ribosyl)ation may facilitate the DNA repair by regulating DNA ligase activity, by affecting chromatin conformation, by supressing action of endogenous nucleases (27). It has been shown that ADP–ribosylation may be involved only in certain stages of the cell–cycle (30).

Several factors may influence the adaptive response: the total adapting dose, the rate at which this dose is given, the time interval between adapting and challenge dose, and the variability of the human population in the adaptive response to ionizing radiation.

The importance of the level of adapting dose in the induction of adaptive response was examined for Chinese hamster cells. The chronic exposure of cells to low concentration of ^{3}H–thymidine induced the adaptive response only within certain dose–range. i.e. if the concentrations of ^{3}H–thymidine were between 0.185 and 3.7 kBq/ml (23). The adaptive response could be induced also by external, single exposure to x–or gamma–rays, if the adapting dose was 0.01 or 0.05 Gy (16,23), but not with the doses higher than 0.2 Gy (16). For human lymphocytes the concentration of the ^{3}H–thymidine could increase up to 37 kBq/ml, and still be capable of inducing adaptive response (17).

The chronic pretreatment with ^{3}H–thymidine at a dose that produced equivalent amounts of chromatid breakage as 0.5 Gy of x–rays did induce adaptive response (17). However, no adaptive response was observed for lymphocytes pretreated with acute dose of 0.5 Gy of x–rays and challenged subsequently with 1.5 Gy dose (16). To explain this difference in biological response, Shadley and Wiencke (19) examined the role of pretreatment dose rate. Pretreatment dose delivered at 0.2–0.05 Gy/min could induce the adaptive response, while slower dose–rate did not. The experiments were done also with the pretreatment dose of 0.5 Gy delivered at 0.5 to 0.005 Gy/min. Significantly fewer chromatid breaks were observed with the dose rate 0.05 to 0.005 Gy/min, with the greatest reduction for the lowest dose–rate examined. Both pretreatment doses, 0.5 and 0.01 Gy, when given at 0.05 Gy/min, are capable to induce the adaptive response. At the same time lowering the challenge dose rate from 1 to 0.01 Gy/min had no effect on the adaptive response indicating that the dose rate effect is limited only to the pretreatment dose.

The inducing signal for he adaptive response is thought to be the damage either to DNA or chromatin. A certain number of lesions have to be produced within appropriate period of time to turn on the response. When a low dose is give at the low dose–rate, the lesions may not be produced at high enough rate to turn the response on. When a high dose is given at a high dose–rate, too many lesions may be formed in the required period of time, leading to a saturation of the effect that prevents the induction of the response. Alternatively, the lesions may interact with each other removing the inducing signal and forming other types of lesions that will not turn on the response. This dose–rate effect may serve as the fine regulator of adaptive response induction turning it on only for the exposures higher than normal background radiation or to radiation below a certain level (19).

Such threshold for low dose inducible repair system has a been reported by several groups. They noted a plateau effect in induction of chromosomal aberrations in human lymphocytes with a threshold at 0.01 to 0.3 Gy (31-37). This effect has been attributed to the induction and saturation of chromosomal repair system. There are, however, some differences between this phenomenon and the adaptive response to ionizing radiation. The major is that at this time there is no evidence that low doses of gamma or alpha radiation will induce adaptive response, or that the response will work on chromosome type damage in lymphocytes, as the chromatide damage is known to work on. A minor difference is that the reports mentioned above were done with lymphocytes irradiated in G_0 phase of the cell–cycle, and the adaptive response has been observed only for proliferating lymphocytes stimulated by PHA.

Time interval between adapting and challenge dose can influence the induction and full expression of adaptive response. It was found that 4-h interval was sufficient for the expression of adaptive response (18,23), but 5-6 h were needed for full expression in human lymphocytes

(18). This phenomenom persists for at least three cell–cycles in human lymphocytes (18).

The variance in donor effect could be involved in modified adaptive response. Using radiation as both initial treatment and challenge, response Bosi and Olivieri (20) found that 4 out of 18 donors showed no adaptive response and in some of these the response was synergistic. With a similar experimental design Sankaranarayanan et al. (21) found a smaller but consistently positive adaptive response varying in magnitude between the donors.,

The variation in the induction of adaptive response could explain the negative results reported by Schmid et al. (38). Using virtually identical culture condition and irradiation conditions as Shadley and Wolff (16), they did not confirm their results. The minor variations in culture conditions (concentration of fetal calf serum, penicillin and streptomycin) seems unlikely to be the cause of different results. Alternatively, the increased level of PHA used by Schmid et al. (38) could influence the results because mitogenic stimulation has shown to induce an anti–mutagenic repair system ih human lymphocytes (39). PHA stimulation could therefore affect the induction of chromosomal changes. Sanderson and Morley (40) observed no adaptive response in human lymphocytes: adapting dose prior to X–radiation had no effect on X–radiation related lethality, but produced a significant decrease in the number of mutations. This »no adaptive« response can be explained by the fact that their protocols suggest treatment of G_0 human lymphocytes– a stage in cell cycle, in which no adaptive response with respect to chromosomal damage was observed (18, 41, 42). Therefore, in apears, that adaptation of cells to low doses of ionizing radiation requires mitogenic stimulation of the lymphocytes. This is in agreement with other reports showing that stimulated lymphocytes have higher repair capacity than do unstimulated lymphocytes (43, 44).

Adaptive response reaction to some chemicals have been examined. Adaptive response was generally found to be limited to these cases where the same type of DNA lesions were induced by the initial priming exposure and by the subsequent challenge (8, 45). Irradiation appears to result in the induction of a broader range of responses capable of repairing a wider variety of primary lesions, suggesting that radiation inducible repair process differs from that in the adaptive response to alkylating agents. Human lymphocytes preirradiated with low levels od ^{h3}H–thymidine or low doses of x–rays become cross–resistant to mitomycin C (MMC) (42, 46) and bleomycin (46), but not to methylmethanesulfonate (46). Cross–reactivity of gamma ray induced adaptive response was observed also for Chinese hamster V79 cells to DNA lesions produced by mitomycin C, and near ultraviolet light, but not to those of ethylmethansulfonate or cis–dichlorodiammineplatinum (II) (23). Human lymphocytes pretreated with low concentration of bleomycin (an S–independent radiomimetic agent, which, like ionizing radiation, induces double strand breaks in DNA) became significantly less sensitive to induction of chromosomal damage of subsequent high concentration of the same agent and cross–resistant to x–rays (47).

The significance of an inducible repair prosess under in vivo conditions cannot be assessed at present due to too few empyrical data. Jacobson–Kramm and Williams (48) reported that there was no adaptive response of bone marrov cells under the experimental conditions they used (adapting dose of 0.125 Gy and challenge dose of 1.5 Gy of gamma–radiation. This failure to induce adaptive response could be due to a too high adapting dose. Contrary to that, Wojcik and Tuschl (49) report that whole-body irradiation of mice with low doses of gamma–radiation causes an increase in the cellular repair capacity of spleen lymphocytes. It lasts approximately 12 days and manifests itself as higher in vitro UV–light induced unscheduled DNA synthesis (USD) rates and lower in vitro MMC–induced sister chromatide exchange (SCE) (49).

The beneficial effect from low doses of an otherwise harmful agent has been termed hormesis. The possibility that hormesis could also occur in response to ionizing radiation was advanced by Luckey (50). He published a monograph on this subject summarizing the animal data from over 1200 papers. The biopositive effects of low–dose radiation comprise: improved healing rate for wounds, accelerated embryo development, increased resistance to effects of subsequent high–dose radiation exposures, increased immunological response, increased weight and increased longevity (reviewed in 51). Hormetic effects might also occur in humans. Several studies indicate a lower cancer incidence in high radiation background areas as compared to control population in low background areas (reviewed in 51). Antitumor effects of low–dose radiation were observed in some human tumors and on experimental mice tumors (52–54, reviewed in 55), but in some cases an increase in neoplasia at low–level exposures was seen (56). Hormetic response has been found also in most

plant species involving the stimulation of growth (57), being most evident at the early stage of growth (58).

The exact mechanism of radiation hormesis is not known. One of the possibile explanations was given by Kondo (55). he proposes that radiation hormesis results from altruistic (in animals) or non–altruistic (in plants) cell death. The inactivation of radiosensitiv cells by low dose radiation of growing or slowly renewing organs stimulates proliferation of healthy primordial cells. The resulting increase in cell proliferation may lead, at least for limited period of time, to an increase in the functional activity of the organ. This hypothesis is assessed in relation to the reported effects of low–dose radiation on the immune system in mice (59,60) and on the growth potential of plants (57,58). Adaptive response to ionizing radiation reviewed in this paper may be an other aspect of the defence–adaptive mechanism of cells to ionizing radiation.

Sažetak

Humani limfociti i stanice kineskog hrčka zračene malim dozama ionizirajućeg zračenja (koje potječe od inkorporacije radioaktivnog ^{3}H–timidina ili x– ili gama zraka), postaju manje osjetljive na klastogeni efekt slijedeće veće doze. Taj fenomen naziva se adaptivni odgovor na ionizirajuće zračenje. Mogućnost, da je fenomen adaptacije zapravo uzrokovan različitom osjetljivošću stanica na zračenje ovisno o njihovoj fazi u staničnom ciklusu ili selektivnim ubijanjem subpopulacije je stanica osjetljivih na zračenje, odbačena je na temelju eksperimentalnih rezultata. U stanicama zračenim malim dozama induciraju se različiti proteini (kojih nema u kontrolnim stanicama), koji bi mogli biti odgovorni za adaptivni odgovor. Jedan od njih je i poli (ADP–riboza) polimeraza. Brojni faktori mogu utjecati na adaptivni odgovor: ukupna adaptivna doza, brzina te doze, faza staničnog ciklusa u kojoj se stanice adaptiraju, vremenski interval između adaptive i slijedeće doze, te varijabilnost u adaptivnom odgovoru unutar humane populacije. Stanice adaptirane malim dozama ionizirajućeg zračenja pokazuju unakrsnu rezistanciju na mitomicin C, bleomicin i ultravioletno svjetlo (UVA), ali ne na metil metan sulfonat, etil metan sulfonat ili cis–diklorodiamin platinu (II). Možemo zaključiti, da je adaptivni odgovor na ionizirajuće zračenje jedan od sistema popravka koje mogu inducirati oštećenja u DNA, kao što je SOS odgovor, adaptivni odgovor na oštećenja nastala djelovanjem alkilirajućih agensa, inducibilni sistem za popravak oksidativnih oštećenja i, možda, inducibilni sistem za popravak oštećenja nastalih djelovanjem povišene temperature.

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INFLUENCE OF INTERLEUKIN–2 AND DACARBAZINE ON PERIPHERAL BLOOD LEUKOCYTES IN MICE

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Abstract – It is important to combine myelosuppressive chemotherapeutic drugs and immunostimulating agents in the right treatment schedule not to negate the effects of each other. Therefore the aim of this study was to search for optimal treatment schedule of dacarbazine (DTIC) and interleukin–2 (IL–2) to produce the least myelosuppression. Simultaneous treatment with both agents induced a profound leukopenia in mice. Successive treatment with DTIC and IL–2, after 7–dav interval did not result in a quicker recovery after DTIC. Pretreatment of mice with IL–2 also had no effect on DTIC induced leukopenia. The results indicate that DTICX induces myelosuppression which cannot be restored by IL–2 treatment. The two agents influence peripheral blood leukocytes (PBL) population by different mechanisms, which do not interfere with each other. This fact might be important for the therapeutic regimen when the combined treatment is planned in patients with malignant disease.

UDC: 612.112.014.46

Key words: leukocyte–drug effects, interleukin–2, dacarbazine, mice

Orig sci paper

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Introduction – Biological response modifiers (BRM) play an important role in cancer therapy, but as single agents have proved to be insufficiently effective (1, 2, 3). Presently, the role of IL–2 is under intensive investigation, a T–cell growth factor which can in animal models activate antitumor mechanisms and suppress tumor growth or in some instances, induce tumor regression (2, 4, 5, 6, 7). Better effects were obtained by combining the IL–2 therapy with adoptive transfer of activated lymphocytes (8).

Also, new approaches in combining BRM with other cytotoxic agents to potentate the effect are in progress (8, 9, 10, 11, 12). Attempts have been made to combine IL–2 therapy with chemoterapeutic drugs such as cyclophosphamide (CY), doxorubicin (Dox), and bischloroethylnitrosourea (BCNU) (8, 10, 12, 13). Especially effective was a combination of Cy and IL–2 where the effectiveness of Cy was attributed to reduction of the tumor burden, an increase in susceptibility of tumor cells to immune lysis, and/or decrease in suppressor cell activity (12). Experimental and clinical reports on combination of dacarbazine (DTIC) and IL–2 in the treatment of malignant melanoma show that the treatment in this combination is feasible and effective (14, 15, 16).

Since the antitumor effect depends on the quantitiy of chemotherapeutic applied, treatment with the highest necessary dose seems logical. In such cases the limiting factor of the chemotherapeutic applied is the myelosuppressive effect. In order to study the restoring effect of IL–2 on myelosuppression induced by chemotherapy, we followed the effect with PBL count as the indicator of bone marrow cellularitiy. Therefore, the aim of the present study was to evaluate the influence of IL–2 in combination with DTIC on PBL number in normal mice to determine whether IL–2 treatment can interfere with DTIC–induced leukopenia.

Materials and methods – Animals: Female C57Bl/6 mice, 8 to 10 weeks old were purchased from the Institute Ruđer Bošković, Zagreb, Yugoslavia. The animals were kept in groups 7 to 8 per cage in housing with environmental circadian rhythm.

Lymphokine and DTIC protocol: Recombinant human Interleukin–2 (IL–2) was generously provided by Cetus Corporation, Emeryville, CA, U.S.A. It was more than 99% pure by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Specific activity was $3x10^6$ U/mg protein. Lyophilized IL-2 was stored at –70°C

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and reconstituted with sterile double distilled water to make $3x10^5$ U/ml concentration. Final dilution was made with phosphate buffer solution (PBS) and used immediately or stored at –70° until used.

Dacarbazine (DTIC) was supplied from Lek, Ljubljana, Yugoslavia. It was stored at –4°C and diluted with PBS to appropriate concentration immediately before use.

IL–2 and/or DTIC were administered in the mice intraperitoneally for 5 consecutive days in the volume of 0.5 ml. Daily dose applied per 10 g of animal weight was $1.5x10^4$ U of IL–2 and 1 mg DTIC.

Three different schedules of therapy were studied. One group of animals was treated first with DTIC and after a 7–day interval with IL–2. The second group of animals was treated first with IL–2 and thereafter with DTIC, whereas the third group received both therapeutics simultaneously. Control mice consisted of a group of animals treated with PBS and the two groups treated with either single therapy of IL–2 or DTIC.

Assessment of lymphokine and DTIC therapy : Influence of the therapy on the bone marrow cellularity was followed by the determination of total PBL count. Blood samples were collected on every second day. Venous blood was obtained by incision of the lateral tail vein. Fifty microliters of the blood were diluted in 450 μl of Turk solution for the evaluation of total PBL count.

Statistical analysis : A minimum of 7 mice were included in each group. The results were presented as arithmetic means (AM) and standard errors of the mean (SE). The comparison between the groups was done by the Student's t test.

Results – The effect of IL–2 and DTIC treatment on peripheral blood leukocyte count (PBL) was assessed in healthy mice (Figure 1). DTIC treatment with 1 mg/10 g body weight for five consecutive days intraperitoneally resulted in leukopenia. The lowest number of PBL was noted immediately after the cessation of therapy, and lasted for two days. Thereafter, the number of PBL was steadily increasing and resched normal PBL count after 21 days. The normal range of PBL number was determined in a group of 15 animals.

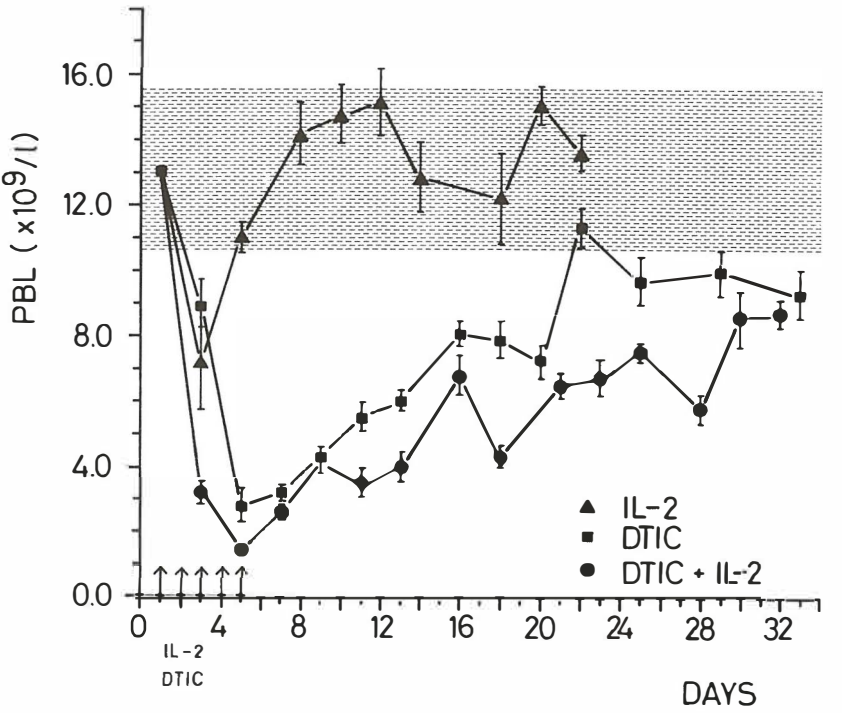

Fig. 1 – Effect of simultaneous application of IL-2 and DTIC on PBL count compared to the effect of single DTIC and IL-2 therapy. Dots represent AM+/–SE of PBL counts in groups of 7 to 12 animals. Dashed area represents PBL counts (AM+/–SD) in untreated group of 15 animals. Arrows indicate applications of IL-2 and/or DTIC.

Treatment with high bolus IL–2 ($1.5x10^4$ U / 10 g body weight) injections intraperitoneally for five consecutive days produced a short term drop in PBL number (Figure 1). The drop had its nadir two days after the beginning of treatment and within three days PBL number returned to normal range and continued to increase to the highest levels within normal range.

In combined treatment we tested whether simultaneous application of IL–2 and DTIC can interact with each other (Figure 1). Treatment with DTIC and IL–2 produced almost the same decrease in PBL number as DTIC therapy alone ($p>0.05$). The recovery of PBL number was not accelerated in combined treatment schedule compared to only DTIC treatment.

In the schedule where IL–2 therapy was the first, followed by DTIC after a seven day interval, the same phenomenon was observed (Figure 2). IL–2 did not interfere with the effect od DTIC treatment measured by PBL number. DTIC treatment started when PBL number returned to normal values. The drop in PBL number in combined treatment and recovery time were the same as in the DTIC group ($p>0.05$). This indicated that the IL–2 treatment did not predispose the organism to leukopenia induced by DTIC.

The same happened when the therapy schedule was reversed, i.e. DTIC first and IL–2 second ($p>0.05$) (Figure 3). IL–2 therapy which followed the DTIC treatment did not attenuate with recovery time of PBL number after DTIC therapy.

Discussion – Biological response modifiers (BRM) are important new class of agents for the treatment of different malignancies. Some of these BRM's such as IFN–alpha and IL–2 have already proved to be effective antitumor agents in clinical trials (1, 2, 3). Additionally, BRM's are also able to increase the host's ability to better tolerate cytotoxic treatment in different ways (17). They can promote incorporation of cytotoxic substances as well as increase the sensitivity of tumor tissue to irradiation. Finally, they are able to modulate the immunological mechanisms reacting against the tumor (11).

Malignant melanoma has proved to respond to IL–2 treatment, however, the results could be further improved using combination with DTIC

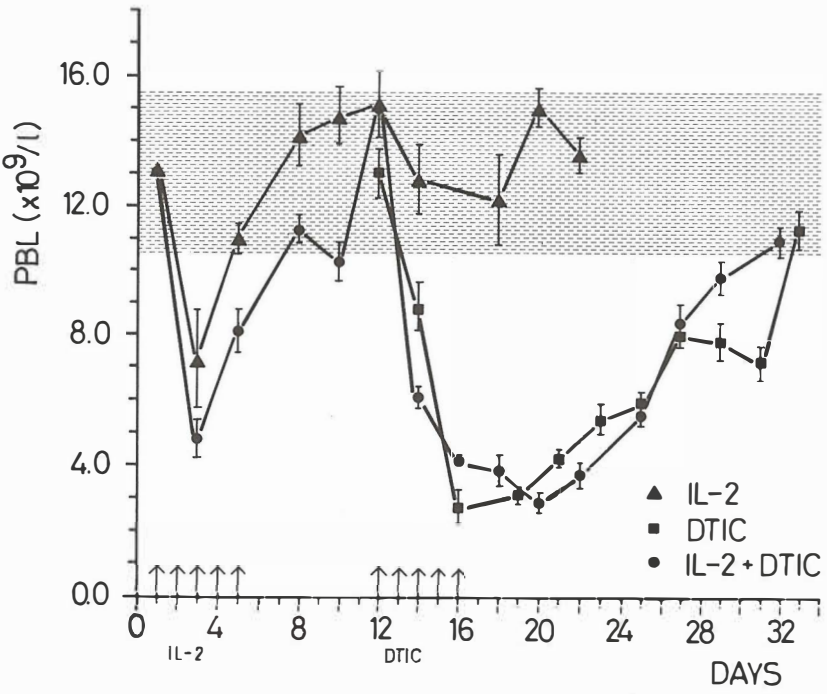

Fig. 2 – Effect of therapy with IL-2 and DTIC on PBL counts compared to single drug therapies. Animals were treated for 5 days with IL-2, and after a 7-day delay with DTIC for 5 days. Dots represent AM+/–SE of PBL counts detected in groups of 7 to 12 animals. Dashed area represents PBL counts (AM+/–SD) detected in the untreated group of 15 animals. Arrows indicate applications of IL-2 and/or DTIC.

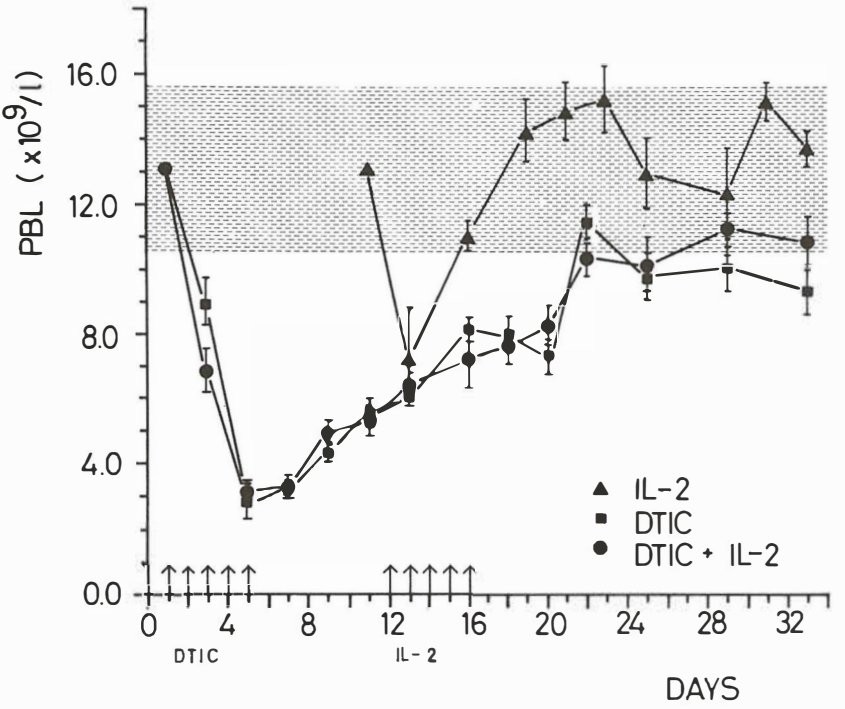

Fig. 3 – Effect of therapy with DTIC and IL-2 on PBL counts compared to single therapies. Animals were treated for 5 consecutive days with DTIC and after a 7-day delay with IL-2 for 5 days. Dots represent AM+/–SE of PBL counts detected in groups of 7 to 12 animals. Dashed area represents PBL counts (AM+/–SD) detected in the untreated group of 15 animals. Arrows indicate applications of IL-2 and/or DTIC.

(2, 3, 9, 18). Clinical trials using similar drug combination as ours have proved that this treatment regimen is active in metastatic melanoma (14, 15). The limiting factor for high dose treatment is the myelosuppression induced by chemotherapeutic agent. In a situation when IL–2 is given concomitantly, it would be desirable to have more information regarding the effect od IL–2 on myelosuppression induced by DTIC.

It is known that IL–2 administered intravenously in experimental animals as in humans depresses the PBL count for approximately 50% in treated subjects (17, 19). However, after cessation of treatment the PBL counts return to normal value in a short time, e.g. in a few days (18, 19). The mechanism responsible for the depression is the extravasation of PBL, facilitated by the vascular leak syndrome, which is caused by the endothelial damage by lympohocyte activated killer (LAK) cells (20,21). But it is known that IL–2 can induce bone marrow stem cell proliferation most probably by inducing T–cells to produce colony stimulating factors and IL–3 (17). In mice, this myelostimulatory effect od IL–2 is reflected also in PBL rebound lymphocytosis but only after a certain lag period.

On the other hand, DTIC which directly affects blood cell formation, can cause profound myelosuppression manifested as a marked decrease in PBL cells. This depression lasting for longer period of time was observed in experimental animals as well as in humans (22, 23).

In the present study it has been ascertained that both agents induce leukopenia. It has been observed, however, that the IL–2 caused depression was transient, the cell counts returning to normal values within five days, whereas the DTIC induced myelosuppression was profound, recovering only after two weeks. This sequence of events was observed regardless the time sequence of DTIC and IL–2 application. In fact, the observed myelosuppression occurred in situations when DTIC and IL–2 were applied simultaneously, or DTIC first, followed by IL–2, or by reversed application. The results indicated that the treatment with DTIC induced leukopenia which could not be reversed by IL–2 application despite its myelostimulatory activity demonstra-

ted in mice (17). Therefore, it could be accepted that these two agents induced leukopenia by independent and different mechanisms which do not interfere with each other. This is of particular importance when the combined treatment is planned in patients with malignant disease.

Izvleček

VPLIV INTERLEUKINA–2 IN DAKARBAZINA NA PERIFERNO KRVNO SLIKO MIŠI

Pomembno je uporabljati pri zdravljenju kemoterapevtike in imunostimulatorje v pravilnem vrstnem redu, da se ne izniči njihov protitumorski učinek. Namen študije je bil, da se poišče optimalno zaporedje uporabe dakarbazina (DTIC) in interleukina-2 (IL-2), za najmanjši vpliv na mielosupresijo. Sočasna uporaba obeh agensov je povzročila močno leukopenijo v miših. Zaporedna terapija z DTIC in nato z IL–2, po sedem dnevni pavzi, ni pripomogla k hitrejšem zvišanju števila levkocitov v periferni krvi živali. Tudi obratna shema terapije ni vplivala na potek leukopenije inducirane z DTIC. Rezultati nakazujejo, da z IL–2 ni mogoče vplivati na mielosupresijo inducirano z DTIC. Vsak od agensov vpliva na število leukocitov v krvi na različen način in ne vplivata eden na drugega. To ima lahko pomemben terapevtski pomen, ko se načrtuje zdravljenje pri bolnikih z rakom.

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LABORATORIJ ZA EKSPERIMENTALNU KANCEROLOGIJU, ZAGREB

THE ROLE OF FULVIC ACIDS DURING TRANSPORT OF TRACE ELEMENTS IN THE SAVA RIVER BIOCYCLE

Huljev D

Abstract – Fulvic acids isolated from the Sava river sediments near Zagreb were characterized by the elementary composition and qualitative and quantitative determination of trace elements. Metal concentrations in the investigated fulvic acids were determined by the neutron activation analysis. The trace elements measured were: Co, Fe, ZN, Se, Sr, Cs, Eu, Sc and Sb. The concentrations ranged from 0.16-12,040.0 μg of specific microconstituent per gram of samples (μg/g=ppm). The calculated concentration of metals in fulvic acid molecules increased in the following order: Eu<Sc<Se<Cs<Co<Zn<Sb<Sr and Fe. The role of fulvic acids in the cycle of trace elements in the Sava river biocycle are discussed. These data suggest the ecological importance of trace elements bound to fulvic acids in a certain region.

UDC: 614.77:543.36

Key words: water pollutants; trace elements; fulvic acids

Profess paper

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Introduction – Fulvic and humic acids and related substances are widely distributed in terrestrial soils, natural waters, marine, river and lake sediments, peat bogs, shales, and brown coals (1, 2). They are important in the transportation and enrichment of mineral substances in sediments and sedimentary soils (3), and they serve as the precursors of coal and kerogen. In classical terminology, humic acid is defined as the material which is extracted from soil and sediments by alkaline solutions and which is percipitated upon acidification; fulvic acid is the alkali-soluble material which remains in solution upon acidification. Fulvic acids are lower in molecular weight than humic acids, and they are the constituent often found in the colored waters of lakes, streams and swamps. They represent a heterogeneous mixture of molecules, which, in any given soil or sediment, may range in molecular weight from as low as 200 to over 3,500 (4). Fulvic acids can form stable water-soluble and water-insoluble complexes with metal ions and hydrous oxides, interact with clay minerals, combine with hydrophobic organic compounds such as alkanes, fatty acids, and dialkyl phthalates and make them soluble in water (5, 6). Fulvic acids can interact with substantial amounts of hydrophobic organic compounds (some of which may be toxic pollutants such as herbicides, pesticides and oil) solubilize them, water and thus modify their mobility and possibly their activity in aquatic environments (7). Fulvic acids can alco exert considerable physiological activity in the areas of cell division and cell elongation (8). All of these properties point to the significant role of fulvic acids in reactions occurring in soil and waters, including those associated with pollution.

The major oxygen-containing functional groups present in various fractions of fulvic and humic acids extracted from different marine clays are carboxyls, phenolic and alcoholic hydroxyls and carbonyls (9). The functional group present in the periphery of many organic molecules is important for characterizing and determining the constitution of organic matter. This is particularly helpful with natural polymeric substances, such as fulvic and humic acids, because the functional group approach is one of the best means of obtaining structural information on highly complex polymers which are difficult to characterize by other than empirical methods. This may be helpful in determining the nature of the association of organic matter with inorganic substrate, and in determining the role of fulvic and humic

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acids in the accumulation of metallic elements (5, 10).

Materials and methods – Fulvic acids used in this work were isolated from the Sava river sediments near Zagreb. Methods of extraction and purification of fulvic acids were analogous to those described in 1969 (11). The fulvic acid solution was flash evaporated under reduced pressure and temperature, dialyzed against destilled water and freeze-dried. Since fulvic acids present a group of compounds with relative high molecular weight, they are characterized by elementary composition and by their content of trace elements.

The content of trace elements fixed to fulvic acids were investigated by neutron activation analysis for which samples and standard bovine liver (1577 NBS) were dried at 383 K (120 hours), transferred into quartz ampules and irradiated in a TRIGA reactor near Ljubljana for 120 hours at a neutron flux of 1.8×10^{12}N cm^{-2}n $cm^{-2}s^{-1}$ and temperature of 323 K.

After irradiation, samples were cooled for several days, and then their gamma-ray spectra were measured using 25 cm^3 Ge/Li semi-conductor crystal attached to a 4096-channel pulse-height analyser.

Gamma-ray spectra were analysed, characteristic photopeaks identified and quantities of trace elements calculated according to the areas under the photopeaks. All necessary corrections for geometry, efficiency, decay scheme of the nuclide etc., were applied. The quantitative content of elements in measured samples was calculated with activation analysis formula (10).

Results and discussion – Trace element concentrations in the investigated fulvic acids were determined by the neutron activation analysis. Our results indicate that a number of trace elements could be bound to fulvic acids under natural conditions of Sava river environment. The origin of trace elements in fulvic acids could vary, i.e. certain trace elements were already constituents of plant and animal tissues from which fulvic acids were formed, or some of the trace elements may join these organic compounds during metabolic processes of micro-organisms on detritus; finally, the charge of physico-chemical conditions of the aquatic environment could result in certain exchange reactions. In such a complicated case, stabilites of various metal complexes or chelates play an important role. For this reason, determinations of stability constants of metal complexes with fulvic acids and with amino acids, sugars or phenols were investigated under fresh-water conditions (5, 6). Stability constants for metal-fulvic acid complexes are one or two orders of magnitude higher than those for metal-amino acids, sugars or, phenols complexes. The elementary composition of fulvic acids isolated from the Sava river sediments are presented in Table 1. The results indicate the mean values of several independent sets of experiments. From their elementary composition one can see that they contain a relatively high amount of nitrogen. This indicates that not

Table 1 – Elementary composition of fulvic acid molecules. Contents %.

Element	C	H	N	S	0, metals, ash
Total range	40.1-45.7	3.5-5.2	1.7-3.9	0.20.-0.26	45.7-52.9
Mean	41.4	4.0	2.1	0.25	52.25

Table 2 – Concentrations of metals in fulvic acids

Metals determined	Mass fractions μg/g (ppm) (total range)	Mass fractions μg/g (ppm) (mean)
Co	10.0–13.7	11.0
Fe	9,520.0–12,040.0	10,200.0
Zn	42.0–56.0	50.0
Se	1.9–2.8	2.5
Sr	560.0–670.0	620.0
Cs	2.0–4.0	3.8
Eu	0.16–0.28	0.2
Sc	1.4–1.5	1.42
Sb	50.0–70.0	59.0

only dead Sava river plants, but some components of animal origin are responsible for the constitution of the fundamental matrix of fulvic acids. Table 2 indicates that the mass fraction (concentration) of metals in samples of the Sava river fulvic acids obtained from the same geographic microlocality slightly differs. This table also shows that the fulvic acid has a proportinally high mass fraction of iron, strontium and zinc. Interestingly, all of these are essential elements. The amounts of trace elements in the fulvic acids may be separated in four groups. The first group comprises strontium and iron (560.0-12,040.0 μg/g), the second antimony and zinc (42.0-70.0 μRg/g), the third cobalt, selenium and cesium (1.9-13.7 μg/g), and the fourth group comprises europium and scandium (0.16-0.4 μg/g). The fulvic acids bind metals and it is believed that an important role in such a process is played by COOH, –OH, and –CO groups, N(–NH^2) and S(–SH, –SS–) atoms forming various chelates. In general, the functional groups in the fulvic acid molecules determine the reactivity of the material.

Most trace metals determined in fulvic acids may serve as catalysts in enzymatic reactions of microorganisms on fulvic acids. This step is very important for the biocycle of those microelements and their interaction with the Sava river food chain. Thus, the elements present in fulvic acids are likely to enter the Sava river food chain. This is an important fact because of nutrients and especially for studying the fate of certain pollutants in the Sava river environment. The fact that certain pollutants fixed to fulvic acids (6) which could strongly influence the growth of micro-organisms, plankton etc. proves the statement that fulvic acids and microelements associated in their structure are significant in the Sava river food chain and in the transport of trace elements in the Sava river biocycle.

Sažetak

ULOGA FULVIČNIH KISELINA U TRANSPORTU ELEMENATA U TRAGOVIMA U BIOCIKLUSU RIJEKE SAVE

Fulvične kiseline su izolirane iz sedimenta rijeke Save i karakterizirane elementarnom, kvalitativnom i kvantitativnom analizom elemenata. Koncentracija metala u fulvičnim kiselinama je određena neutronskom aktivacijskom analizom. Određeni su slijedeći elementi u tragovima: Co, Fe, Zn, Se, Sr, Cs, Eu, Sc i Sb. Koncentracije variraju od 0,16-12.040,0 μg po gramu uzorka. Koncentracije metala rastu prema slijedećem redosljedu: Eu<Sc<Se<Cs<Co<Zn<Sb<Sr<Fe. Diskutirana je uloga fulvičnih kiselina u ciklusu tragova elemenata u biociklusu rijeke Save. Ovi podaci navode na ekološku važnost tragova elemenata koji su vezani na fulvične kiseline u određenoj geografskoj regiji.

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SEKCIJA ZA RADIOLOGIJU HRVATSKOG LIJEČNIČKOG ZBORA
ODJEL ZA RADIOLOGIJU MEDICINSKOG CENTRA VARAŽDIN

JUBILARNI DESETI ZNANSTVENI SKUP RADIOLOGA HRVATSKE

Varaždin, 4. – 7. prosinca 1991. godine.

DRUGA OBAVIJEST

Teme:

1. Dijagnostička i intervencijska radiologija probavnog sustava
2. Dijagnostička i intervencijska neuroradiologija
3. Slobodne teme

Prijave predavanja i kratke sažetke poslati do 30. 6. 1991. godine na adresu: Medicinski centar, odjel za radiologiju, A. Mihinjača bb, 42000 Varaždin.

Trajanje predavanja do 10 minuta.
Osigurana mogućnost paralelne projekcije standardnih dijapozitiva.
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BOOK REVIEW

IIIrd Italian–Yugoslav Symposium. Low Level Radiation: Achievements, Concerns and Future Aspects. June 11–13, 1990, Plitvice, Yugoslavia.

Edited by Dj. Horvat and P. Stegnar. 312 pp., illustrated. Institut »Jožef Stefan«, Ljubljana, 1991.

The papers published in this book were presented at the Third Joint Symposium of the Italian and Yugoslav Radiation Protection Association, held from June 11–13, 1990 in Plitvice, Yugoslavia.

The publication represent a relevant contribution to the problems of radiation protection in the field of low level radiation, pointing out the achievements, concerns and future aspects. The material is divided by chapters into six thematic units, thus following the form of the syposium where it was presented in six sessions according to subject matter.

The 1st chapter comprises 11 articles on biological effects of low level radiation so in experimental conditions as well as in clinical practice.

In the 2nd chapter 3 reports on epidemiological studies dealing with the catastrophic Chernobil accident, uranium mine Žirovski vrh and protection against environmental agents are presented.

The 3rd chapter entitled Dosimetry of Low Level Exposure is dedicated to different, not only theoretical, aspects of dosimetry.

The 4th chapter on environmental measurements is most extensive. It comprises 17 articles on methodological problems, which provide very interesting information pertinent to the low dosis of environmental radiation on the territory of Italy and Yugoslavia.

In the 5th chapter entitled Technologically modified exposure to natural radiation the radiation exposure which comes from manmade natural sources and is called »technologically enhanced natural radiation« is discussed in 8 papers.

Some Practical Aspects is the title of the last, 6th chapter, comprising different topics that could not be clasified into any of the previously mentioned thematic units. The latter fact, however, by no means renders these papers less interesting.

This compilation represents one of the few professional pubications in the field of radiation protection that have been published in our country. Despite the diversity of authors and topics, the material is organized in a clear and systematic manner. All chapters are richly illustrated with pictures, graphs and tables which are of reasonably good quality for a desk–top edition.

The book is not intended exclusively for professionals dealing with radiation, e.g. radiophysicists, radiobiologists, radiopharmacologists, ecologists, radiologists, radiotherapists, epidemiologists, oncologists, geneticists, specialists in nuclear medicine, specialists in social medicine and others involved with the problems of radiation protection; it can be warmly recommended to everyone interested in this field of research. Its interdisciplinary character renders this publication worth of a broad public attention.

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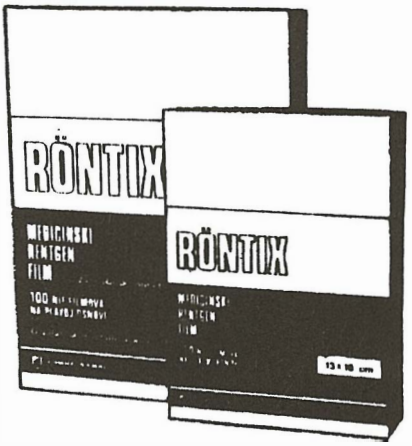

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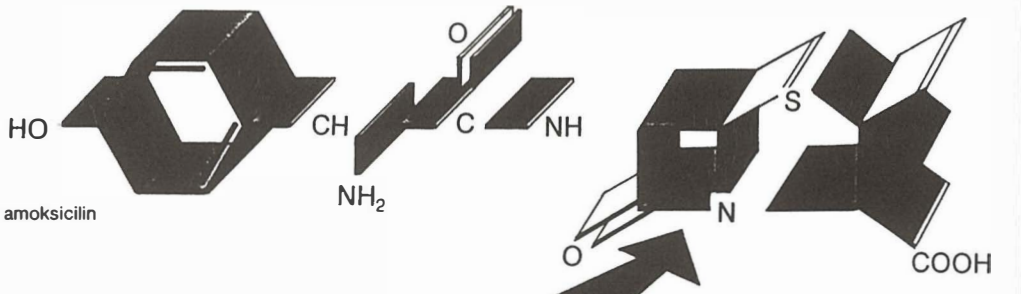

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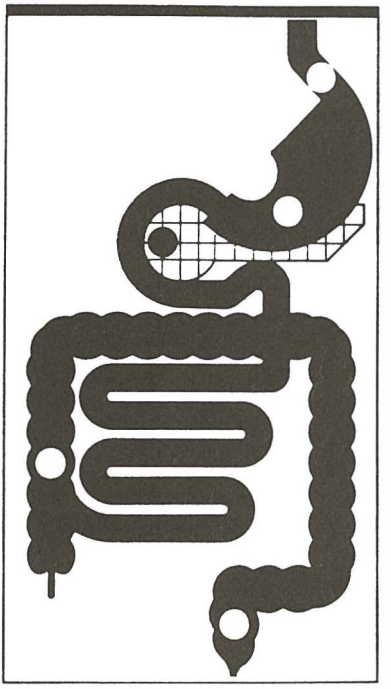

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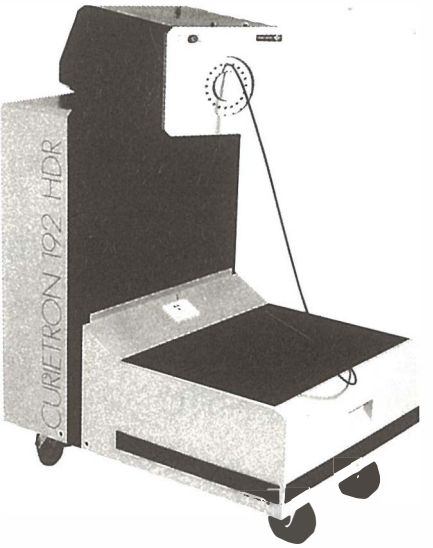

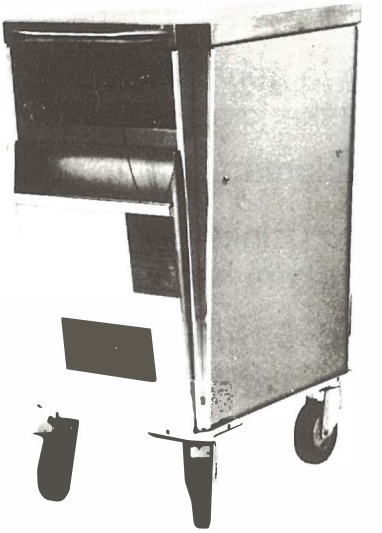

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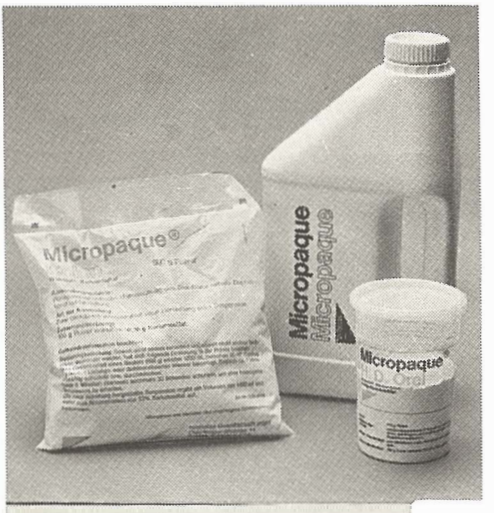

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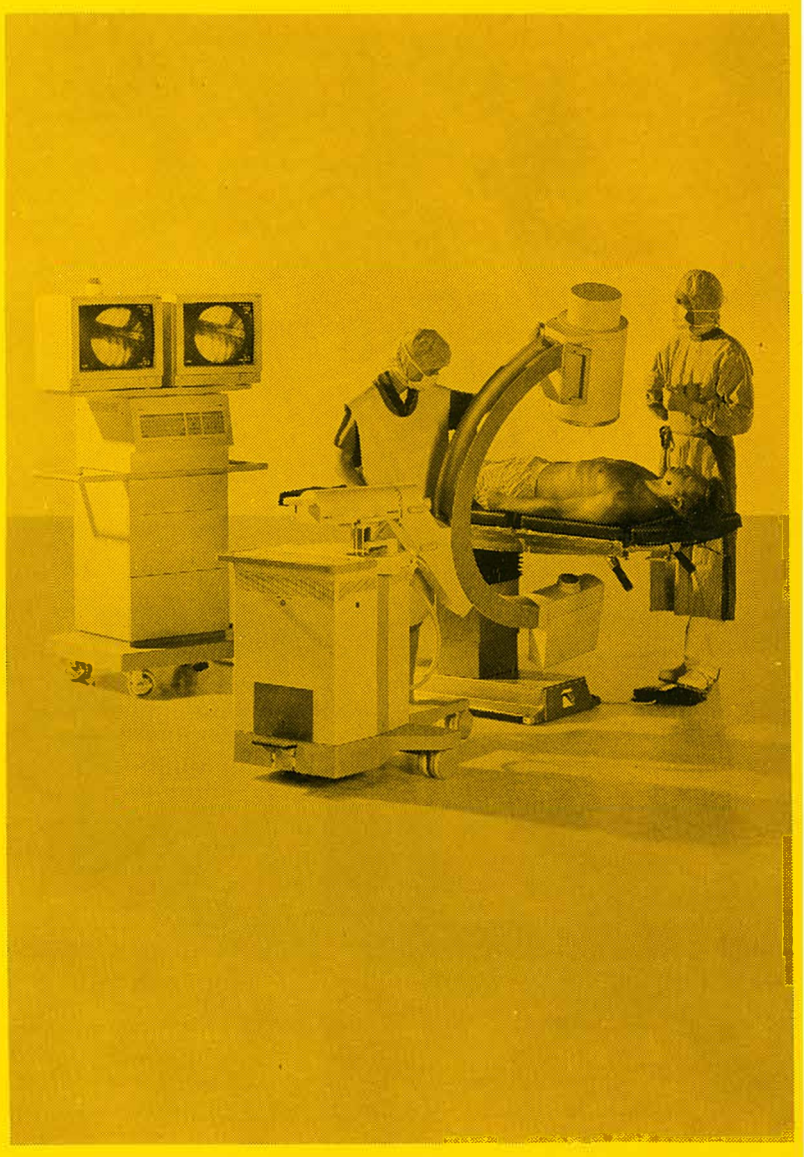

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