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Phone: +386 1 4320 068
Phone/Fax: +386 1 4337 410
E-mail: gsersa@onko-i.si

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Biliary small intestinal submucosa covered Z-stents: preliminary results in an animal model

Koichiro Yamakado [1,3], Dušan Pavčnik [1], Barry T Uchida [1], Hans Timmermans [1], Christopher L. Corless [2], Joong Wha Park [1], Katsuyuki Yamada [1], Frederic S. Keller [1], Josef Rösch[1]

[1] Dotter Interventional Institute, Oregon Health Science University, Portland, Oregon,
[2] Department of Pathology, Oregon Health Science University and Portland Veterans Administration Medical Center, Portland, Oregon, USA,
[3] Mie University School of Medicine, Japan

Background. *Purpose of the study was to test the function and biological response of metallic stents covered with small intestinal submucosa (SIS) in the swine biliary system.*

Materials and methods. *A total of 9 SIS-covered single Z-stents were placed in the common bile duct (CBD) in 6 pigs. Stents were delivered into the CBD at laparotomy via the gall bladder and the cystic duct. Animals were sacrificed or died at 2 weeks (n=1), 4 weeks (n=1), 8 weeks (n=2), and 10 weeks (n=2) after stenting and histological studies were performed.*

Results. *Nine stents were deployed in 6 animals. During follow-up, 3 stents in 3 animals (2, 4, and 10 weeks) remained stable, while one stent shifted distally in CBD and 5 of them turned sideways. All stents remained patent. Duct dilatation and bile slugging were noted at 10 weeks. The SIS-membrane was present at 2 weeks, but was not histologically distinct at 4 weeks and later. Histological study showed no significant inflammatory changes in the bile duct in any pig. Mucosal hyperplasia was absent in 2 of 3 stable stents at 2 and 10 weeks, and 1 distally shifted stent at 10 weeks. Mild mucosal hyperplasia was seen at the distal stent end in 1 stable stent at 4 weeks and in 5 dislodged stents at 8 and 10 weeks.*

Conclusions. *Even when the study is limited by dislodgment of high percentage of placed stents, the results in stable stents conducting the bile flow suggest that SIS helps to prevent bile duct inflammation and mucosal hyperplasia typical for uncoated stents. Further studies, particularly with improved wet SIS are warranted.*

Key words: bile ducts, stents; intestinal mucosa

Correspondence to: Dušan Pavčnik, MD, Ph.D., Dotter Interventional Institute, Oregon Health Science University, L342, 3181 SW Sam Jackson Park Road, Portland, Oregon, 97201, USA. Phone: (503) 494 8396, Fax: (503) 494 4258, E-mail: pavcnikd@ohsu.edu

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Introduction

Expandable metallic stents have been established as useful devices for the treatment of large bile duct obstructions whether caused by benign or malignant processes.[1-7] Their long-term patency, however, remains a major problem. Mucosal hyperplasia, bile sludging and stone formation resulting from significant foreign body-type inflammatory reaction often block expandable stents.[1-4] In malignancies, direct tumor ingrowth or overgrowth also obstructs stents.[8-10]

Stents coated or covered with synthetic polymer material have been explored experimentally for potential improvement in a long-term biliary stent patency.[11-15] Generally, stent coated or covered with polyester, polyurethane or polycaprolectone resulted in lesser degree of mucosal hyperplasia and reactive inflammatory or dysplastic changes than with bare stents.[11-13] The results with stents coated or covered with silicone were less uniform showing a decrease of reactive changes in some experiments [11,12,14], while leading to stent occlusion in others.[15] A few clinical studies with prototype stents coated or covered with polyurethane showed promise in prevention of tumor ingrowth into the stent and all investigators called for an improvement of stent covering.[16-18]

We explored a biomaterial- small intestinal submucosa (SIS) as stent cover for potential biliary use. SIS is a relatively acellular, collagen-rich, degradable biomaterial harvested from pig small intestines. It is resistant to infection, does not produce an adverse immunologic response and is remodeled and replaced by host tissue.[19-26] SIS has been successfully used on grafting arteries[19-21], veins[22], and in the defects of the urinary bladder[23,24], diaphragm[25], tendon[26], fascia[27], and abdominal wall.[28]

Material and methods

Animals

Six young domestic swine weighing from 26 Kg to 28 Kg underwent SIS covered stent placement into the common bile duct. The study was approved by the institutional animal care and use committee of Oregon Health Science University in accordance with the guideline established by the Animal Welfare Act.

Covered stents

Single Gianturco-Rösh type Z-stents were used (Figure 1). They were hand-made in our research laboratory of 0.075-inch stainless steel wire and consisted of six legs. They were

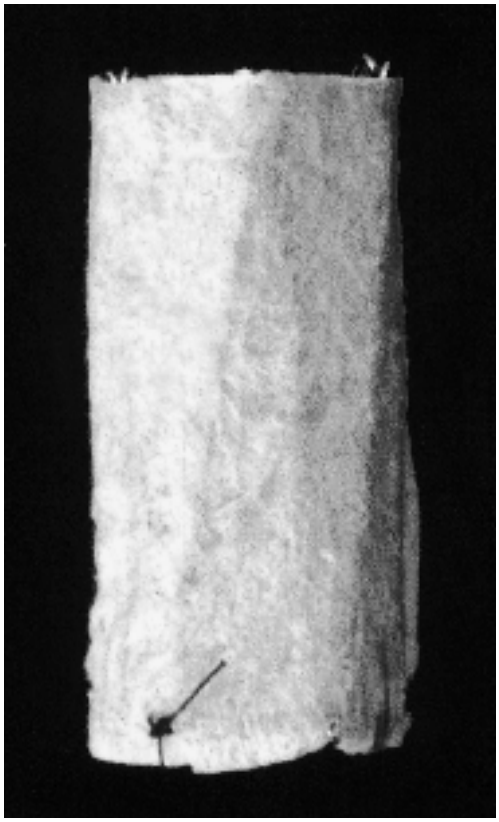


Figure 1. Biliary endograft. A single Z-stent 6-mm in diameter covered with lyophilized dry small intestinal submucosa-sheet.

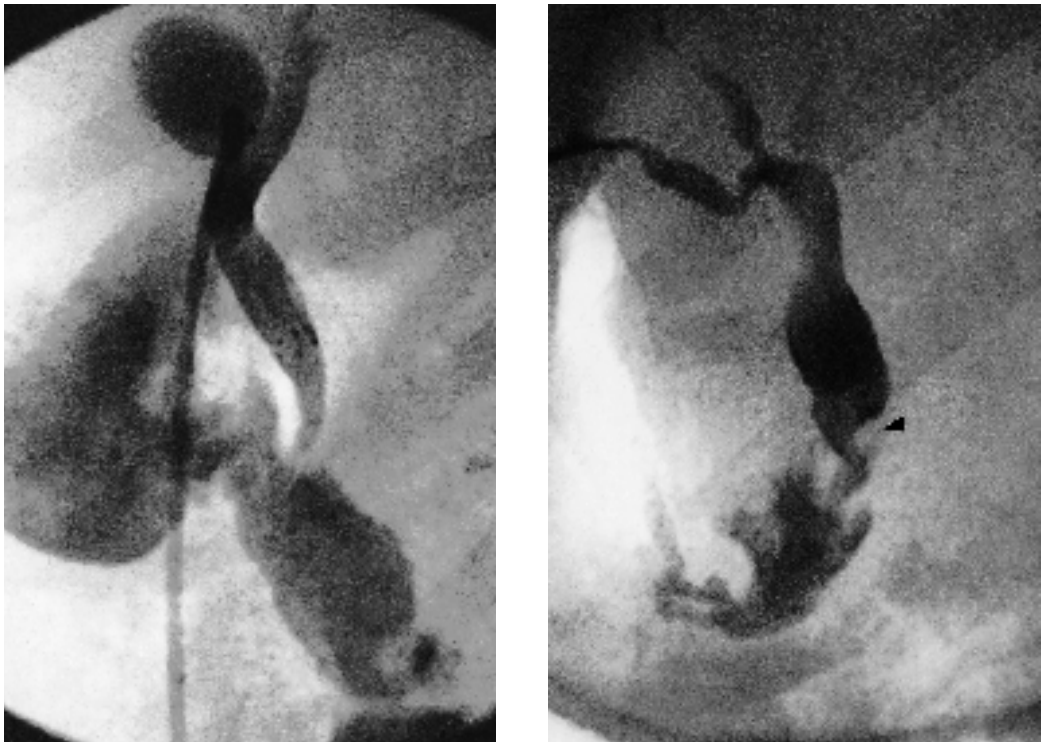


Figure 2a-b. Placement of SIS endograft in the common bile duct. (a) Cholangiography immediately after endograft placement. (b) Cholangiography at 8 weeks before sacrifice shows slightly dilated common bile duct. The stent turned sideways (arrow), and a defect corresponding to mucosal hyperplasia is seen in the bile duct wall where the stent end was located (arrow head).

11 mm long and 6 or 7 mm in diameter, depending on the size of the swine common bile duct. The stent cover was cut out of a 0.1 mm thick, dry SIS-sheet (Cook, Biotech Inc, Lafayette, IN). The sheet was cut to match the stent length and diameter and was rolled into a tube that was wrapped around the outside of the stent and attached to it at both ends with 7-0 polypropylene (Prolene, Ethicon Inc, Somerville, NJ).

Stent placement

Each animal was tranquilized with 1.5mL tiletamine hydrochloride, intubated and maintained with 2% isoflurane and 2L/min O_2. After a small central incision of the abdominal wall just below the sternum, the gallbladder was mobilized with forceps, and the tip of its fundus was pulled up to the central incision. There, it was punctured with an 18G needle, and a 0.035-inch guidewire (Roadrunner, Cook Inc, Bloomington, IN) was advanced through the cystic duct into the common bile duct. A 4-F catheter was then advanced over the guidewire into the common bile duct. After the Roadrunner guidewire was exchanged for a 0.035-inch Super-Stiff guide wire (Medi-Tech/Boston Scientific, Watertown, MA), a 5-F vascular sheath was inserted over the wire deep in the common bile duct. Cholangiography was performed using the sheath for injection. The 5-F sheath was also used for stent placement into the common bile duct between the ampulla and entrance of the cystic duct. The stent diameter was selected to be about 1-1.5 mm

larger than the diameter of the common bile duct. Altogether 9 single stents were implanted in 6 animals. Four animals received six stents of 6 mm in diameter, two receiving one stent and two receiving two stents. The other two animals received three stents with the diameter of 7 mm, one receiving one stent and the other two stents. When two stents were placed into the common bile duct, they were separated only by a few millimeters.

After the placement of stents, a cholangiogram was repeated and the sheath was removed (Figure2a). After the puncture site in the gallbladder was sutured, the gallbladder fundus was pulled up to the incision and secured to the inner abdominal wall. A metallic ring was then sutured together with the secured gallbladder fundus. This ring facilitated the identification of the fixation area for fluoroscopically guided percutaneous puncture for follow-up cholangiography.

Follow-up

Animals were followed up for a maximum period of 10 weeks with a plan to sacrifice two animals at each 4, 8 and 10 weeks after stenting. Cholangiography was obtained at the second weeks of follow-up and at the sacrifice or immediately after death. The two-week cholangiography was performed percutaneously using a 21-G needle. The terminal cholangiogram was performed by the same method as during the original stent placement. A 4-F catheter was inserted into the common bile duct through the gallbladder and cystic duct under general anesthesia. Cholangiography was then performed (Figure 2b). Euthanasia was carried out with a solution of pentobarbital and phenytoin sodium (Euthasol, Delmarva Lab, Inc., Midlothian, VA).

Histology

Segments of the bile duct proximal and distal to the stent, as well as at the center of the stent were placed in neutral-buffered zinc formalin. After a minimum of 24 h of fixation, the specimens were further sectioned into tissue cassettes, processed through alcohol and xylene, and embedded in paraffin. Five-micron paraffin sections were cut and stained with hematoxylin and eosin, or with Masson's trichrome stain.

Results

Stent deployment and clinical course

Stents were successfully placed in the common bile duct in all animals. The diameter of the stented common bile ducts ranged from 5.0 mm to 5.5 mm (mean, 5.3 mm) before stent placement. Stents with a diameter 1-1.5mm larger than the common bile duct remained in place during the initial study. During the follow-up, none of the animals developed jaundice. One animal developed ileus caused by a gauze pad left in the peritoneal cavity during initial laparotomy and died 16 days after stenting. Five animals were doing well, eating and gaining weight, and were sacrificed at the planned intervals of 4 weeks (n=1), 8 weeks (n=2), and 10 weeks (n=2) after stenting.

Cholangiography

The two-week percutaneous cholangiography was successfully performed in 4 out of 6 animals. In the other two animals, it was abandoned because of the failure to enter the gallbladder. One of these two animals, however, died 2 days later and cholangiography was performed immediately after death. Therefore, cholangiograms were obtained at approximately 2 weeks in five animals with 7 stents. They showed good patency and normal size of the stented common bile duct. Three stents remained in their original site of placement. Four stents slipped distally. There was no defect suggesting mucosal hyperplasia in any stent. Two stents in one animal could not be evaluated.

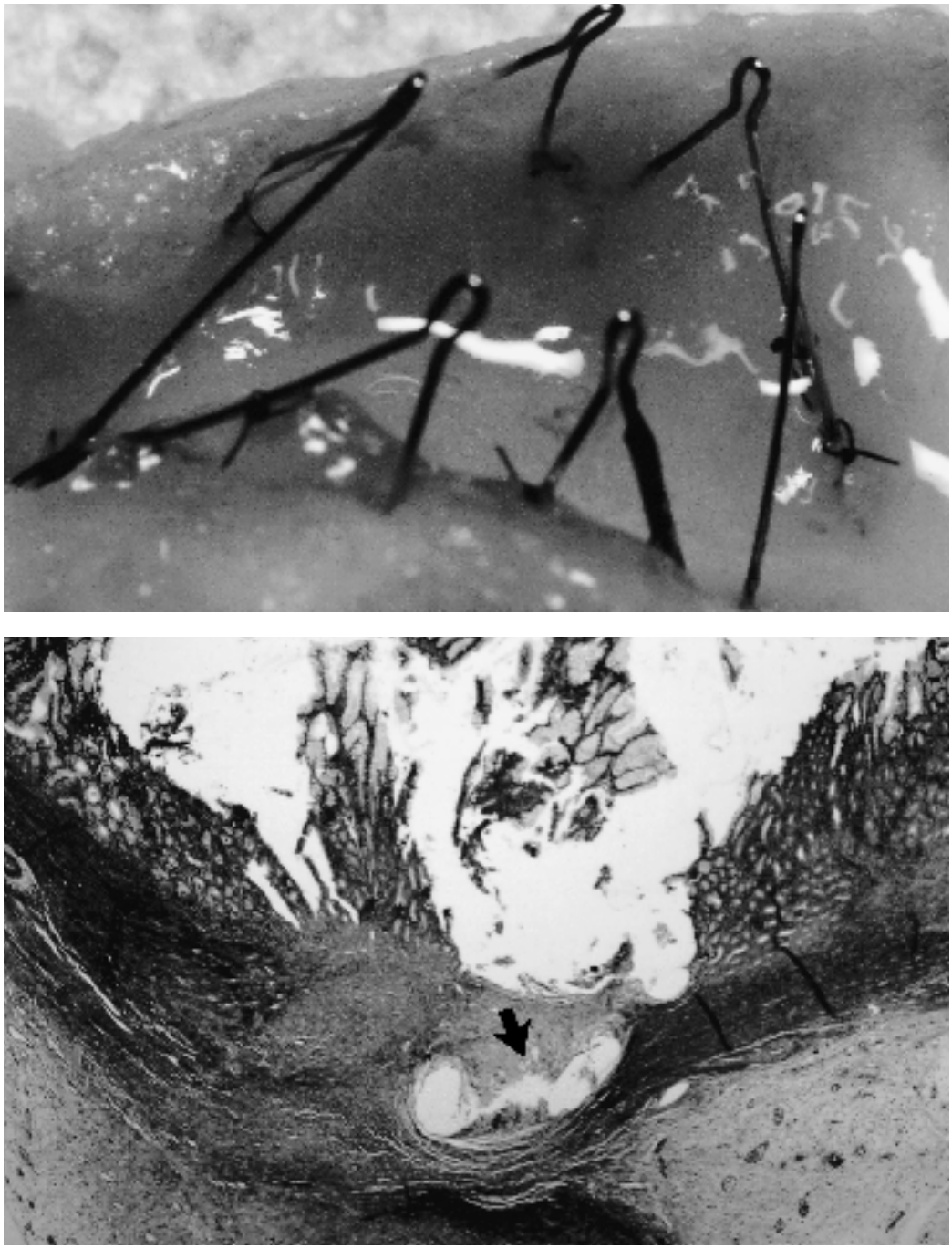


Figure 2c-d. (c) Explanted bile duct after 8 weeks after stenting. The stent ends of the sideways turned stent are embedded in the bile duct wall. (d) Photomicrograph of common bile duct wall in area of the stent. The defect in the wall was caused by two stent struts (arrow). Their mucosal hyperplasia and the adjacent wall show slight compression atrophy. [Masson Trichrome, 25x original magnification]

The four week follow up cholangiogram done in one animal showed well patent normal sized common bile duct with stent remaining in its original place. A smooth small defect suggesting mucosal hyperplasia was found at the distal end of the stent. The eight-week cholangiograms done in 2 animals showed slightly enlarged and well patent common bile ducts. All three stents were found dislodged from their original place, turned sideways and laying across the common bile duct. There were defects, which were considered to be mucosal hyperplasia at the bile duct wall where stents turned sideways (Figure 2b). The ten-week cholan-

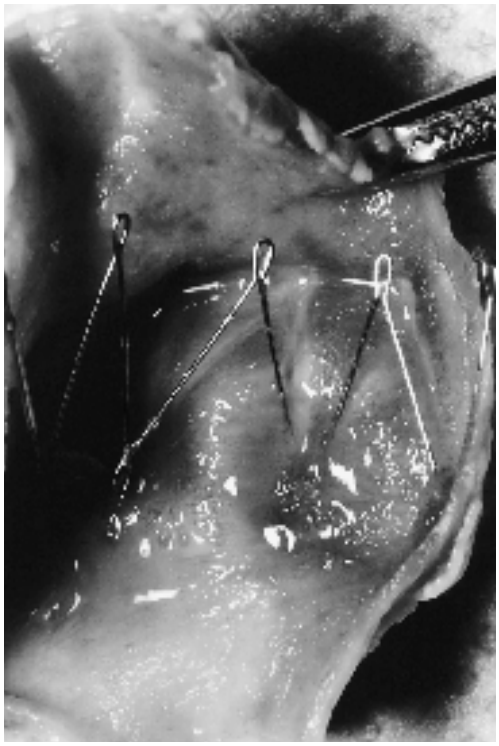
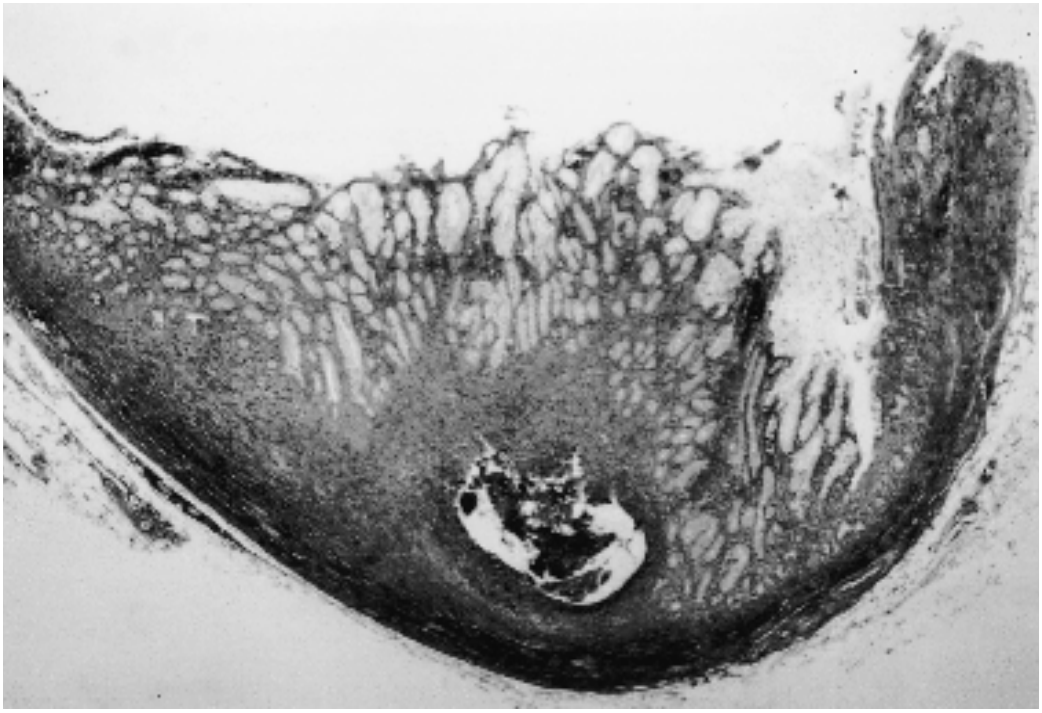


Figure 3a-b. Biliary endograft ex-vivo 4 weeks after placement in the common bile duct. (a) Dissected bile duct specimen shows partially embedded distal end of the Z-stent without SIS-cover in the bile duct wall. (b) The defect at the base of the mucosa corresponds to the location of a stent strut. There is mild inflammation and hyperplasia of the overlying biliary mucosa. [Hematoxylin & eosin, 25x original magnification]



giograms in two animals showed common bile duct dilation and some defects from sludge formation around the stents. Two stents in one animal were turned sideways. In the other animal, one stent stayed in its original position while the other was dislodged distally from the original site of placement. Mucosal hyperplasia was not evaluated cholangiographically because of associated bile sludge.

Histological study

Macroscopically, the SIS sheet covering the stent was identifiable at 2 weeks. Its color turned from white to blackish green, consistent with bile staining. After 4 weeks, the SIS-sheets were not grossly nor microscopically detectable (Figure 3a,b). The two stents, which did not dislodge at 2 and 10 weeks, had intact bile duct mucosa with no apparent hyperplasia (Figure 4a). In the third stent, which had not dislodged for 4 weeks, there was mild mucosal hyperplasia at the distal end (Figure 3a). Beneath this mucosa, there was a localized foreign body-type inflammatory reaction to the stent strut (Figure 3B). Mucosal proliferation was observed adjacent to the stents that had turned sideways (Figure 2c,d); in no case did the hyperplasia significantly narrow the duct lumen. In the stent dislodged distally, the bile duct wall was normal and no mucosal hyperplasia was seen. (Figure 4a,b).

Discussion

For the evaluation of the function and biological response of SIS covered metallic stents in the swine biliary system, only the data from four (45%) stents which remained in the longitudinal position in the common bile duct can be used. Three of them remained in the original position and one slipped distally from the original position. Their average implantation time in the common bile duct was 6.5 weeks with the range from 2 to 10 weeks. Only in these 4 stents, SIS cover was continuously in contact with the common bile duct mucosa and exposed to bile flow. SIS cover prevented focal denudation and reactive proliferation of the mucosa, inflammation in the submucosa, and narrowing of the bile duct lumen often seen after the placement of bare, non-covered stents.[15,29] SIS cover helped to decrease the foreign body-type inflammatory response to Z-stents and, of these four stents, only one showed mild inflammation and mild mucosal hyperplasia of overlying mucosa in a focal area of distal struts. There was no narrowing of common bile duct lumen; on the contrary, a slight, common bile duct dilatation developed at 10 weeks. At four weeks and later, the SIS cover was not microscopically detectable. Whether the membrane simply dissolved or was incorporated into the duct wall as a result of tissue remodeling remains unclear. It is interesting that even after 10 weeks of stenting when SIS membrane was no longer detectable the Z-stent wires did not cause a significant reaction. Whether hyperplasia and obstruction develop at a later time remains to be tested.

Five stents (55%) which dislodged from their original position and turned sideways across the common bile duct caused mucosal proliferation in the wall adjacent to the struts at their ends. This mucosal proliferation, however, was only mild and did not cause significant narrowing of the common bile duct lumen. The type, size, and smooth surface of SIS covered stents, absence of reactive changes in common bile duct wall together with rapid growth of animals must be considered as the main causes of frequent stent dislodgment found in our animals. Single Z-stents used in our animals have a tendency to jump off of the catheter during delivery and remain unstable after their placement, unless their diameter is significantly larger than the lumen of the stented structure. We selected only the stents that were about 15% larger

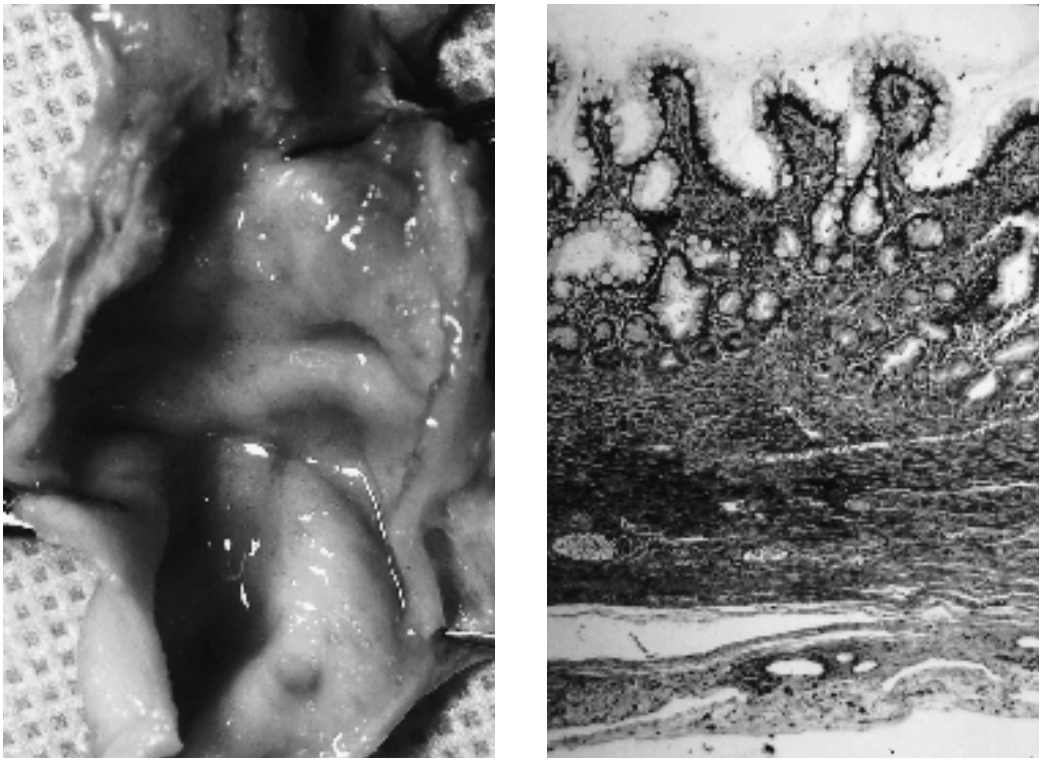


Figure 4a-b. Specimen and low power photomicrograph of common duct wall after 10 weeks of stenting. (a) Dissected bile duct after stent removal demonstrates intact mucosa. (b) The biliary mucosa is intact and shows only mild chronic inflammation. [Masson Trichrome, 200x original magnification]

than the common bile duct diameter. Yet, that was not sufficient in the fast growing animals. For future work, we plan to use larger double body Z-stents which are more stable at the delivery and after the placement. Tendency for migration of covered or coated stents with their minimized surface friction and minimal reactive changes in the duct mucosa, however, will be always a problem, particularly with their use in a nonstenotic duct.

Even when our study is limited in scope, it showed promise of SIS cover for biliary stenting. It showed that SIS is biocompatible and helps to decrease the foreign body-type inflammatory reaction to metallic stents. Further detailed study will be necessary to confirm our initial results and particularly evaluate long term effect of SIS covered stents. For our study we used a dry form of SIS which has several disadvantages, particularly difficulty in attachment and suturing to the stent base. It is also fragile and may break during catheter delivery. For future work we plan to use most recently available and improved wet form of SIS which can be easily and safely attached to the stent, does not leak and can be easily introduced through a catheter.

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Radiol Oncol 2001; 35(1): 11-6.

Diagnostic imaging of hypertrophic pyloric stenosis (HPS)

Marija Frković, Marina Šeronja Kuhar, Željka Perhoč, Vinka Barbarić-Babić, Melita Molnar, Jurica Vuković

Clinical Institute for Diagnostic and Interventional Radiology, Clinical Hospital Centre Zagreb - Rebro, Croatia

Background. *Imaging of the abdomen in children with suspected hypertrophic pyloric stenosis has been traditionally performed by plain film radiography and upper gastrointestinal contrast studies. In many clinical situations, this approach has been modified or replaced by ultrasound examination. The authors aimed to analyse the value of diagnostic algorithm in children with hypertrophic pyloric stenosis confirmed at surgery in our hospital.*

Patients and methods. *The authors made a five year retrospective review of hospital records of all children operated on for HPS in Clinical Hospital Centre Zagreb - Rebro and found out that 14 boys, between 2 (17 days) and 10 weeks of life (75 days) underwent surgery due to HPS.*

Results. *Specific radiographic signs were: string sign, double track sign, elongation and narrowing of pyloric canal, mushroom sign, gastric distension with fluid and beak sign. Ultrasound was performed in 9 patients, one of them was false negative (sonographer admitted that he had no experience), the rest were positive.*

Conclusions. *If the physical examination is negative or equivocal, sonography by an experienced sonographer must be performed. If the ultrasound finding is negative, than the infant should undergo to barium upper gastrointestinal studies (UGI). If HPS isn't a primary diagnostic question, it's better to perform UGI first in order to make a correct diagnosis.*

Key words: pyloric stenosis - radiography - surgery; hyperthrophy; child

Introduction

Hypertrophic pyloric stenosis (HPS) is actually idiopathic hypertrophy and hyperplasia of the circular muscle fibers of the pylorus with proximal extension into the gastric antrum.[1] The cause of HPS remains unknown. HPS is inherited as a dominant polygenic trait. Some authors reported even familial occurrence of HPS in twins.[2] This, however, was rather an acquired than congenital condition.[1] Others presented an example of "secondary" HPS in a patient with

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Correspondence to: Marija Frković, M.D., Ph.D. radiologist, Clinical Institute for Diagnostic and Interventional Radiology, Clinical Hospital Centre Zagreb - Rebro, Kišpatićeva 12, 10000 Zagreb, Croatia; Phone: +385 1 238 84 54; Fax.: +385 1 233 37 25; e-mail: marijan.frkovic@zg.tel.hr

prostaglandin - induced foveolar hyperplasia of antrum.[3]

Recently, it has assumed that, in some cases, HPS is caused by Helicobacter pylori.[4] The latest research supports the hypothesis of a selective immaturity of the enteric glia in the muscular layers of infantile HPS.[5]

Hypertrophic pyloric stenosis is the most common acquired obstruction of the young infant. It is more common in boys than girls, by a 5:1 ratio and develops usually between the second and eighth weeks of life.

The clinical features of bile-free progressive projectile vomiting, visible gastric peristaltic waves, and an olive shaped palpable abdominal mass in the right upper quadrant are frequently diagnostic. Depending on how long symptoms have been present, little patients may present with dehydration and hypokalemic alkalosis, irritability, weight loss, and failure to thrive.

Plain film radiography has no role in the diagnosis of pyloric stenosis. Massive gastric distension (>7 cm diameter) is seen commonly in other conditions and is not at all specific. If the child vomits before the filming, the gastric distension may be relieved.

For *barium upper gastrointestinal studies* (UGI), we must empty gastric contents via nasogastric tube before and after the study due to a high incidence of reflux in these patients. Positive fluoroscopic and radiographic signs include elongated pyloric canal (string sign), antral beaking, pyloric teat, flattening of the prepyloric area of the lesser curvature (shoulder sign), and usually active gastric hyperperistalsis (caterpillar sign). Sometimes a double or triple column of barium is present as two or three parallel lines (double/triple track sign) caused by the crowding of mucosal folds in the pyloric canal. The base of the bulb can be indented by thickened shoulder of pyloric muscle (mushroom sign). Delayed gastric emptying is the least reliable indicator of HPS and can be seen with pylorospasm, gastric hypotonia, sepsis and ileus.

The ultrasound (US) examination is performed with the patient in the supine, and later, in the right lateral decubitus position. Overlying bowel gas or gastric distension may occasionally hinder the sonographic diagnosis of HPS. To resolve this problem, a novel approach for obtaining posterior views of the pylorus was reported.[6]

Ultrasound examination of the pyloric region includes both transverse and longitudinal images of the pylorus. The most common measurement used is *pyloric muscle thickness* obtained with transverse scanning of the pylorus. The muscle is usually hypoechoic, but it can have a nonuniform pattern.[7] The muscle appeared to be more echogenic in its near and far fields and less echogenic on its sides due to anisotropic effect which is related to the orientation of the ultrasound beam with respect to the circular fibbers of the pyloric muscle. The *transverse pyloric diameter*, including the lumen and both walls of the pylorus, is less frequently measured. The *pyloric canal length* (echogenic) may be measured, and is shorter than the surrounding *pyloric muscle length* (hypoechoic structures). Several different pyloric muscle indices also have been used to detect HPS.[8-10]

There has been disagreement as to the exact measurements to be used for pyloric stenosis. Authors have published different numbers for these different measurements.[11-13]

Dähnert [1] suggested, that pyloric muscle thickness >=3 mm, transverse pyloric diameter >=13 mm with pyloric canal closed and pyloric canal length >=17 mm are diagnostic of HPS.

Other sonographic signs are: "target sign" (hypoechoic ring of the hypertrophied pyloric muscle around echogenic mucosa centrally on cross-section), "cervix sign" (indentation of the muscle mass on the fluid-filled antrum on longitudinal section), "antral nipple sign"[14] (redundant pyloric canal mucosa protruding into the gastric antrum), exaggerated retrograde peristaltic waves and

delayed gastric emptying of fluid into the duodenum.

The authors aimed to analyse the value of diagnostic algorithm in children with hypertrophic pyloric stenosis confirmed at surgery in Clinical Hospital Rebro.

Patients and method

This is a retrospective review of hospital records of all children operated on for pyloric stenosis in Clinical Hospital Centre Zagreb - Rebro from 1st January 1995 to 31st December 1999. Fourteen infants underwent surgery due to hypertrophic pyloric stenosis during the period in question. They were all boys, between 2 (17 days) and 10 weeks of life (75 days).

UGI study was performed with 5-10 ml of diluted barium on Siemens Sireskop 3. Sonographic examination was performed in the standard supine and right lateral decubitus position, using a GE Logiq 400 scanner and 5.0-MHz convex traducer and 6.6-MHz linear traducer.

Results

Clinical findings in our patients are presented in Table 1.

In all infants, the radiological diagnosis was made on the basis of upper gastrointestinal series (Table 2).

Specific radiographic signs were: string sign, double track sign, elongation and narrowing of pyloric canal, mushroom sign, gastric distension with fluid and beak sign. Ultrasound was performed in 9 patients, one of them was false negative (the sonographer admitted that he has no experience), the rest were positive. Ultrasound signs and measurements were: target sign, transverse pyloric diameter, pyloric muscle wall thickness and pyloric canal length. All measurements were consistent with the diagnosis of HPS.

Table 1. Clinical symptoms and laboratory data

Clinical symptoms and laboratory data	No.
Bile-free projectile vomiting	14
Olive shaped muscular mass	2
Dehydration and hypokalemic alkalosis	9
Weight loss, failure to thrive	3

Table 2. Methods of imaging

No.	UGI	US
14	14 (100%)	9 (64%)

UGI= barium upper gastrointestinal studies; US= ultrasound examination

Discussion

Nowadays, the reliance on diagnostic imaging has been increasing.[15] During palpation performed by paediatrician or surgeon the infant must be calm; this is time consuming, and may even be impossible, if the stomach is distended. Some authors stated that the technique of palpating a pyloric mass became "a declining art".[16] Many publications on this subject stressed that the diagnosis often can be made by physical examination and that imaging procedures don't need to be routinely performed.[17-20] Only children with a negative or equivocal physical examination should go to ultrasonography. Currently, ultrasonography has replaced the upper gastrointestinal (UGI) examination as the method of choice for establishing the diagnosis.[21-23] US is more economical, there is no exposure to ionising radiation such as in UGI studies, and allows to follow up the patients, but it demands a highly experienced sonographer. It has also been reported that over-reliance on ultrasound scans only lead to negative explorations.[24]

There are also other opinions: that the UGI is less expensive than the US as the first strategy in the evaluation of the infant with sus-

pected HPS.[25, 26] An advantage of the UGI is that it has slightly higher sensitivity for pyloric stenosis than does US scan. UGI also provides definitive information in the evaluation of the vomiting infant regarding other potential diagnoses such as gastroesophageal reflux, malrotation and intestinal obstruction. If the clinical findings are doubtful, it is justified to perform UGI because of concomitant pathology. One of the papers presented the cases of pyloric stenosis associated with malrotation.[27]

In a recent publication, reporting of the attempts to develop a cost- and time-effective algorithm for differentiating HPS from other medical causes of emesis in infants, it is recommended that the child is given nothing by mouth for 3 to 4 hours before gastric aspiration. The aspirated volume >= 5ml implicated gastric outlet obstruction and ultrasonography was performed. If this examination was positive for HPS, the child was referred for surgery. If US was negative, upper gastrointestinal series were performed. The aspirated stomach contents volume <5ml suggested another medical cause of emesis; therefore UGI was performed.[28, 29]

In our hospital UGI was performed always on surgeon's request, even clinical and US findings were positive. Surgeon's trust and confidence in UGI versus US is changing very. They sometimes neglect the ionising radiation during UGI studies. On the other hand, because US is very operator -dependent imaging modality, false positive and false negative results can compromise this method. This is no wonder because HPS is rare pathology. An additional problem is that, in large centres like our hospital, we have no department of paediatric radiology.

Differential diagnosis of HPS after the imaging includes infantile pylorospasm in which the muscle thickness is between 1.5 and 3 mm. In this condition, antral narrowing is of variable calibre, gastric emptying is delayed, the pylorus is elongated, antral peristalsis is functioning. Muscle thickness or pyloric length measurements may overlap those accepted as positive for HPS. Image or measurement variability is an important clue for diagnosing pylorospasm.[30] Milk allergy and eosinophilic gastroenteritis can also mimic the clinical symptoms and US appearance of idiopathic HPS.[31] Eosinophilic gastro-enteritis is characterised by hypertrophy of the hypoechoic muscular layer and also thickening of the mucosal and submucosal layers of the pylorus. It is also helpful to search for thickening of the antral wall. The differential diagnosis for possible HPS encompasses several other gastrointestinal tract abnormalities, including gastroesophageal reflux, duodenal obstruction, and pyloric membrane, or webs. After the imaging we didn't have any differential diagnostic difficulties.

Treatment is surgical (pyloromyotomy). We follow up the operated children with US. Recently, some attempts have been made in the treatment with atropine sulfate; all infants were followed by sonography to observe the anatomical changes (shortening of the pyloric canal, followed by thinning of the muscular layer).[32, 33] We have no experience in such treatment. Our review of the literature suggests that this kind of treatment hasn't found general clinical acceptance.

The infant with symptoms that clearly suggests pyloric stenosis must be examined by an experienced physician prior to imaging. If the physical examination is negative or equivocal, sonography by an experienced sonographer must be performed.

If the US is negative, than the infant should go to UGI.

If HPS isn't primary diagnostic question, it's better to perform UGI first to establish the correct diagnosis.

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Computer systems for determination of pressure distribution in the hip joint articular surface: validation and results

Vlado Stankovski and Dragica Smrke

Department of Surgery, University Medical Centre, Ljubljana, Slovenia

Background. *In this work, we describe the computer systems Viprecox and Active Contours that are used in the process of realistic estimation of some biomechanical parameters of the hip joint, including the maximal value of the stress in the hip joint p_{max}. The computer system Active Contours uses standard anteroposterior radiographs of the whole pelvis and both hips for its calculations and Viprecox in its kernel uses a relatively simple three-dimensional mathematical model of stress distribution in the hip-joint articular surface which has been extensively described elsewhere (e.g. Iglič 1996).*

Material and methods. *Both state-of-the-art computer systems were tested by analysing the calculated values of p_{max} for 81 patients (37 males and 44 females).*

Conclusions. *In this way we prove that the described computer systems can be used for the determination of the contact stress distribution from standard AP radiographs.*

Key words: hip joint; biomechanics; computer systems; weight bearing

Introduction

Higher and unevenly distributed contact stress in the hip-joint is a risk factor for the development of arthrosis.[1,2,3] There are several biomechanical parameters that describe the distribution and the peak value of the stress in the hip joint, such as the gradient of the stress at different positions of the articular surface or the maximal value of the pressure on the articular surface of the hip joint $p_{\max}$. The realistic measurement or the estimation of these parameters would be helpful in exploring the incidence of degenerative joint diseases.

In this work, we describe the computer systems *Viprecox* and *Active Contours* that are used in the process of a realistic estimation of some biomechanical parameters of the hip joint including the value of the parameter $p_{\max}$. Our additional purpose is to test these *state-of-the-art* computer systems by analysing the calculated values of $p_{\max}$ for 81 patients (37 males and 44 females).

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Correspondence to: Assist. Prof. Dragica Smrke, Ph.D., M.D., Department of Surgery, Zaloška 2, SI-1000 Ljubljana, Slovenia; Phone: +386 1 543 1419; Fax: +386 1 231 6889; E-mail: dsmrke@hotmail.com

Materials and methods

The computer system Active Contours uses

standard antero-posterior radiographs of the whole pelvis and the both hips for its calculations (Figure1) and *Viprecox* in its kernel uses a relatively simple three-dimensional mathematical model of stress distribution in the hip-joint articular surface, which has been extensively described elsewhere.[4]

The system *Viprecox* was developed as a 100% pure Java application, which enables the compatibility with any platform that uses the Java Virtual Machine. In the process of design and application development the object-oriented paradigm was used. The use of the object-oriented programming technique will allow the system easy maintenance and upgrades, but it will also allow a conversion to other platforms.

The system *Active Contours* uses digitised profiles of standard antero-posterior radiographs of the pelvis and the both hips in order to extract the important data about the geometry of the both hips and the pelvis (Figure 1). These data are then transformed by using a non-homogeneous tailoring procedure[5] in order to prepare the input data for the three-dimensional mathematical model of stress distribution in the hip-joint articular surface.[4] For this purpose a reference model of the hip-joint musculature is used.[6]

As a result of the non-homogeneous tailoring procedure certain muscles' origin and insertion points are estimated. The reference muscles' origin points[6] on the pelvis and the reference insertion points on the femur were not corrected in the antero-posterior direction because of the lack of data. All other coordinates are corrected as follows:

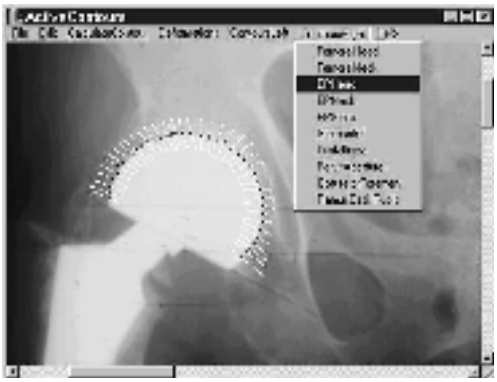

Figure 1. The system *Active Contours*: detection of points that lie on the contour of the endoprosthesis head.

The reference origin points on the pelvis for all muscles were corrected in the medio-lateral direction by using the ratio C/C_{ref}, where C is the distance between the sagital plane passing through the femoral head centre and the most lateral point on the pelvis. The system *Viprecox* automatically measures this point. C_{ref} is the corresponding distance in the model of Dostal and Andrews[6] $C_{ref}=(B_{ref}-L_{ref})/2$. The insertion points on the femur are divided into three groups: 1. m. gluteus medius and m. gluteus minimus, 2. the lateral point of m. piriformis and 3. the inferior points of m. tensor fasciae latae and m. rectus femoris. The system *Viprecox* automatically measures the Cartesian coordinates of the insertion points of the gluteus muscles in the frontal plane from the digitised antero-posterior radiographs. The insertion point of m. piriformis lies laterally and was therefore corrected only its medio-lateral coordinate by using the ratio between the already corrected medio-lateral coordinates of the gluteus muscles and the corresponding reference values. The distance L between the two centres of rotation of both hips was taken as automatically measured by the system *Viprecox*.

After such non-homogeneous tailoring procedure the prepared data are presented to the mathematical model of the hip-joint.[4] In this way the maximal pressure on the hip joint articular surface p_{max} is calculated.

Results and conclusions

Figure 2 shows the calculated hip joint contact stress for a patient with implanted hip endoprosthesis (for the other healthy side). In order to establish the clinical relevance of the

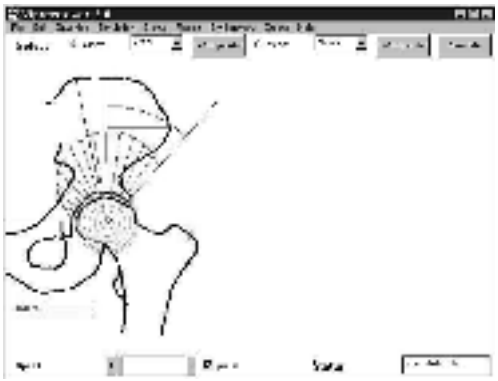

Figure 2. An example of distribution of the stress on the hip joint articular surface graphically presented by the system *Viprecox*.

parameter p_{max} the computer system should be applied to various populations of patients where the correlation between the clinical status and the hip stress may be studied. Recently, these systems have been used in order to determine the peak contact stress in the articular surface of the hip joint from standard AP radiographs for 37 male and 44 female healthy hips of patients subject to trauma of the other hip (Figure 2). It was shown that the peak contact stress is considerably higher (cca 20%) ($p<0.00005$) in the female population (1.99 MPa) than in the male population (1.63 MPa). These results are in favour of the hypothesis that the increased hip joint contact stress in the female population could contribute to the greater incidence of arthrosis in the female population relative to the male population.

To conclude, the described computer systems *Active Contours* and *Viprecox* can be used for the determination of the contact stress distribution from standard AP radiographs. The systems can be applied in the clinical practice to predict an optimal stress distribution in different operative interventions in the hip and to analyse the short and long term outcome of the treatment of various conditions of the hip.

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Ultrasonography of pleural effusion: the quantification of minimal detectable volume

Alan Šustić[1], Igor Medved[2], Dražen Kovač[3], Nikola Ivaniš[4], Darko Ekl[2], Ognjen Šimić[2]

[1]Dept. of Anaesthesiology and ICU, [2]Dept. of Surgery, [3]Dept. of Pathology, University Hospital Rijeka, Croatia, [4]Private ultrasound laboratory, Rijeka, Croatia

Background. *The aim of this study was to establish a minimal volume of free thoracic fluid in the pleural space of the supine cadaver detectable by ultrasonography.*

Material and methods. *A prospective study with an experimental model on 20 cadavers (10 male, 10 female; age 66 ±11 yr.; height 172 ±9 cm; weight 75 ±12.6 kg; body surface area (BSA) 1.87 ±0.2 m^2) was used. Each cadaver was punctured bilaterally in 5^{th} or 6^{th} intercostal space at the medioclavicular line with venous cannula infusing in NaCl 0,9% solution at randomised speed in the chest. During the procedure the laterodorsal part of the thoracic wall next to the pulmonal base and phrenicocostal sinus was ultrasonographically scanned. At the moment of the visualisation of anechogenic line pertaining to the free fluid between dorsal thoracic wall and lungs, the installation was stopped and the amount of injected fluid verified.*

Results*. Minimal, by ultrasonography detectable amount of free fluid in the right pleural space was 223±52 ml with the significant positive correlation to height ($r = 0.69$; $p < 0.001$), weight ($r = 0.68$; $p < 0.01$) and the BSA ($r = 0.71$; $p < 0.001$) of cadaver. Detectable volume in the left pleural space was notably smaller than contra lateral, namely 172±53 ml also with a significant correlation to the cadaver's height ($r = 0.55$; $p < 0.05$), weight ($r = 0.59$; $p < 0.01$) and BSA ($r = 0.60$; $p < 0.01$).*

Conclusions. *The authors affirm that ultrasonographically detectable quantity of free fluid in the chest positively correlates with height, weight and BSA of cadavers, and that the measured amount in the supine position is approximately 223 ml for the right space versus 172 ml for the left pleural space.*

Key words: pleural effusion, ultrasonography, quantification.

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Correspondence to: Alan Šustić, M.D., Ph.D., Dept. of Anaesthesiology and ICU, Clinical Hospital Rijeka, T. Strižića 3, Rijeka 51000, Croatia. Phone: + 385 51 21 84 07; Fax: + 385 51 21 84 07, E-mail: alan.sustic@mamed.medri.hr

Introduction

The diagnosis of pleural effusion in critically ill patients frequently presents a serious problem. Transportation risks, the uncoordinated co-operation and difficulties in adequate positioning of those patients in the intensive care unit (ICU) make radiological

methods often inadequate or unperformable.[1,2] Ultrasonography provides a rapid, convenient, economic and bedside method for detecting pleural effusion in supine patients.[3-6] Meanwhile, there are no data in the pertinent literature, which could suggest what the minimal is, by ultrasonography detectable fluid volume in the pleural space. The aim of our study was to establish the smallest, by ultrasonography visible amounts of fluid in the cadaver (human body) in the supine position.

Materials and methods

An experimental model with 20 cadavers (10 male and 10 female; age 66 ±11 yr.; height 172 ±9 cm; weight 75 ±12.6 kg; body surface area (BSA) 1.87 ± 0.2 m^2) was used. Each cadaver was punctured bilaterally in 5th or 6th intercostal space at the medioclavicular line with venous cannula (1.5 mm x 44 mm; maximal possible flow of 142 ml/min) infusing in the pleural space NaCl 0.9% solution at randomised speed. During the whole procedure the laterodorsal part of the thoracic wall next to the pulmonal base and phrenicocostal sinus was ultrasonographically scanned. The lungs of the cadavers were not insuflated. At the moment of the first visualisation of anechogenic line pertaining to the free fluid between the dorsal thoracic wall and lungs, the installation was stopped and the amount of injected fluid verified. All cadavers were examined in the supine position by the same physician using portable scanner Hitachi 405 EUB with a 3.5/5 MHz narrow convex transducer (Hitachi Medical Corporation, Tokyo, Japan). The ultrasonographer was not previously informed about the chosen velocity of infusion flow and the volume infused. Average minimal detectable quantity of fluid in the left and right hemi thorax was compared and correlated with height, weight and BSA of each cadaver. A statistical method was Mann-Whitney U test and Pearson's moment of correlation.

Results

Minimal, by ultrasonography detectable amount of free fluid in the right pleural space was 223 ± 52 ml (range: 105 - 295 ml) with significant positive correlation to height ($r = 0.6849$; $p < 0.001$), weight ($r = 0.6799$; $p < 0.01$) and the BSA (Figure 1) of cadaver ($r = 0.7075$; $p < 0.001$). Minimal detected volume in the left pleural space was notably smaller ($p < 0.001$) than contra lateral, namely 172 ±53 ml (range: 80 - 240 ml) also with a significant correlation to the cadaver's height ($r = 0.5532$; $p < 0.05$), weight ($r = 0.5886$; $p < 0.01$) and BSA ($r = 0.6042$; $p < 0.01$) (Figure 2).

Discussion

The clinical routine in the diagnosis of pleural effusions uses a conventional posterior to anterior (PA) chest radiography in the erect or high sitting position (≥45°) or a lateral decubitus radiography (LDR) where patients are in lying position. Both radiographic methods in standard hospital conditions have satisfac-

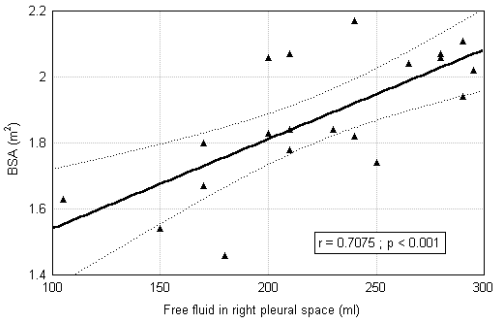

Figure 1. Correlation between the cadavers body surface area (BSA) and minimal, by ultrasonography detectable amount of free fluid in the right pleural space. Solid line: regression line; dotted lines, 95% confidence interval.

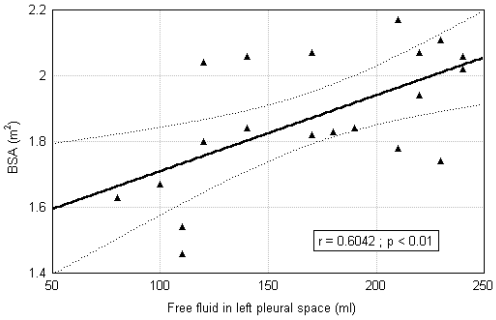

Figure 2. Correlation between the cadavers body surface area (BSA) and minimal, by ultrasonography detectable amount of free fluid in the left pleural space. Solid line: regression line; dotted lines, 95% confidence interval.

tory accuracy, however, in the ICU setting where the quality of radiograph is sub optimal and where adequate positioning of the patient is impossible, the sensitivity of those methods in the detection of minor effusions is not convincing.[1,2] A computed tomography is often used in the diagnosis of pleural effusions (quantitative and qualitative), but it is connected with the transport of patients from ICU and is not always available in all hospitals.[1,2]

Recently, ultrasonography has been recognised as a superior method in the diagnostics of pleural effusions in the supine position, particularly in critically ill ICU or trauma patients.[4-6]

In the presented study, average minimal, by ultrasonography detectable, fluid volume in the right pleural space was 223 ml, while the mean volume of fluid in the left pleural space was 172 ml. Such discrepancy is probably due to the position of cardiac massive, which is situated predominately in the left hemithorax. Classic anatomical studies confirm that the transversal diameter of the lung base is significantly smaller on the left side (7-9 cm left *vs.* 10-13 cm right); that the left lung is smaller than the right and consequently, the overall volume of the left hemithorax is smaller than the overall volume of the right hemithorax.[7] It follows that the required quantity of pleural fluid necessary for the ultrasonographic visualisation in the left thorax is much smaller than on the right side.

In the study a statistically significant correlation between the minimal detectable volume of pleural effusion and cadaver's height, weight and BSA was demonstrated.

It is logical to presume that in more corpulent patients with greater BSA more liquid will be needed to diagnosticate pleural effusion by ultrasonography. It is important to point out the great variability in the amount of minimal detectable fluid in the thorax between cadavers varying from 160 ml on the left side to over 190 ml on the right side. Such large range together with a significant correlation between a minimal detectable volume of fluid in the thorax and cadaver's height, weight and BSA, shows that in clinical preconditions negative ultrasound findings do not exclude the presence of a small pleural effusion. Such findings should be interpreted in the context of all available information about the patient's habitus.

However, this study has an important deficiency. First, data of a cadaver study cannot be quite transferable to the clinical examination of patients (respiratory effects, lung compliance, etc.). Furthermore, in clinical conditions it is usually possible to position a patient to a half-sitting position. It is presumable that such movement, difficult to perform on cadavers, could influence on the delectability of fluids.

On the basis of the results from the experimental, cadaveric model it can be concluded that ultrasonography enables the visualisation of relatively small amount of pleural fluid in patients in the supine position, but negative finding does not exclude minimal effusion.

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review

Bone scintigraphy in clinical routine

Vika Müller[1], Jörn Steinhagen[2], Maike de Wit[3], Karl H. Bohuslavizki[1]

Departments of [1]Nuclear Medicine, [2]Orthopedic Surgery and [3]Hematology and Oncology, University Hospital Eppendorf, 20246 Hamburg, Germany

Background. *In 1971, bone scintigraphy was performed the first time using ^{99m}Tc-labeled polyphosphonates. Since that time, bone scintigraphy has become one of the most frequent diagnostic procedures in nuclear medicine departments. However, in the last decade, indications for this skeletal imaging procedure have been changing continuously. This paper, therefore gives a concise review of the current spectrum of indications for bone scintigraphy and its realization.*

Conclusions. *Just as many other nuclear medicine procedures, the bone scintigraphy has a high sensitivity, and the changes of the bone metabolism are seen often earlier than the changes in bone structure developing after x-ray. Therefore, occult lesions in the whole skeleton might be detected early by bone scintigraphy. On the other hand, bone turnover is increased in various bone diseases. Consequently, bone scintigraphy usually has a low specificity, and differential diagnosis of the underlying etiology is often not feasible. However, three-phase bone scintigraphy and SPECT can significantly increase the specificity in some skeletal areas.*

Key words: Bone diseases-radionuclide imaging; technetium; diphosphonates; bone neoplasms; bone scintigraphy, ^{99m}Tc-diphosphonates, indications

Introduction

Since 1961 bone turnover has been examined using various radio-labeled substances. In 1971 bone scintigraphy was performed the first time using modern ^{99m}Tc-labeled polyphosphonates, e.g. ^{99m}Tc-hydroxyethylenephosphonate(HDP) or ^{99m}Tc-methoxyethylenephosphonate (MDP). After intravenous injection, these radiopharmaceuticals are adsorbed at the bone surface within some hours. The amount of adsorption depends both on the perfusion of the bones and the intensity of bone metabolism. Moreover, bone-seeking radiopharmaceuticals are excreted by the kidneys, and the kidneys and bladder can be seen routinely on a bone scan. Thus, total bone uptake depends not only on the perfusion and metabolic turnover, but also on renal function. In regions with a high bone metabolism, e.g. epiphyseal plates of children or mechanically stressed regions, e.g. ileosacral

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Correspondence to: Karl H. Bohuslavizki, MD, PhD, Department of Nuclear Medicine, University Hospital Eppendorf, Martinistr. 52, D-20246 Hamburg, Germany. Phone: +49 40 42803 4047; Fax: +49 40 42803 6775; E-mail: bohu@uke.uni-hamburg.de

joints, the radiopharmaceutical uptake is increased physiologically. Additionally, in several pathophysiological conditions, even extraskeletal accumulation of tracer can be seen, e.g. in scars, myositis ossificans, liver metastases or tumors.[1-3] On the other hand, fat patients (high absorption of radiation) and patients with renal failure show a reduced bone-to-background contrast resulting in degraded images.

Since the first bone scans using ^{99m}Tc-labeled polyphosphonates by Subramanian and Mc Affee[4] in 1971, the radioactive load has decreased continuously for the patient due to radiopharmaceutical and technological advantages, and bone scintigraphy has become a routine method in clinical nuclear medicine. However, in the last decade, the indications for bone scanning have changed dramatically. Therefore, the current spectrum of indications for bone scintigraphy and its realization are reviewed concisely in this paper.

Indications in benign bone diseases

In inflammatory joint diseases, both soft tissue and bone metabolism can be affected. The three-phase bone scintigraphy can image the activity of both processes. Increased perfusion, higher blood pool and raised activity of osteoblasts may be demonstrated by bone scan. Moreover, bone scan may contribute to the differential diagnosis of rheumatical joint diseases due to specific distribution patterns of several joint affections.

Fractures are seen primarily in radiographic images. Nevertheless, fractures in radiographically unclear regions can be excluded sufficiently by bone scintigraphy, and bone scanning also allows establishing the vitality of bone grafts or the loosening and infections of prostheses.

Current clinical indications for bone scintigraphy in benign bone diseases are listed in Table 1.

Table 1. Bone scanning in benign bone diseases

Disease	To be mentioned
Osteomyelitis	In 3-phase bone scintigraphy, the activity of the process and other bone lesions can be seen early in acute osteomyelitis.[9-11] In newborn the sensitivity is as low as 50 %.[1,2] In children with acute osteomyelitis MRI has the highest sensitivity (90%).[12] In diabetic foot, 3-phase bone scintigraphy should be first in the diagnostic cascade.[13] However, 3-phase bone scintigraphy is sensitive but not specific in osteomyelitis of diabetic foot.[14]
Evaluation of prostheses	Normal 3-phase bone scintigraphy excludes infection or loosening of hip prostheses.[1,2] Sensitivity of 3-phase bone scintigraphy in knee prostheses is low.[15]
Arthritis or rheumatoid diseases Psoriatic arthritis Ankylosing spondylitis Reiter's syndrome	Bone scintigraphy can be used to confirm arthritis if x-ray is normal. Scintigraphy may show arthritis earlier, may explore the severity of arthritis and may be used for evaluation of therapy.[2,16-18] Distribution of joint diseases may allow differential diagnosis.[16,19] 3-phase bone scintigraphy can be used to evaluate the therapeutic success after radiosynoviorthesis.[20]

Degenerative joint diseases - osteoarthroses	Bone scintigraphy is uncommon
Avascular necrosis Perthe's disease Osteonecrosis	3-phase bone scintigraphy may help, if MRI is not predicative.[1,2,21] MRI is the method of choice for avascular necrosis of the hip.[22]
Bone fractures and stress fractures	Normal bone scan can exclude bone fractures after distinct time intervals,[1,2,23] especially in carpal bones[24,25] and tarsal bones, in scapula, vertebrae, proximal femur, sternum, pelvic bones,[26] sacrum.[27]
Reflex sympathetic dystrophy	3-phase bone scan is of major importance for establishing the diagnosis, in staging and to control results of therapy.[28]
Child abuse	Bone scan provides an overview over the whole skeleton, and periostal lesions can be seen.[1,2,29] Metaphyseal lesions in younger children, multiple fractures in different stages of healing, posterior rib fractures, long-bone fractures in younger children are typical signs.
Frostbite and ischemic injuries	Bone scan may help to specify the need and the line of amputation.[2,30]
Paget's disease	Normal 3-phase bone scintigraphy excludes dedifferentiation, helps to screen both regions and extent of bone involvement.[2,11]
Plantar fasciitis, archilles tendinitis, osteitis pubis	Normal 3-phase bone scan excludes inflammation in patients with clinical symptoms and negative x-ray.[2]
Heterotopic ossification	Bone scan is abnormal before radiographic lesions show up.[2]
Osteoporosis	Bone scan is usually used to exclude stress and compression fractures.[2,31]
Osteomalacia	Bone scan excludes pseudofractures earlier than x-ray.[2]
Benign bone tumors (enchondroma, chondroblastoma, giant cell tumors, eosinophilic granuloma, fibrous dysplasia, brown tumors of hyperparathyroidism, osteoid osteoma, aneurysmal bone cyst, vertebral hemangioma)	Normal 3-phase bone scintigraphy excludes any bone involvement if radiographically no lesion is shown. However, bone scan has low specifity since most lesions will accumulate radioactive tracer. Characteristic findings are rare, e.g. in osteoid osteoma.[11] Usually, vertebral hemangioma show normal uptake in planar scintigraphy.[32] Malignancy cannot be excluded by bone scintigraphy.[2]
Bone infarction	Bone scan has a high sensitivity but is less specific.
Erdheim-Chester disease	Scintigraphic patterns of involved skeletal sites may lead to the diagnosis.[33]
"Bone" pain of unknown origin	Bone scan allows the differential diagnosis between soft tissue and bone lesion.[2] In patients older than 50 years a bone scan is useful to exclude occult malignancy or metastases.[34]
Myositis ossificans	3-phase bone scan may demonstrate the activity of the process.

Indications in malignant bone diseases

In primary bone tumors, the three-phase bone scintigraphy is often used to evaluate the primary lesion and to search for other occult bone lesions. In oncology, bone scintigraphy is used to exclude bone metastases of various malignancies. Current recommendations for bone scanning in daily clinical nuclear medicine are given in Table 2.

Bone scanning

The injected activity of ^{99m}Tc-polyphosphonates varies from 700 to 800 MBq. In children, the activity is adapted to body weight, with a minimum of 80 MBq. Younger children should get a sedative during image acquisition in order to reduce movement arti-

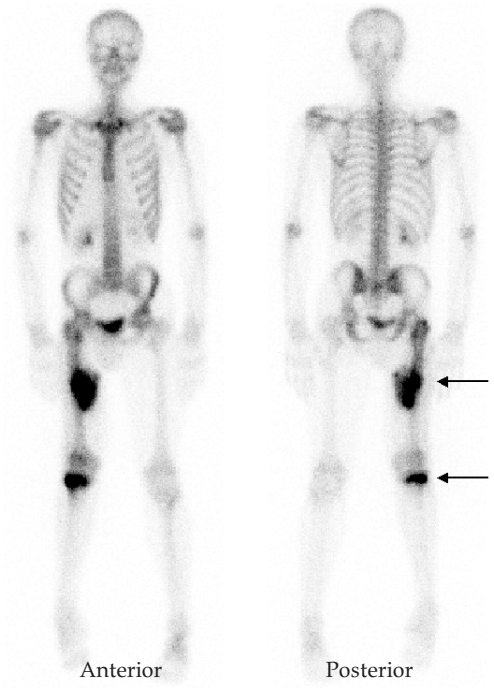

Figure 1. Recurrent osteosarcoma in the right femur in a 17-year-old boy and metastatic disease in the right tibia (arrows).

Table 2. Bone scanning in malignant bone diseases

Disease	To be mentioned
Primary bone tumors (Osteosarcoma, Ewing's Sarcoma, Chondrosarcoma)	Bone scan is not useful to exclude primary bone malignancies. Bone scan is helpful to search for bone metastases or to exclude a local recurrence after treatment.[2,35,36] 3-phase bone scan is useful to evaluate treatment efficacy[37] or viability of bone grafts.
Screening for metastases	Bone scan allows screening of the whole skeleton with a high sensitivity.[38,39]
Prostate cancer	Bone scan is useful in preoperative staging when PSA is increasing ≥30 ng/ml or in patients with clinical evidence of bone metastases. Control of progression of known bone metastases with scintigraphy.[40-42] Evaluation of therapeutic effects in bone metastases following endocrine therapy.[43]
Breast cancer	Bone scan is indicated in primary staging of high-risk patients (axillary lymph nodes positive), clinical evidence of bone metastases or if CA 15-3 is elevated.[44,45] In known skeletal metastases bone scan allows to look for potential pathological fractures.[3] Treatment control is also possible by bone scan, if flare phenomenon is taken into account.[46] About 5% of metastases are missed due to pure osteolyses.[1]

Lung cancer	Bone scan in primary staging only in resectable tumors[47,48] or in clinical evidence.[46,49] About 10% of metastases are missed due to pure osteolyses.[1]
Renal cell or bladder carcinoma	Bone scan should be done in patients with clinical evidence of bone metastases only.[2,50]
Differentiated thyroid cancer	In advanced follicular thyroid tumors or increasing Tg-levels without any correlates in 131I-scan or in bone pain. About 30-50% of metastases may be missed due to pure osteolyses.[1] Patients with elevated serum calcitonin and patients with medullary thyroid carcinoma should undergo bone scintigraphy.[2]
Gastrointestinal cancer	Only in patients with advanced regional tumors and clinical evidence of bone metastases or in patients in whom an infiltration of sacrum is possible.
Malignant Melanoma	In patients with clinical evidence of bone metastases or in patients with advanced regional tumors or histological positive lymph nodes. Bone scan cannot exclude bone metastases.[2]
Squamous-cell carcinoma of the upper aerodigestive tract	Only in patients with an advanced-stage disease, local and regional recurrences, and in second primaries located below the clavicle.[51]
Cervical carcinoma, endometrial carcinoma, ovarian carcinoma	Only in patients with clinical evidence of bone metastases or with advanced regional or histologically poorly differentiated tumors.[2]
Testicular carcinoma	Only in patients with stage IV seminoma with bone pain.[2]
Neuroblastoma	^{123}I-MIBG-scintigraphy is more sensitive.[2] Bone scan can show MIBG-negative metastases.[52]
Lymphoma	Useful in primary lymphoma of the bone and in reticulum cell sarcoma.[3]
Multiple Myeloma	Not useful since metastases are missed in 60-80% due to pure osteolyses.[1]
Systemic Mastocytosis	Bone marrow scintigraphy is more sensitive.[2] The degree of uptake and progress in serial scans marks more aggressive bone marrow disease.[53]
Langerhans cell histiocytosis	Bone scan may detect additional regions of bone involvement.[54]
Palliative pain-therapy with osteotrope radiopharmaceuticals.	Bone scan is a prerequisite for palliative pain-treatment with ^{186}Re-HEDP or ^{153}Sm-HDTMP
Soft tissue tumors	Bone scintigraphy can establish the activity and perfusion of soft tissue processes. Screening for bone metastases or postoperative recurrences is also possible.

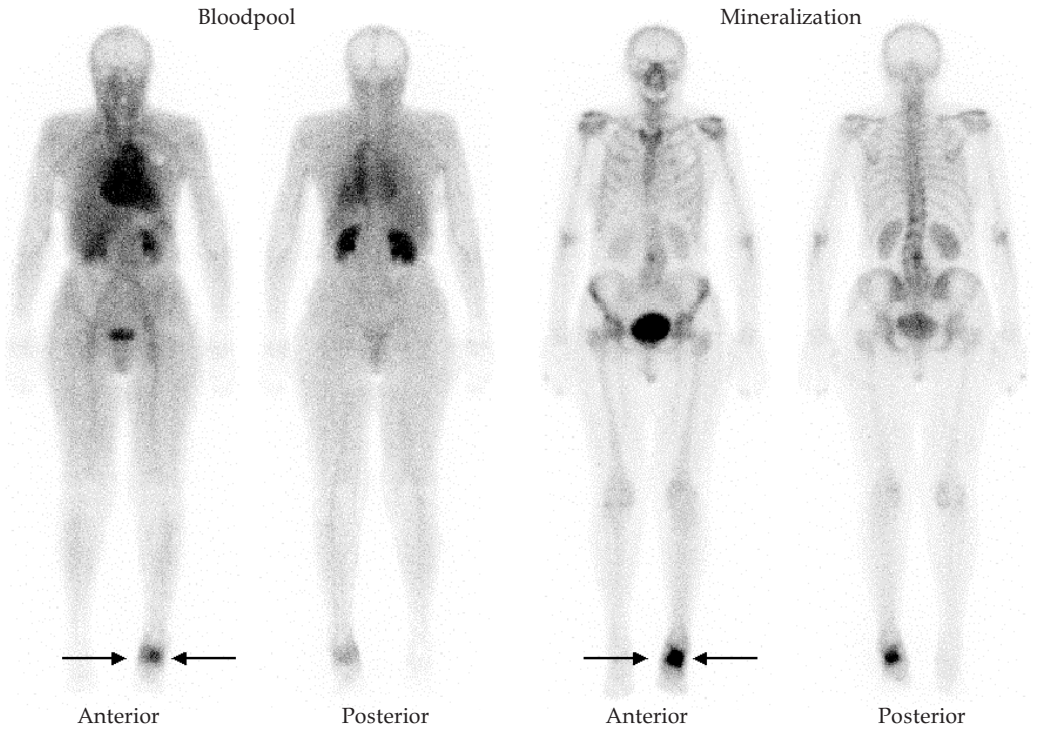

Figure 2. Bloodpool and late whole body images in a 75-year-old women with diabetes. Images show active osteomyelitis of the talus (arrows) and degenerative disease in the lumbar spine due to scoliosis. Artificial photopenia in the left thorax is caused by a pacemaker.

facts. In standard bone scintigraphy, images are acquired approximately 3 hours after injection. In the interim period, the patients should drink at least 1 liter of fluid. Immediately before image acquisition, the patients are asked to empty their bladder. In order to reduce the radiation burden of physicians and nurses, bone scintigraphy should be performed directly after dialysis of the patients with renal failure.

In several focused problems, the three-phase bone scintigrams may give an overview of perfusion, blood pool, and bone mineralization. Dynamic image acquisition is started directly after intravenous injection of ^{99m}Tc-polyphosphonates (perfusion phase). After the first minute, a static image is acquired for 5 minutes (blood pool phase). Late static images (mineralization phase) are performed at least after three hours. Usually, whole-body images are acquired at a double-headed gamma camera with large field-of-view.

The quantification of images may help to establish specific diagnoses, e.g. in sacroileitis, or may help to monitor treatment regimen, e.g. during chemotherapy of primary bone tumors. Additional images may be acquired from unusual angles optimized for best views of distinct bone areas. The images with a pinhole collimator permit clear identifications of small lesions, e.g. of bone infarction in the femoral head of children. Additionally, tomographic image acquisition using single photon emission computed tomography (SPECT) allows to separate overlapping bone structures, e.g. in pelvic, vertebrae, or in hip joints in transaxial, coronal and sagittal projections.

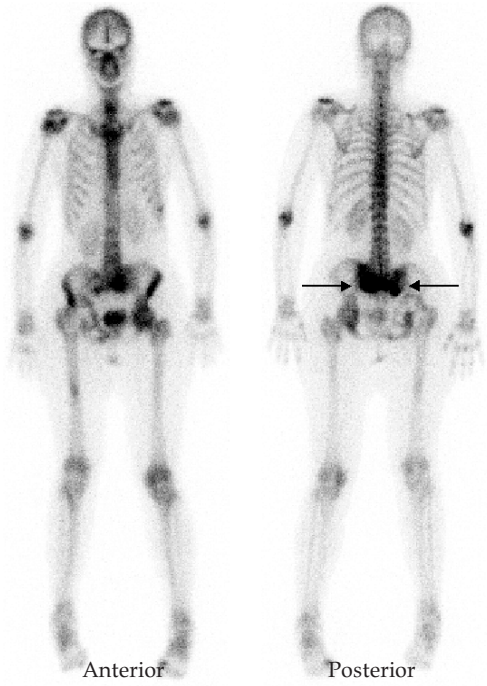

Figure 3. 61-year-old women with radiological obscure findings in the sacrum. Bone scintigraphy performed 6 days after trauma revealed sacrum fracture (arrows). Additionally, hip prosthesis on the right side without any signs of loosening or infection and degenerative changes of bone metabolism in the left hip, both shoulders and in the left big toe can be seen.

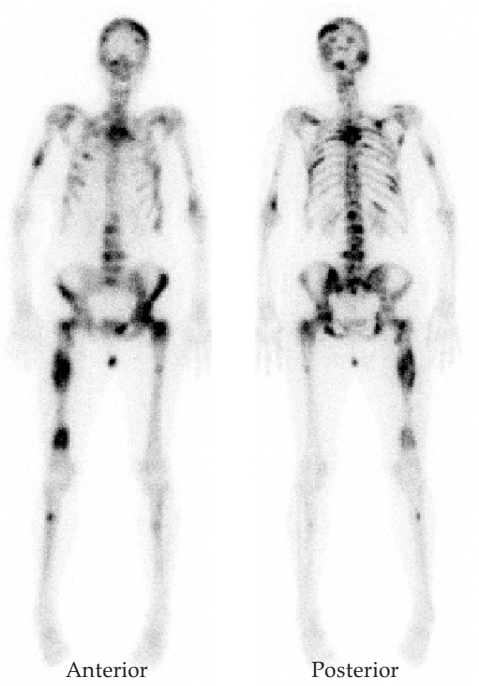

Figure 4. Multilocalar bone metastases in a 73-year-old woman with breast cancer.

Contraindications

Bone scintigraphy will usually not be performed during pregnancy, and only life-threatening indications will lead to bone scanning in breast-feeding women. In these patients, breast-feeding should be discontinued for 48 hours after injection. In children, repeated imaging need rigorous indication, particularly because of the higher radioactive load in their epiphyseal plates.

Radiation load

The effective dose in normal bone metabolism and regular renal function amounts to 0.008 mSv/MBq, which is equivalent to 6 mSv per study.[5]

Conclusion

Just as many other nuclear medicine procedures, the bone scintigraphy has a high sensitivity, and changes of the bone metabolism are often seen earlier than the subsequent changes in bone structure in x-ray. Therefore, occult lesions in the whole skeleton might be detected early by bone scintigraphy.[6] On the other hand, bone turnover is increased in various bone diseases. Consequently, bone scintigraphy usually has a low specificity, and the differential diagnosis of the underlying etiology is often not feasible. However, three-phase bone scintigraphy and SPECT[7,8] can significantly increase the specificity in some skeletal areas.

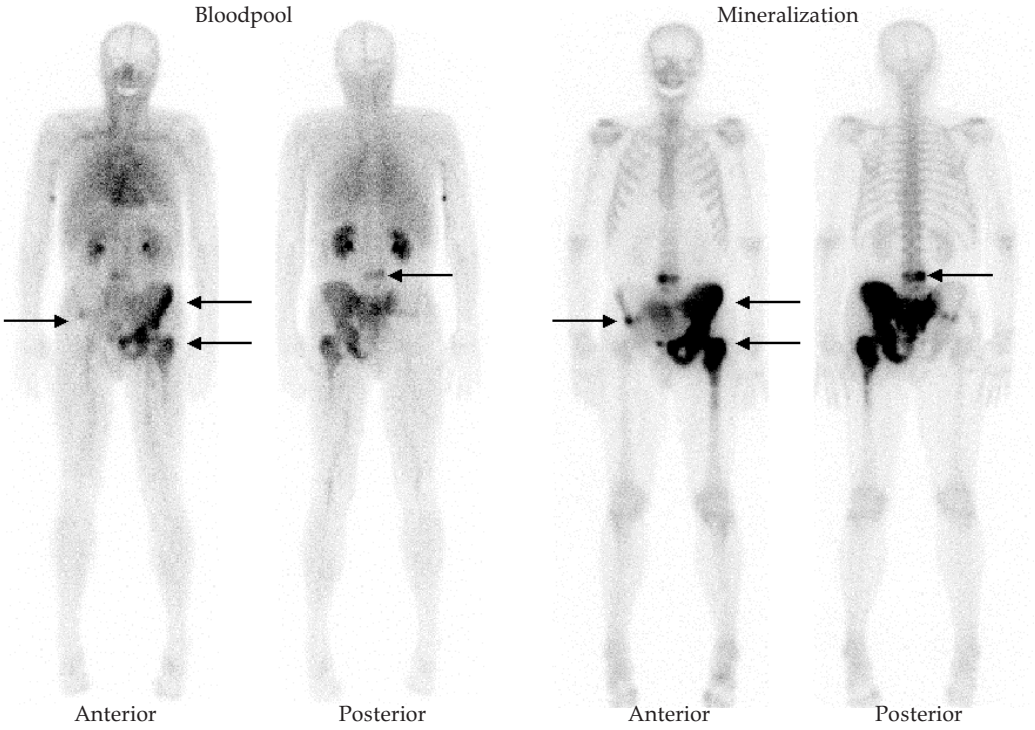

Figure 5. Bloodpool and late whole body images of 67-years-old man with Paget's disease in the pelvis (arrows).

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Intraoperative radiation therapy (IORT) to the tumor bed only for breast cancer: technique and outcome

Gary M. Proulx[1], Thelma Hurd[2], R. Jeffrey Lee[1], Paul C. Stomper[3], Matthew B. Podgorsak[1], Stephen B. Edge[2]

[1]Radiation Oncology, [2]Surgical Oncology, [3]Diagnostic Imaging-Mammography, State University of New York at Buffalo, Roswell Park Cancer Institute, Buffalo, NY 14263

Background. *Recent published reports have demonstrated that not all patients with early stage breast cancer need the entire breast irradiated for local control of their disease. To address the difficulties of several weeks of irradiation treatment, investigators have utilized different radiation techniques and treatment schedules that reduce the overall treatment time without compromising outcome.*

Patients and methods. *An analysis was made of 7 patients treated on protocol with local intraoperative radiation (IORT) alone to the lumpectomy site after surgery with or without axillary dissection. All patients received IORT with 120 kV x-rays to the tumor bed at the time of resection. Doses ranged from 1500 cGy to 2000 cGy. Three patients were stage I, two stage IIA, and two stage IIB.*

Results. *With a mean follow up of 123 months (range 86 to 139 months), two of seven patients developed a local recurrence which were treated with mastectomy. The disease specific survival is 100% and overall survival is 86% with one patient being dead without disease. The cosmetic outcome of the 5 patients with their treated breast remaining have expressed satisfaction with the results. No treatment related complications have occurred.*

Conclusions. *The results of our pilot study support the findings that not all patients with early stage breast cancer need the entire breast irradiated for durable local control of their disease. However, patient numbers in this study are low and any conclusions need further evaluation with larger trials.*

Key words: breast neoplasms-radiotherapy; intraoperative radiation, breast cancer, breast conservation therapy

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Correspondence to: Gary M. Proulx, MD, Roswell Park Cancer Institute, Department of Radiation Oncology, Elm & Carlton Streets, Buffalo, NY 14263. Phone: +1 716 845 3172; Fax: +1 716 845-7616; E-mail: gary.proulx@RoswellPark.org

Introduction

Breast conserving therapy (BCT) is a well established mode of treating early stage breast cancer. Several prospective randomized studies have demonstrated equivalent efficacy in overall and disease-free survival in patients undergoing either BCT or mastectomy.[1-8]

Furthermore, BCT eliminates the emotional and psychological stress associated with removal of the breast. Currently, standard radiation treatment after lumpectomy involves treating the entire breast with external beam irradiation often followed by a local boost to the tumor bed. The rationale for the boost is that most recurrences involve the tumor site or near it.[9,10] Radiation treatment generally involves 6-7 weeks of once-a-day treatment. The difficulties to patients with such lengthy treatment involve transportation issues, employment issues and physical limitations of the patient. These difficulties may be a major reason why many eligible patients for BCT do not receive it.

These factors have led to the hypothesis that radiation alone to the primary tumor bed may be enough for local control of disease with BCT. We report here on the long-term outcome of seven patients treated on a pilot study at Roswell Park Cancer Institute for their breast cancer with local radiation alone using intraoperative irradiation (IORT) to the tumor bed after lumpectomy with or without axillary dissection.

Patients and methods

Seven patients with breast carcinomas were treated with adjuvant radiation using IORT alone to the surgical bed after lumpectomy with or without axillary dissection.

Patients were assessed for age, race, menopausal status, family history, T-stage, nodal status, hormone receptor status, margin status, and grade. Details of patient and tumor characteristics are outlined in Tables 1 and 2.

The mean age of the patients treated was 58 years (range 43-70 years). Six of the seven patients were Caucasian and one patient was Hispanic. Two of the seven were premenopausal defined by cessation of menses at the time of treatment. Two patients had a positive family history of breast cancer with having one or more members of the immediate family diagnosed with breast cancer.

Patients were staged according to the American Joint Committee on Cancer (AJCC). Three patients had stage I and four stage II disease. Tumor staging include T1c (3), T1b (1), T2 (2), and T3 (1). Axillary nodal status was assessed in six of seven patients. One patient did not have the axilla surgically assessed because of medical reasons and was clinically negative. Four of the six were node negative and two were positive, one with 4/37 nodes positive and one with 3/13 nodes positive. Five of seven patients were hormone receptor positive. Margins were negative in all patients.

All of the patients had serial post-treatment mammograms at Roswell Park Cancer Institute (RPCI). These were reviewed in-house with specific attention to any alteration of the appearance of the surgical excision site or changes associated with whole breast irradiation (*i.e.*, increased parenchymal density and/or skin thickening).[11]

All patients were treated with intraoperative radiation using orthovoltage 120 kVp x-rays to the tumor bed at the time of resection. A Picker Zephyr 120 machine was rebuilt into a compact portable unit for use in a designated operating suite. The applicator size and prescribed dose were selected at the time of surgery following lumpectomy with or without axillary node dissection. Five of the seven patients received a dose of 1500 cGy to the tumor bed and two patients received 2000 cGy.

All patients have been followed closely since completion of treatment with physical examinations, mammograms, chest x-rays, and standard laboratory studies. Cosmetics has been assessed by both the patient and physician by expression of either satisfaction or dissatisfaction with the appearance of their breast. This included shape and texture of the breast as well as the skin color.

A retrospective review of the medical records was made to determine treatment

Table 1. Patient characteristics

Patient	Age	Race	Stage	Menopausal Status	Fm Hx	Birth Control Use
1	70	Caucasian	IIA (T1cN1)	Post	no	no
2	43	Caucasian	IIA (T2N0)	Pre	yes	no
3	51	Caucasian	I (T1cN0)	Pre	no	no
4	62	Hispanic	IIB (T2N1)	Post	no	no
5	56	Caucasian	I (T1bN0)	Post	no	no
6	63	Caucasian	I (T1bN0)	Post	no	no
7	60	Caucasian	IIB (T3N0)	Post	yes	no

Fm Hx = positive family history of breast cancer

Table 2. Tumor characteristics

Patient	Pathology	Quadrant	Margins	Grading	T Stage	Nodal Status	ECE	ER/PR
1	IDC	UOQ	(-)	high	Tic	pN1(4/37)	(+)	(+)/(+)
2	IDC	UIQ	(-)	high	T2	pN0(0/9)	(-)	(+)/(-)
3	IDC	LOQ	(-)*	high	T1c	pN0(0/29)	(-)	(+)/(-)
4	IDC	UOQ	(-)	high	T2	pN1(3/13)	(-)	(-)/(-)
5	IDC	UOQ	(-)	inter	T1c	pN0(0/15)	(-)	(-)/(-)
6	IDC	UOQ	(-)	high	T1b	pN0(0/25)	(-)	(+)/(+)
7	ILC	UOQ	(-)	inter	T3	not assessed	(-)	(+)/(+)

* Close: < 2 mm

IDC = Invasive ductal carcinoma; ILC = Invasive lobular carcinoma; UOQ = upper-outer quadrant; UIQ = upper-inner quadrant; LOQ = lower-outer quadrant; ECE = Extra capsular extension; ER/PR = estrogen and progesterone receptors

rendered and the events of local control, distant failure, disease-specific survival, overall survival, cosmetic outcome, and complications (Table 3).

Results

Serial post-treatment mammograms were available for review on each patient and showed no alteration of the post-excision mammographic appearance for a median follow-up of 6 years (range 2-10 years). Five of 7 (71%) patients had mammographic evidence of post-surgical scarring consisting of architectural distortion and focal skin thickening. There was no short or long-term alteration of the appearance of the primary excision site after intraoperative radiation treatment. There was no identifiable skin thickening or increased mammographic parenchymal density attributable to IORT.

After a mean follow-up of 123 months (range of 86 to 139 months), 6 of 7 patients were free of disease. Two of seven patients recurred locally. One patient with stage I, T1cN0M0 recurred in the surgical scar 36 months after local treatment, while the second patient with local recurrence, stage IIB, T2N1, recurred within the treatment bed at 120 months. These patients both underwent mastectomy and remain disease-free 70 months later and 12 months respectively. Therefore, the disease-specific survival is 100%. One patient died of other causes without evidence of disease. Regarding cosmetic outcome, the 5 patients who have successfully preserved their affected breast have expressed personal satisfaction with the results, as had the two patients with local failures up

Table 3. Treatment given and outcome

Patient	Surgery	TAM	Surface Dose	Follow Up (month)	Local Failure	Distant Failure	Status
1	Lump + Ax	+	1500 cGy	139	no	no	ANED
2	Lump + Ax	-	1500 cGy	132	no	no	ANED
3	Lump + Ax	+	1500 cGy	133	yes	no	ANED
4	Lump + Ax	+	1500 cGy	135	yes	no	ANED
5	Lump + Ax	-	2000 cGy	137	no	no	ANED
6	Lump + Ax	+	2000 cGy	132	no	no	ANED
7	Lump	+	1500 cGy	86	no	no	DNED

TAM = tamoxifen; Lump = lumpectomy; Ax = axillary dissection; ANED = alive, no evidence of disease; DNED = died of other causes, no evidence of disease

until the time of their mastectomy. No treatment related complications have occurred.

Discussion

To address the difficulties of several weeks of irradiation treatment, investigators have utilized different radiation techniques and treatment schedules that reduce the overall treatment time without compromising outcome. By reducing the overall treatment time, many patients could potentially be able to receive BCT who might not otherwise because of difficulties related to a several week course of radiation. One technique employs the use of hypofractionated external beam radiation treatment (EBRT) of the entire breast with the number of treatments reduced by delivering higher doses per fraction.[12] Another technique combines whole breast EBRT with intraoperative electrons to boost the surgical bed, thereby reducing the number of boost treatments by giving only one treatment at the time of surgery.[13] In addition to different techniques and treatment schedules to reduce the overall treatment time, the possibility of treating only the tumor bed and not the entire breast is currently under investigation.

The rationale for giving only local irradiation to the tumor bed region is supported by both pathologic data from mastectomy specimens and patients treated with tumorectomy alone that has shown a relatively low risk of tumor burden and failure rate distant from the primary tumor site. In evaluating over 200 mastectomy specimens, Holland *et al.* found 32% of patients with extensive intraductal component (EIC) and only 12% of patients without EIC had residual disease greater than 4 cm from the cancer removed by surgery.[14] In another report as high as 36% of mastectomy specimens had either in-situ disease or invasive disease between 2 and 4 cm from the tumor site.[15]

In addition several reports of patients treated with local surgery alone have identified subsets of patients that have the tumor bed quadrant as the predominate site of recurrence and are consequently at a very low risk of recurrence elsewhere within the breast. Fisher *et al.* found that of 1108 pathologically patients able to be evaluated and treated with lumpectomy (9.9%) from the NSABP protocol 6, 110 patients developed a local breast recurrence. All 110 patients had their recurrence within or close to the quadrant of the initial or index cancer.[9] In another series, Liljegren *et al.* had 33/36 (77%) of all local recurrences within the surgical field after wide excision alone.[10]

Since the risk of recurrence appears to be low outside a margin around the surgical resection, can irradiation of the surgical bed achieve the same local control as irradiating the entire breast with a boost to the tumor

bed? The use of local irradiation alone to the surgical bed with radioactive implants or IORT electrons would significantly reduce the number of treatments that patients would receive from several weeks of once-a-day treatment to only a single day of treatment. The use of IORT with electrons is not a new concept with its benefits having been reported for solid tumors, most notably for intraabdominal or pelvic tumors;[16,17] however, its use in breast cancer, however, has mainly been limited to boosting after external beam radiation treatment (EBRT) to the entire breast.[14]

Furthermore, IORT with orthovoltage has been successfully utilized for other sites including the treatment of rectal, gynecologic, and pancreatic malignancies.[18-20] In our series, orthovoltage was selected over the use of electrons at the time because of difficulties with transporting the patient to the radiation department where electrons could be delivered. Other advantages of using the 120 kVp machine included low cost, ease of radiation protection, and direct observation of the patient 5 ft away from the anesthetist with immediate access to the patient if needed. Disadvantages of the system included a shallow fall-off of dose, and a relatively low output of 100 cGy per minute. Orthovoltage x-ray beams can potentially offer a simple, generally applicable, alternative treatment modality for intraoperative radiotherapy. The limited choice of x-ray energy, however, requires that a compromise be made between providing an adequate depth of penetration to cover the tumor volume while minimizing the dose to underlying tissues.

The use of local irradiation alone after tumorectomy in early stage breast cancer is currently being explored in subsets of patients felt to be at low risk for a recurrence outside of the surgical bed. Recent reports using brachytherapy alone to the tumor bed have encouraging results. Perera *et al.* reported only 1 infield recurrence out of 39 patients treated with high dose rate brachytherapy (HDR) to the primary tumor bed at a median time of 20 months.[21] Similarly a pilot study using low dose rate brachytherapy (LDR) by Vincini *et al.* demonstrated no local recurrences for 51 women at a median of 20 months follow-up. Selection criteria required tumors to be 3 cm or less, margins greater than or equal to 2 mm, no extensive intraductal component (EIC), a level I and II axillary dissection with up to 3 lymph nodes positive, pre- and post-operative mammograms, breast technically suitable for implant, implant performed within 8 weeks of last breast surgery, and patients at least 40 years of age.[22]

Additionally, Kuske *et al.* have had no local breast recurrences involving 51 patients treated with either LDR or HDR brachytherapy with a four year median follow-up. Cosmetics was good to excellent in 78% treated with LDR and 67% for HDR.[23] The Guy's Hospital experience using local LDR brachytherapy reports only two isolated local regional recurrences (7.5%) and a 96% good to excellent outcome.[24] In contrast, Ribeiro *et al.* had inferior results when local radiation to the involved quadrant using 10 MeV electrons was utilized vs treating the entire breast with tangent fields. At six years follow-up, both axillary and breast reccurrence were higher for the local radiation treatment arm. A 20% recurrence rate in the breast for lobular carcinomas in the quadrant - radiation arm was felt to contribute to this difference.[25] A current phase II Radiation Therapy Oncology Group (RTOG) trial is ongoing comparing low dose rate (LDR) with 45Gy vs high dose rate (HDR) with 34 Gy brachytherapy in patients meeting criteria for low risk for recurrence outside of the surgical bed.

Our observation that intraoperative radiation treatment does not alter the mammographic appearance of the primary excision site is important because a majority of early local recurrences after breast-conserving therapies occur at or near the primary exci-

sion site. Stability or resolution of the mammographic post-surgical changes on serial mammograms is an essential component of the mammographic analysis in the follow-up of these patients.[11] The lack of any appreciable mammographic changes often associated with whole breast irradiation may improve the sensitivity for detection of recurrence for some patients.

Our study and the brachytherapy studies suggest that tumor bed irradiation alone can be effective in controlling disease within the breast for selected early-stage patients and provide good to excellent cosmetics as judged by both patient and physician. In our series, despite not all of the patients fitting the strict criteria of more modern studies exploring the use local radiation alone (*e.g.*, no lobular histologies, no tumors larger than 3 cm, no associated extensive intraductal component), five of seven have achieved local control with the two local failures occurring at very long intervals after treatment (Table 3).

The optimal treatment for breast cancer patients desiring breast preservation is in evolution. In our pilot study, two patients have failed locally within the treatment site at long intervals from treatment, which indicates that patients may require lifetime follow-up and perhaps higher local doses to the local field than were given in this study. The benefits of treating locally with IORT with one treatment include more convenience to the patient, lower treatment costs, and less volume of normal tissue irradiated. Our results would seem to suggest that not all patients with breast cancer need the entire breast irradiated to obtain local control of their disease. However, patient numbers in this study are low and any conclusions need further evaluation with larger patient numbers using prospective studies.

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Sentinel lymph nodes identification in early breast cancer - peritumoral or subareolar injection of lymphotropic blue dye?

George Baichev[1], Sonia Sergieva[2], Grigor Gorchev[1]

[1]Dept. of Surgical Oncology, University Centre of Oncology, Pleven, Bulgaria
[2]Dept. of Nuclear Medicine, National Centre of Oncology, Sofia, Bulgaria

Background. *The sentinel lymph node (SLN) biopsy is a recently developed, minimally invasive method for staging the axilla in patients with early breast cancer. The authors investigated the optimal technique - peritumoral versus subareolar injection for the localization of the SLN.*
Patients and methods. *192 procedures out of 238 ones were performed using a blue dye peritumoral injection at the early breast cancer site against 46, with a subareolar technique. All patients underwent sentinel node biopsy, followed by an axillary lymph node dissection.*
Results. *The SLN were metastatic in 69 out of 80 axillary positive patients that accounted for 86,3%. The sentinel node histology correctly predicted the axillary disease in 90,6% with a peritumoral injection versus 68,8 % with a subareolar lymphatic mapping.*
Conclusions. *This experience indicates that the peritumoral injection of blue dye is a more accurate than the subareolar one for axillary staging.*

Key words: breast neoplasms; lymphatic metastasis; axilla; lymph nodes-pathology; biopsy; early breast cancer; sentinel lymph node biopsy

Introduction

Axillary staging operations in patients with breast cancer range from sampling with a blind biopsy alone to complete or with a total lymph node dissection. The concept of the sentinel lymph node (SLN) has profound consequences for our understanding of the process of tumour cell spread.

The sentinel lymphadenectomy has been shown as an attractive technique in multiple studies, carried out recently as a part of ongoing effort to find a less invasive and still adequate method for axillary staging (N+ or N-) in the cases of early breast cancer. The first SLN or SLNs along the lymphatic pathways have never before been traced by the preoperative instillation, both of the blue dye[1] or ra-

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Correspondence to: George Baitchev, MD, Dept. of Surgical Oncology, Centre of Oncology, Medical University, 1st Kl. Ohridsky str., 5800 Pleven, Bulgaria. Phone: +359 64 427245; Fax: 359 64 801603; E-mail: oncology@el-soft.com

dioactive nanocolloid[2] peritumorally. The histological assessment of this "strategic spot" after the biopsy was compared with the results of the axillary dissection. The accuracy is reported to be up to 87-100%.[1-3]

The extensive research of the lymphatic drainage and metastatic mapping led some authors up to the idea of employing the alternative approach, namely - the subareolar injection of radiocolloids, aiming the indication of the SLN.[4,5]

There is no sufficient data in the literature related to subareolar mapping of SLN. Hence, the purpose of the current study was to examine the both methods comparatively and to submit the results of the analyses.

Patients and methods

During the period from February 1995 through June 2000, 238 women with primary early invasive, unilateral breast carcinoma (T_{1-2}, N_{0-1}, M_0) scheduled for the surgical treatment at our department were enrolled in this study. The median age of the group was 56.1 years (range 24 to 75).

We excluded pregnant or lactating women, those who had previously undergone biopsy or received radiotherapy to the axilla. Patients with multicentrical or multiphocal breast carcinoma, mammographically confirmed, were also excluded. Informed consent was obtained in all cases.

The technique of lymphatic mapping and sentinel node biopsy included the following: in 192 patients, 2 ml of lymphotropic blue dye were injected immediately before the introduction of anaesthesia with a fine needle (21-22 G) around the tumour. In the majority of cases - 147 (76.6 %), Patent blue V (BYK Gulden) was applied, and 19 patients received Drimaren Brilliant blue (Fluka). The study also included 26 females with breast cancer in whom locoregional perioperative chemotherapy with Mitoxantrone (Novantrone, Wyeth-Lederle) was carried out. Two sites around the tumour were injected with 0.5 ml (1 mg) Mitoxantrone. It was established that Mitoxantrone dyes the lymphatic system very well, so this drug was used as a dye occasionally.

The rest 46 patients received the subareolar injections into two different zones by 0,5 - 1,5 ml each, into the respective quadrant where the carcinoma had been localized.

Preoperative lymphoscintigraphy was performed in 9 patients. ^{99m}Tc - sulphur colloid (Solco Lymphoscint, Sorin) with the particle average diameter of 50 nm was injected in the subareolar area in volume of 0,2 - 0,3 ml. The specific radioactivity of the injection zone was 20 mBq. Planar images - in frontal and inclined positions were obtained by rotative - gamma camera (Diacam, Siemens). The visualization achieved: the early one - at the 20-th minute and the late one - at the 120 to180-th minute after the application, respectively.

In most of the cases - 201 (84,5%) a modified radical mastectomy was performed and in 37 (15,5%) - quadrantectomy with axillary dissection. Lymphadenectomy in 215 cases (90,3%) includes I, II and III axillary anatomic levels and in 23 cases (9,7%) with minimal size of the tumour (<1cm) - I and II levels. All nodes in the axillary dissection specimen were processed for histologic examination using hematoxylin and eosin (H&E). Immunohistochemical techniques to identify micrometastases were not performed.

Results

The median amount of the removed and examined lymph nodes is 12,6 (range 10-21). The identified blue-stained SLNs ranged 1 to 3, i.e. 1,5 per case at the average. Sentinel nodes were located on level I in 193 cases, in 34 cases - on level I and II, and in 11 cases SLN mapped only on level II.

Lymph node metastases had been found in

80 patients that accounted for 33,6% of the background - 64 of them from the group with peritumoral application of blue dye and 16 belonged to the group with subareolar application. Sixty-nine women (86,3%) had positive SLNs (Table 1).

Table 1. The axillary status of the two groups of patients studied

	Lymph dissection		
SLN	(+)	(-)	Total
Peritumoral			
(+)	58	-	58
(-)	6	128	134
Subareolar			
(+)	11	-	11
(-)	5	30	35
Total	80	158	238

SLN= sentinel lymph node

In most cases with mapped metastatic SLN the primary tumour is located in the lateral quadrants (53 cases). In 16 patients the carcinoma is localized centrally and in the rest 11 cases the tumour had medial location (Table 2).

After the preoperative lymphoscintigraphy hot spots were identified in 7 cases. In five women one SLN in each case were scanned in the axilla site zone on level I - as at the early so at the late stage of scanning. In other two patients with medial location of the tumour 1 sentinel node in each case was visualized in the area of ipsilateral lymphatic parasternal chain. With only two patients none SLN was visualized neither at the early nor at the late stage of the study most likely due to microembolies in the lymphatic vessels, draining the tumour-bearing breast.

Discussion

Metastatic lymph nodes involvement proved to be the basic principal in the clinical strategic assignment and prognostication in cases of early breast cancer. The removal of the nodes from the levels I and II is a routine surgery operation when the primary breast cancer is diagnosed and thus, up to 98 % of the cases with positive axilla are identified.[6] At the same time, the relatively high percentage (67-80%) with early disease with tested negative lymph nodes, as well as possible postoperative complications (lymphoedema), approved the necessity of a sentinel lymphadenectomy as an alternative to the lymph node dissection over the last decade.

The accuracy of this procedure is confirmed in numerous studies. There is a probability of only 0-6% of detecting false negative SLNs after the peritumoral application of blue dye or radiocolloids.[1-3,6]

According to the results of the two studies of Klimberg et al. and Mertz et al., published so far, the exactness of 100% was reported to be achieved with 68 and 47 patients, respectively, who had received ^{99m}Tc sulfocolloid subareolar injection.[4,5]

As to the accuracy after the peritumoral mapping, our results (90,6% of background) concur with those, performed by the other authors employing this method.

Simultaneously, some differences are ob-

Table 2. Location of the primary tumour in the cases with metastatic SLN

Localization	Peritumoral		Subareolar	
	Axilla (+)	SLN (+)	Axilla (+)	SLN (+)
Lateral	44	42	9	5
Central	12	11	4	4
Medial	8	5	3	2
Total	64	58 (90,6%)	16	11 (68,8%)

served between our results and figures, given in the literature, regarding the subareolar technique. We achieved 68,8% of diagnostic precision, using this method that appears to be much lower, in comparison to the percentage, presented in the other two studies, mentioned above.

These results may be explained as follows:

- The subareolar technique, being new and at its first stages, may give the accuracy which still remains debatable.
- The investigation was conducted up to now on an insufficient number of patients;
- Lymphatic drainage might be traced incompletely and further combination of blue dye and radiocolloids may raise the rate of strictness of this method;
- Metastatic SLN are not localized precisely by a microscope examination. We assume that in an additional immunohistochemical investigation micrometastases might be found.

In conclusion, the authors of the current study state that the peritumoral application of blue dye or radiocolloids technique is considered to be a reliable tool in determination of axillary status, verified histologically, whereas subareolar SLN mapping is still disputable and only further extending research would correctly evaluate its efficiency and positive/negative predictive values.

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What is current practice in soft tissue sarcoma grading?

Rastko Golouh, Matej Bračko

Department of Pathology, Institute of Oncology, Ljubljana, Slovenia

Purpose. *Most published grading systems of soft tissue sarcomas (STS) are somewhat subjective and it seems that there is no definite consensus among experts which of them is the most effective. The aim of this study was to collect data from practicing pathologists and to get some insight in the practice of STS grading.*
Subjects. *A questionnaire was sent to 135 pathologists chosen randomly.*
Results. *There were 88 responders from 30 countries from 5 continents. Most responders (85%) grade STS, more frequently in Europe than in non-European countries. Three-grade system is preferred by both European and non-European pathologists, who use it in almost 77% and 67%, respectively. They apply the criteria set by FNCLCC in 37.3%, by NCI in 24%, by Broders in 12% and by Markhede in 1.4%. In Europe, FNCLCC system is the most widely used. Beside classical histological criteria, other modern methods are applied by more than one half of the responders. Immunohistochemical evaluation of proliferation markers is the method most widely used, followed by molecular markers and DNA flow cytometry.*
Conclusion. *The results of our study indicate that most pathologists consider histologic grade of STS as a valuable, however not completely satisfactory predictor of a patient's survival.*

Key words: soft tissue neoplasms; sarcoma pathology; neoplasms staging; prognosis

Introduction

No other variable seems to work better in the prediction of the behavior of soft tissue sarcomas (STS) than histological grade, but at the same time, no other prognostic factor has been responsible for so much controversy and debate. Soft tissue sarcomas are a large group of approximately 50 different nosologic entities that, despite sharing common clinical features such as blood-borne metastatic spread, also present significant clinical differences. The value of histopathological grading should, therefore, be balanced against the predictive significance of other morphologic and clinical parameters that vary according to the specific type of sarcoma.

In most sarcoma grading systems, the degree of histological differentiation, cellularity, pleomorphism, mitotic activity, necrosis and vascular invasion are taken into account. In addition, some schemes take the pathological diagnosis of the tumor as a dominant component for grading as it is well known that certain sarcomas have a specific biological be-

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Correspondence to: Rastko Golouh, MD, PhD, Dept. of Pathology, Institute of Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia. Fax: +386 1 43 14 180; E-mail: rgolouh@onko-i.si

havior that is defined mostly by their line of differentiation.

However, many grading systems applied to STS have not been completely satisfactory in terms of predicting prognosis. Therefore, attempts to identify potentially more aggressive sarcomas have been made using additional quantitative methods such as flow cytometry, markers for assessment of proliferative activity as well as molecular techniques looking for oncogenes, suppressor genes and gene product expression.

Although most published grading systems may provide valuable prognostic information, an international consensus on STS grading has not been reached. One may, therefore, suppose that grading of STS varies considerably among different places and even among experts in the field.

The historical and practical aspects of histologic grading of STS have recently been extensively reviewed.[1] In addition, some guidelines regarding STS grading have been proposed in the recently published recommendations for the reporting of soft tissue sarcoma.[2] The aim of the present study was to collect data from practicing pathologists and to get some insight in the current practice of STS grading in different institutions of different countries.

Material and methods

To obtain first-hand information, a questionnaire was sent to 135 pathologists who were chosen at random from the list of participants of the 15th European Congress of Pathology. They were asked to answer to four specific questions, as follows:

1. Do you grade STS (yes, no)?
2. How many grades do you use (two, three, four)?
3. Which grading system do you use (Broders, NCI, Jensen, FNCLCC, other-specify)?
4. Do you use other methods to assess STS prognosis (no, yes - DNA ploidy, S-phase fraction, proliferation markers, molecular markers, other - specify)?

Finally, all potential responders were asked for their comments.

Results

All the data were processed anonymously. In total, there were 88 responders from 30 countries of 5 continents (Table 1). Most of them (74%) were from Europe. Their answers are shown in Table 2.

Table 1. Geographical distribution of the responding pathologists

Australia	2	Iceland	1
Austria	2	Italy	6
Brasil	1	Japan	5
Canada	1	Macedonia	2
Croatia	1	Norway	5
Czech Republic	2	Poland	1
Denmark	3	Portugal	2
Finland	3	Slovenia	1
France	5	Spain	7
Germany	5	Sweden	2
Great Britain	4	Switzerland	3
Greece	2	Turkey	2
The Netherlands	3	Ukraine	1
Hong Kong	2	USA	12
Hungary	1	Yugoslavia	1

Most responders (85%) grade STS. Among them, however, certain geographical differences became evident. Pathologist in Europe use gradation of STS more frequently (in nearly 88%), compared to the pathologists in non-European countries, who grade STS in 78%.

Similarly, number of grades used, namely 2, 3 or 4, also varies considerably - 11%, 74%, and 15%, respectively. Three-grade system is preferred by both European and non-European pathologists, who use it in almost 77% and 67%, respectively.

Table 2. Answers provided by the participating pathologists

	All (n=88)	European (n=65)	non-European (n=23)
grading used	75 (85.2%)	57 (87.7%)	18 (78.3%)
number of grades			
2	8 (9.1%)	5 (8.9%)	3 (16.7%)
3	55 (62.5%)	43 (76.8%)	12 (66.7%)
4	11 (12.5%)	8 (14.3%)	3 (16.7%)
grading system			
Broders	9 (12.0%)	6 (10.5%)	3 (16.7%)
NCI	18 (24.0%)	13 (22.8%)	5 (27.8%)
FNCLCC	28 (37.3%)	26 (45.6%)	2 (11.1%)
other/not specified	20 (26.7%)	12 (21.1%)	8 (44.4%)
other methods used	47 (53.4%)	38 (58.5%)	9 (39.1%)
proliferation markers	38 (43.2%)	31 (47.7%)	7 (30.4%)
SPF and/or DNA ploidy	12 (13.6%)	11 (16.9%)	1 (4.3%)
molecular	15 (17.0%)	12 (18.5%)	3 (13.0%)
other/not specified	10 (11.4%)	8 (12.3%)	2 (8.7%)

Of the 75 individuals who systematically grade STS, only 56 specified the system used. Pathologists apply the criteria set by FNCLCC in 37.3%, by NCI in 24%, by Broders in 12%, and by Markhede in 1.3%; the remaining 25.3% did not specify the system they use. Again the analysis disclosed some differences between the regions studied. While FNCLCC system is the most widely used in Europe (46%), non-European pathologists seem to prefer other systems.

Rather surprisingly, of the 56 pathologists who specified the grading system they use, 11 (19.6%) stated that they use a number of grades different to that applied in the original published grading scheme.

Beside classical histological criteria to assess soft tissue sarcoma prognosis, other modern methods are applied by more than one half of the responders. In Europe, these are used in 59%, compared to 30% in non-European countries. Immunohistochemical evaluation of proliferation markers is the method most widely used, followed by molecular methods and flow-cytometric determination of DNA ploidy and/or S-phase fraction.

Discussion

The results of our study show that the large majority of pathologists apply grading to the diagnosis of soft tissue sarcoma. On the other hand, they also indicate that, in practice, this is done rather inconsistently, that various grading schemes are in use, and that the guidelines set forth by the published grading systems are often only loosely applied. One of the reasons for this, as well as for the fact that as many as 15% of pathologists do not use STS grading, might be the lack of international consensus.

Despite the validation of many histologic grading systems for STS, none have been universally accepted. Because of the overall rarity of specific sarcoma subtypes, the evaluation of grading systems and their prognostic significance have tended to be based on sarcomas as a general group, diminishing the value and significance of histologic subtyping. The same histological criteria have been applied to 50 different types of sarcomas, despite the fact that some behave as borderline or low-grade malignant tumors (dermatofibrosarcoma protuberans, retiform heman-

gioendothelioma) and others are uniformly high grade (clear cell sarcoma, desmoplastic small cell tumor). It has been pointed out that histologic grading may overestimate or underestimate the biological potential of some STS. Therefore, it has been suggested that the grading criteria should be revised for each type of soft tissue tumor. Moreover, the study of each specific type of STS should be subjected to multivariate statistical analysis with simultaneous consideration of histological, clinical and treatment factors.[3]

If histologic grading is to be applied to certain types of STS, which grading should be used and what is the current grading practice?

Most grading systems incorporate similar histologic parameters, namely histologic type, cellularity, tumor necrosis, and mitotic activity. The parameters by which these criteria are applied tend to be less defined in systems of Broders[4] and Markhede[5] both of which use a four-grade scale. The more recent systems, preferred by our responders, the National Cancer Institute (NCI) system as proposed by Costa[6] and the system of Federation Nationale des Centres de la Lutte Contre le Cancer (FNCLCC),[7,8] appear far less subjective than its predecessors and provide specific guidelines for applying tumor grade. They both are 3-tiered. The NCI largely incorporates histologic subtype and extent of necrosis, whereas FNCLCC uses tumor differentiation, mitotic count and volume of tumor necrosis. Although both systems have predictive value for metastatic development and tumor mortality, the FNCLCC system appears to be slightly superior to the NCI system, both in the ability to predict a patient's survival and in the reproducibility of the scoring system among pathologists.[7,9]

In contrast to most previous attempts that tried to evaluate STS as an entire group, predictive value for metastatic disease has recently been specifically assessed for the main histologic types of adult STS.[10] The results of a study of 1240 patients, assessed by FNCLCC system, confirmed the impression that histologic grade is the most important predictor of metastasis development in several malignant soft tissue tumors. In order of importance, the following parameters were reported to have independent predictive value: (1) grade, neurovascular or bone involvement (NBI), tumor size and depth for the whole group; (2) grade and tumor size for liposarcoma (n=188); (3) NBI, grade and tumor size for leiomyosarcoma (n=148); (4) grade and NBI for synovial sarcoma (n=125); (5) grade for unclassified sarcomas (n=140) and sarcomas of other types (n=158). Interestingly, the authors could not identify any prognostic parameter for malignant schwannoma (n=72) and for rhabdomyosarcoma (n=60).

It should be pointed out that both NCI and FNCLCC systems are best applied to adult soft tissue sarcomas. Recognizing the differences between children and adults, Parham *et al.* reported the criteria of Pediatric Oncology group (POG) for nonrhabdomyomatous sarcomas in children.[11] POG system is similar to NCI grading scheme, but takes into account more adequately the unique clinico-pathologic features of children and therefore better suits this age group. On the other hand, for childhood rhabdomyosarcoma the Intergroup Rhabdomyosarcoma Study Group have proposed a grading system which better correlates with prognosis of this specific group of STS.[12] The classification, specifically designated as the International Classification of Rhabdomyosarcoma (IRC), divides RMS in three groups - tumors with superior, intermediate and poor prognosis.

Arguably, the classification, histological subtyping, and grading systems of STS are mostly based on classical, morphologic features. Recent advances in our understanding of the cytogenetic and molecular features of STS have yielded significant insight into STS pathogenesis.[13] It is not surprising that, ac-

cording to our study, more than one half of pathologists apply additional methods, although their value in predicting behavior of STS is not entirely clear at present. Markers such as MIB1 to more accurately assess proliferative activity are most commonly used. They are followed by molecular methods to evaluate the expression of p53, MDM2, RB and other gene products, and flow cytometry to separate diploid from aneuploid tumors and to determine S-phase fraction. Again, it has to be stressed that additional studies of these and many other modern methods are needed to evaluate their specific prognostic significance for each type of STS.

Although the data gathered in this study suggest that certain differences exist in the practice of STS prognostication between European and non-European pathologists, none of this differences proved to be statistically significant. It should be noted, however, that the number of responders from non-European countries was far too small to draw any firm conclusion.

In conclusion, the results of our study indicate that most pathologists are aware of the fact that histologic grade of STS appears to be a valuable, however not completely satisfactory predictor of a patient's survival. Despite the impressive advances in our understanding of STS and high level of expertise in stating accurate diagnosis of common and many recently described entities, there are still many problems that account for the failure of most grading schemes to consistently function well.

Acknowledgement

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Upgrading of gamma cameras for developing countries

Valentin Fidler[1], Milan Prepadnik[1], Yanfen Xie[2]

[1]*Nuclear Medicine Department, University Medical Centre, Ljubljana, Slovenia*
[2]*Nuclear Medicine Section, Division of Human Health, International Atomic Energy Agency, Vienna, Austria*

Background. *The project of upgrading the analog gamma cameras with PC based systems from International Atomic Energy Agency (IAEA) and the Ministry of Science and Technology of RS is presented from the initial basic demands to the final developments. Several national research groups (from China, India, Cuba and Slovenia) were involved in the IAEA development project for the acquisition card with software and the standard set of clinical protocols.*

Conclusions. *The most functionally stable acquisition system tested on several international workshops and in university clinics was the Slovenian one with a complete set of nuclear medicine clinical protocols, documenting, networking and archiving solutions for simple MS Network or server oriented network systems (NT server, etc). More than 300 gamma cameras in 52 countries all over the world were digitized and put in routine clinical work.*

Key words: gamma cameras; computer systems; upgrading of analogue gamma cameras; acquisition card; PIP-GAMMA-PF system.

Introduction

In the last ten years, IAEA put considerable efforts to help developing countries in renewing old gamma cameras and nuclear medicine computer systems. It was high time to take this step because many gamma cameras were already out of function for different reasons. Most of them got broken or computers were too old to suit technologically to new nuclear medicine methods, radiopharmaceuticals and information technology. In many countries, the old analogue gamma cameras (20 years or more) were put out of operation and, as a consequence, the nuclear medicine departments were being closed. Nuclear medicine, though a relatively young medical branch, started to "die away". At the same time, the nuclear medicine staff also started to leave the field for other fields, mostly imaging ones.

For these reasons, the IAEA measures related to the upgrading of analogue gamma cameras have been initiated to help developing countries to revive nuclear medicine or extend its life. Because of high costs of new

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Correspondence to: Valentin Fidler, PhD, Nuclear Medicine Department, University Medical Centre, Zaloška 7, 1000 Ljubljana, Slovenia. Phone: +386 01 5431486; E-mail: Valentin.Fidler@kclj.si

equipment, the idea of the IAEA was to upgrade the old analog and semi-digital gamma cameras and computer systems with low cost interfacing cards, developed under the agency support, and the PC based computer systems with acquisition and processing software, ink-jet or laser printers, CD archive and network. The whole cost per system was limited to 5.000 US $, what is just a small fraction of the price of new commercial systems. Concurrently with upgrading the equipment, the training courses for this technology and validation seminars took place in all the regions of the developing world.

Methods

IAEA established a group of experts for defining the upgrading objectives, criteria for selecting the research institutions for the development of acquisition hardware and software, defining the procedures for following the results of development and creating the final report of the project. The expert group defined the following demands for the upgrading system of analogue gamma cameras.

Basic demands for development of acquisition cards:

- single ISA format acquisition card,
- solution for adjusting amplitude and timings for input signals from a variety of gamma cameras,
- simple installation and setup of X, Y (positional), Z (strobe), E (energy) and G (gated) signals; such that most of the end users can install the system by themselves,
- matrix size up to 256x256,
- acquisition driver incorporated in PIP (Portable Image Processing),
- on-line energy and count correction of image data,
- negligible count loss,
- stable function of the system for all kinds of possible clinical studies (fast and slow dynamic, static, gated and combined studies),
- continuous upgrading,
- low price (less than 3.000 US $),
- 4 years for development and validation.

Basic demands for software development

- MS-DOS operating system in WINDOWS (3.1, 95, 98),
- PIP system for patient database and general data processing,
- tools for end-user development of clinical protocols (C++ library, macro functions),
- algorithms for automatic analysis of clinical data with possible manual intervention,
- tools for image, dynamic curves and ROI processing,
- images from study analysis in standard picture formats (i.e. PCX, BMP),
- set of gamma camera quality control functions (NEMA tests),
- converter to and from "Interfile" format,
- SVGA colour scale for display,
- results of analysis on one page,
- printing of documents in high spatial resolution (1200x1200 dots/inch) and on low cost high quality media (paper, transparencies),
- archiving the original image data and reporting documents on low cost CD as "soft" copy,
- network support,
- user-friendly system,
- clinically validated software.

Three experienced research institutions from developing countries were selected for building the upgrading system: Ljubljana University Medical Center,[1,2] Bombay Nuclear Research Institute[3] and Havana University Institute,[4]

Acquisition system

Basically two different approaches were used in the development:

1. The acquisition card from Bombay Nuclear Research Institute[3] with the signal's gain and offset control, AD conversion, energy correction, creating images and gate control. Communication with computer is triggered by interrupt service. Computer's time control is used. Setup of gamma camera signal's gain and offset is performed manually (Figure 1).

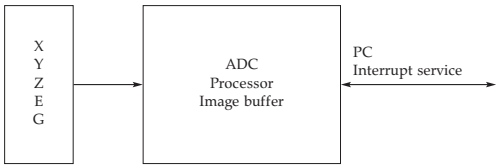


Figure 1. Principle of the Indian acquisition system. Positional (X and Y), strobe (Z), energy (E) and gate (G) signals are converted into digital form in the acquisition card, which also creates image and send it to the computer by applying the interrupt service.

2. The acquisition card from Havana University Institute[4] with the signal's gain and offset control, AD conversion with saving the position, energy and other control data (i.e. gate signal, signal for gantry control) are transferred to the computer's memory using PORT transfer. The interrupt service is used for triggering the data transfer (Figure 2). Gain and offset adjustment is performed manually.

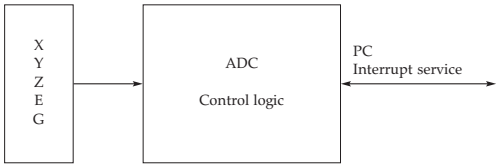


Figure 2. Principle of the Cuban acquisition system. Positional, strobe, energy and gate signals are converted into digital form in the acquisition card, which sends them to the computer by applying the interrupt service.

3. The acquisition card from Ljubljana University Medical Centre[2] with the signal's gain and offset and time control, AD conversion, saving of position, energy and all other control data for each detected gamma event by computer's PORT transfer to the computer memory, software control of analogue signals for zooming, gain, offset and orientation settings. Computer has complete control on the acquisition at every moment. Interrupt pulse is not used for triggering the communication between the acquisition card and computer (Figure 3). The setup of signal's gain and offset (for X, Y and E) is performed automatically through "computer - acquisition card" feedback control (Figure 5) by appropriate software[1] algorithm (Figure 4).

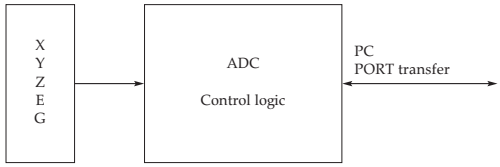
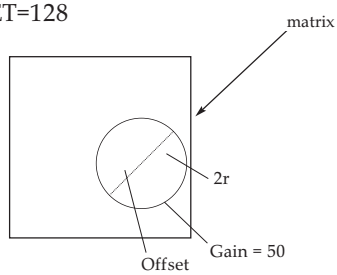
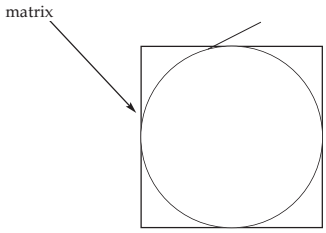


Figure 3. Principle of the Slovenian acquisition system. Positional, strobe, energy and gate signals are converted into digital form in the acquisition card, which sends them to the computer through PORTs without interrupt service.

4a. Initial gain and offset settings:
X, Y range: ±0.5V to ±3V, GAIN = 50,
OFFSET=128



4b. Gain and offset settings at the end of automatic adjustment:
GAIN=200, OFFSET=90,



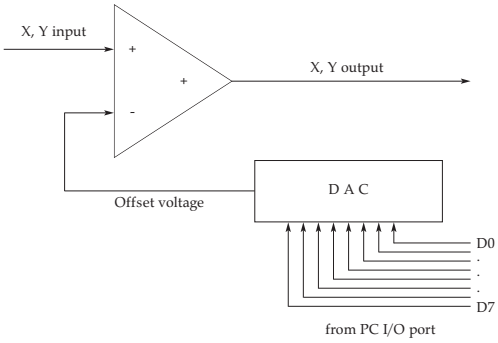
4c. Iterative loop for gain adjustment. By increasing the gain of positional signals the image diameter is proportionally increased.

$$\text{gain} \uparrow \Rightarrow 2r \uparrow$$

Figure 4. Algorithm for automatic adjustment of interfacing card's gain and offset settings for positional signals X and Y.

All manipulations with the data on image creation, time, count and gate control are performed by PC.

a) Offset adjustment



b) Gain adjustment

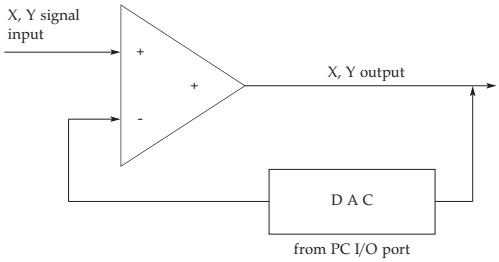


Figure 5. Digital control of offset (a) and gain (b) for analogue positional (X and Y) signals. By reverse control from the computer to the acquisition card, the analogue signals are appropriately adjusted: a definite constant voltage is added for offset adjustment (a) and part of the signal is taken for gain adjustment (b).

Results

Acquisition cards

All three research institutions developed a few prototypes in the project time. The last and the final version was evaluated in details by several institutions: Institute of Biomedical Techniques and Physics, AKH, Vienna, Turkey Atomic Energy Commission, Argentina National Atomic Energy Commission, and at three expert meetings (in Ljubljana, Ankara and Santiago de Chile). The conclusion from all involved testing institutions and experts was that all acquisition cards fulfill most of the required features. The final conclusion of the testing was:[5] "The Slovenian system GAMMA-PF is the most adequate, due to better technical performance, stability of functioning, facility of installation, technical support, lower price, accomplishing in delivery time schedules and professionalism of the involved team". The most probable cause of instability of Indian and Cuban cards is the interrupt service for communication between acquisition card and PC.

Slovenian acquisition and processing system GAMMA-PF

In the following, the features of Slovenian acquisition card are presented:

- standard PC hardware,
- acquisition can not run simultaneously with processing,
- one 16-bit PC AT professionally designed card in four layers,
- range of X and Y analogue bipolar signals from ± 0.5 V to ± 10 V,
- alternative software or manual adjustment of GAIN and OFFSET settings for X, Y and E signals,
- software adjustment of ZOOM (1.0, 1.5, 2.0 and 2.5) to analogue positional signals and image ORIENTATION,
- matrix sizes from 32 x 32 to 256 x 256 in words,

- all standard acquisitions (static, dynamic, gated and combined static-dynamic) with on-line energy and count correction,
- stopping condition: by time, counts or time/counts (which is reached the first),
- persistence scope function for gamma camera tuning with continuous computation of regional count density,
- count loss: < 1 % without energy correction, < 10 % with energy correction measured at count-rate of 50 K c/s,
- energy correction is performed by the acceptance of current pixel's energy from the look-up matrixes of low and high photopeak limits,
- energy correction: integral uniformity index is lowered by factor 2,
- count correction: integral uniformity index is lowered by factor 3 - 5.

One of the most important results of testing the effect of uniformity and energy correction was that the count correction decreases much more (by factor 3-5) the integral uniformity index than the energy correction (by factor 2). This study was performed on GE 300A gamma camera with artificially suppressed one of the PMTs for approximately 60 % (Table 1 and Figure 6).

Another important result is the recommendation that the count correction should be applied only for images from gamma cameras which have integral uniformity index less than 30 %. At higher values the noise amplification overcomes the signal and the false positive spots become visible in the corrected scans at low count images.[2]

Clinical software

Besides the basic tools for image, region of interest and dynamic curves processing functions, the set of most important clinical protocols was developed.

- Heart:
  Gated ventriculography: ejection fraction, amplitude and phase images, phase histogram, contraction images, movie display,
  Shunt: gamma-variate fit, left-right shunt ratio.
- Kidneys:
  Renography (MAG3, DTPA): relative function, Tmax, T1/2, deconvolution analysis.
  DMSA: relative function with attenuation correction.
- Lung perfusion: relative function with attenuation correction.
- Salivaries: pertechnetate uptake, excretion after ascorbic acid stimulation.
- Thyroid: pertechnetate uptake in 15 minutes.
- For all other studies the basic tools for image processing is available (contrasting, movie display, different colour scales, ROI selection, dynamic curves, etc).

Analysis is nearly completely automated with possible quality assurance interventions: correction of automatically determined ROI, manual correction of time intervals for relative function computation in dynamic curves, movie display of sequential images with plotted ROIs, manual correction of automatic selection of end-systolic image, manual correction of time intervals for "shunt" analysis, etc. Most of the patient studies can be

Table 1. Analysis of scan uniformity by NEMA standards

SCAN	Integral uniformity (%)		Differential uniformity (%)	
	UFOV	CFOV	UFOV	CFOV
Original	49.8	49.2	23.2	23.2
Energy corrected	23.6	23.6	9.6	9.6
Count corrected	6.7	6.6	3.4	3.4
Energy and count corrected	4.7	4.6	2.4	2.4

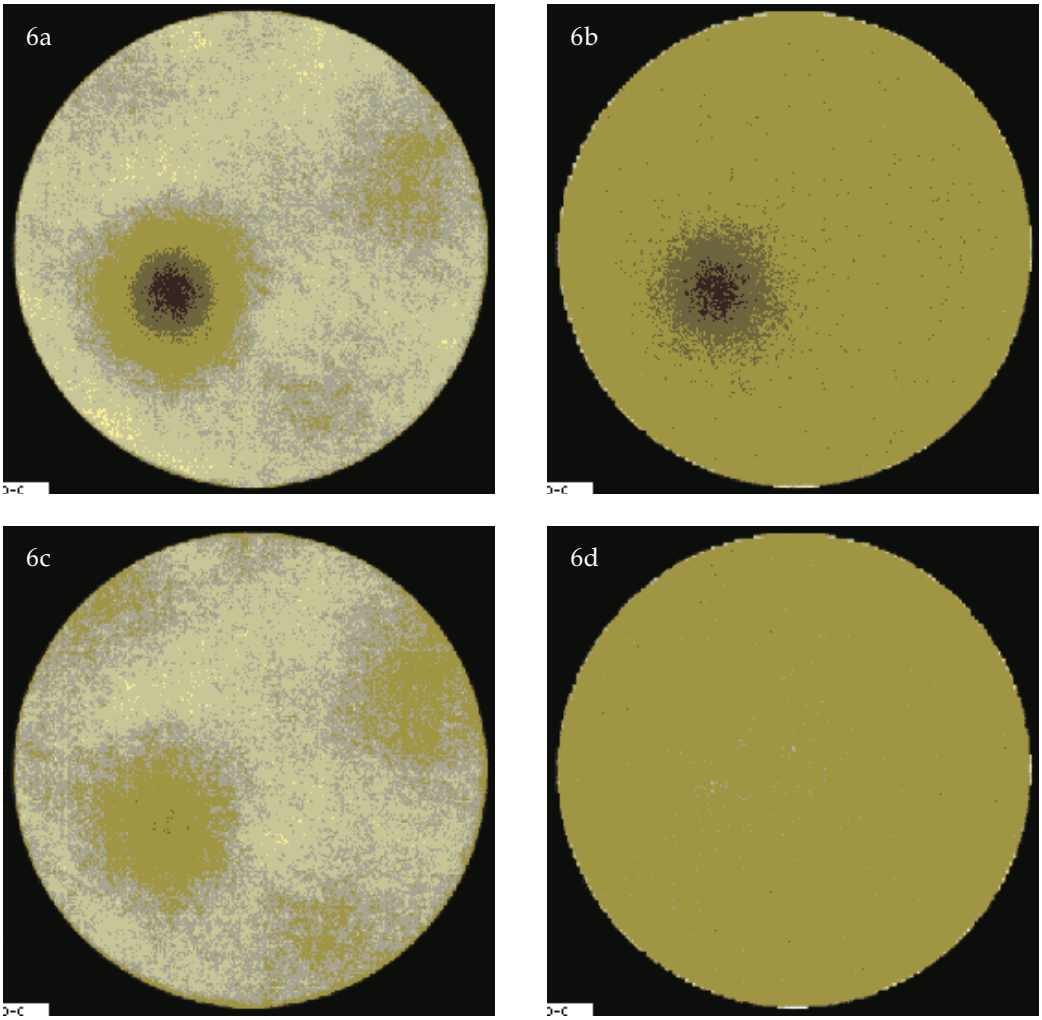


Figure 6. Effect of on-line energy and count correction on gamma camera (GE 300A) image with 60% suppressed one PMT. **6a.** Original image. **6b.** Only count corrected. **6c.** Only energy corrected. **6d.** Energy and count corrected.

processed in less than 2 minutes. An example of MAG3 analysis is shown in Figure 7.

Networking

Setup of network with GAMMA-PF system (Figure 8) can be done either by NOVELL, Microsoft Network or WINDOWS NT network software. The acquired studies, images from analysis and documents are stored on common server's disk, archived on CD or other large scale storage media, printed on high quality ink-jet or laser-jet printers and communication performed through hospital to external lines.

Distribution of acquisition cards with software

In 1998, there were 2689 gamma cameras in the developing world. This is nearly the same as in Japan. In the past 15 years 48 planar and SPECT gamma cameras were donated to 39

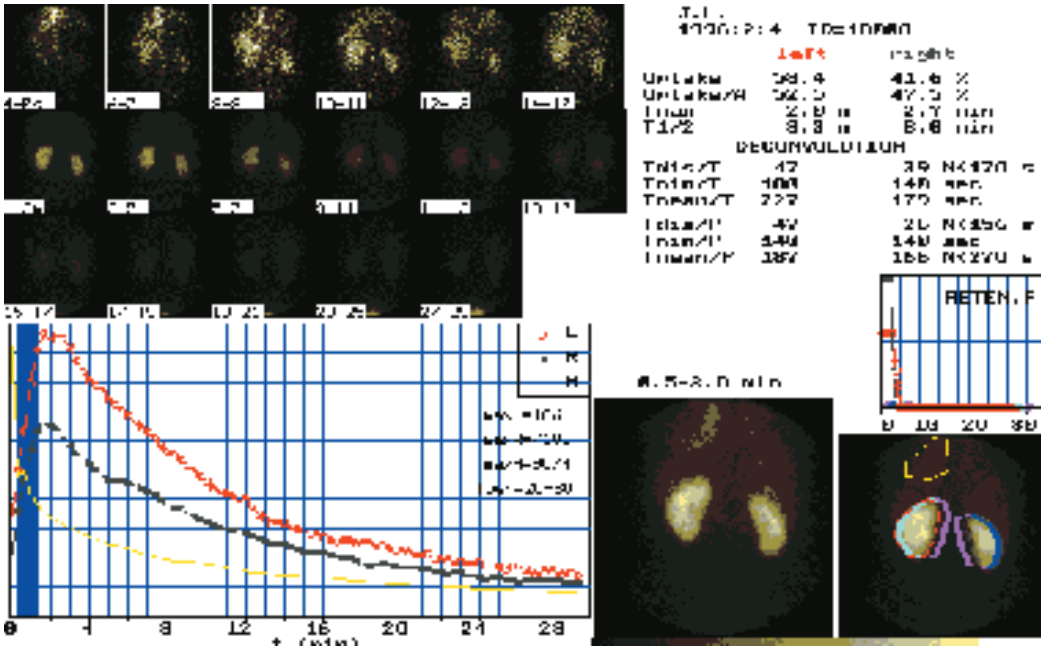


Figure 7. Example of the final results from MAG3 study analysis.

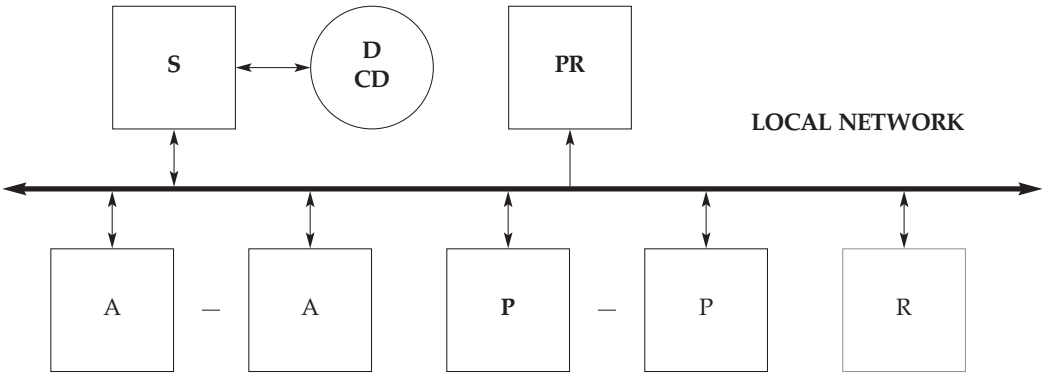


Figure 8. Functional schema of GAMMA-PF network.
A: acquisition; P: processing; R: reporting PC; S: server; D: common hard disk; CD: compact disk (read/write); PR: printer

member states. Along with the donated cameras, IAEA distributed 234 PC gamma interface cards to 52 member states. Main achievements of the IAEA projects on upgrading are the following:[6]

- low cost (about 5.000 US $ including a Pentium PC, gamma camera interfacing card and PIP software),
- significant improvement of old gamma camera images (uniformity from 20 % to 5 % after both on-line energy and count corrections),
- life prolongation of old gamma camera for about 5 - 10 years,
- increment of diagnosis throughput by estimated 30 - 40 %,

- high quality black and white or colour images with new low cost generation of printers instead of film,
- knowledge improvement in nuclear medicine technology for engineers, physicians and technologists on training courses in all regions of the developing world.

Discussion

The IAEA project of upgrading analogue gamma cameras in the developing world gained some important results: prolongation of old analogue planar gamma cameras, improvement of quality assurance of images by online count and energy correction, replacing old computer technology with new PC, introducing computer network, archiving of studies, communication inside nuclear medicine departments and improvement of the technological knowledge of nuclear medicine stuff. These results have a definite limited value. Upgrading project should be implemented also to other nuclear medicine equipment, i.e. thyroid uptake system, gamma counters for RIA, multi-probe systems and monitors. There are also some other detector systems that should be included in the future development, i.e.: radio-chromatograph, whole-body scanning bed (bones, white cells, metastases), monitor for patient whole body radioactivity (for checking patient activity before dismissing form hospital), etc. Also the energy and count correction should be improved in the future by physically more feasible method - equalizing the PMT output (either changing the high voltage setting or changing the PMT gain). This should improve the gamma camera spatial uniformity as well as linearity. But to achieve this the electronics of the gamma camera head and the electronic console should be replaced completely by the digital system.

Conclusions

The IAEA project of upgrading the old analogue gamma cameras by PC based acquisition and processing systems yielded a high promotion of nuclear medicine in the developing world. Besides the immediate help to 52 member states in the life prolongation of old gamma cameras, somewhere also reviving the nuclear medicine, it also improved the technological knowledge of nuclear medicine stuff on several training courses on upgrading and quality assurance of planar and SPECT gamma cameras and programming of clinical protocols. Among the three financially supported projects for development of acquisition system the Slovenian one was assessed by expert testing and end-user evaluation as technically the most advanced, functionally stable, user-friendly concerning the installation with setup of image size, offset and energy settings, simplicity of clinical protocols with quality assurance functions, delivery time, with smallest price and was mostly distributed.

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Design considerations for direct and indirect active matrix flat-panel portal imagers

Martin Lachaine and Biagio Gino Fallone

Department of Medical Physics, Cross Cancer Institute, University of Alberta, Alberta, Canada
Department of Physics, McGill University, Montreal, Canada

Background. *Recent advances in thin film transistor (TFT) technology have allowed the construction of active matrix flat-panel imagers (AMFPI) for various medical imaging modalities. Since the design of such systems is still in the development stage, it is unclear what detector characteristics are required in order to optimize these detectors for portal imaging.*
Material and methods. *In this work, we used cascade analysis and Monte Carlo techniques to calculate the DQE for both direct and indirect AMFPIs for portal imaging, and use these calculations to study the optimal detector characteristics. We validate our calculations with existing experimental data.*
Results. *We show that the for ideal flat-panel characteristics the direct and indirect detection methods have the same DQE for a given mass thickness.*
Conclusions. *We generate graphs which may be helpful in the design of future megavoltage AMFPIs.*

Key words: portal imaging, Monte Carlo method; DQE, AMFPI, EPID; amorphous selenium

Introduction

During a radiation therapy treatment, many factors may influence the proper delivery of a calculated dose distribution. Some of these factors include misalignment of the treatment beam with respect to the patient, external or internal patient motion, or inaccurate positioning of beam-modifying devices.[1] In order to quantify these geometric inaccuracies during treatment, a portal image is typically extracted from the megavoltage treatment beam with a radiation-sensitive detector. In this manner it is possible to verify the position of the radiation field relative to the bony anatomy. Portal imaging has also been studied with varying success for use in exit dosimetry, where the images are used to verify the dose distributions delivered to the patient.[2,3]

Traditionally, film has been used as the portal imaging detector. Over the past decade, several electronic portal imaging devices (EPIDs) have been developed for the

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Correspondence to: Prof. B. Gino Fallone, PhD, FCCPM, ABMP, Medical Physics, Cross Cancer Institute and University of Alberta, 11560 University Avenue, Edmonton, Alberta T6G 1Z2, Canada. Phone: +1 780 432-8750; Fax: +1 780 432-8615; E-mail: Gino.fallone@cancerboard.ab.ca

purpose of replacing film.[4] The inherent advantages of such inherently digital detectors include immediate viewing and the ability to use contrast-enhancing algorithms to improve image quality. Despite these advantages, however, EPIDs have not widely replaced portal films. This has been attributed to poor image quality, limited field of view, and bulkiness.[5]

In recent years, thin film transistor (TFT) technology has lead to the development of a new category of digital x-ray detectors.[6-8] Such detectors, often called *active-matrix flat panel imagers* (AMFPIs), may use either the *indirect* or the *direct* detection of x-rays to form the digital image. The indirect method typically uses a phosphor to convert the incident x-rays into visible light, which are then converted into electron-hole pairs by an array of photodiodes. The charge is collected in the photodiodes during the image formation, and subsequently read out electronically. The direct method, on the other hand, uses a photoconductor such as amorphous selenium (*a*-Se) to directly convert the x-rays into electron-hole pairs, which are collected at pixel electrodes through the use of an applied electric field. The charges are stored in the capacitors of the active matrix during irradiation and subsequently read out.

Characteristics which must be considered when designing AMFPI detectors include the detection method (indirect or direct), detector thickness, pixel size, fill factor, and electronic noise characteristics. Some of these are difficult to quantify experimentally, since construction of AMFPIs is expensive. For this reason, it is useful to use theoretical techniques to describe AMFPI image quality, which is often quantified in terms of the detective quantum efficiency (DQE).

Cascaded systems analysis[9] has successfully been applied to calculate the DQE of AMFPI detectors in the diagnostic energy range.[10,11] These analyses have been useful in studying detector designs for various modalities such as mammography, chest radiography and fluoroscopy. At the energies used in these modalities, there is little spread of the ionizing radiation within the detector and thus this spreading is not taken into account in the analysis. At megavoltage energies, however, x-rays produce high energy electrons within a metal build-up layer (conversion plate) which is placed above the sensitive volume of the detector. These high energy electrons scatter within the detector, resulting in an additional loss of resolution.

Bissonnette *et al.*[12,13] have taken this additional process into account to model both video-based and indirect AMFPI portal imagers. Their analysis, however, did not agree with data measured by Munro and Bouius.[14] This disagreement was attributed to the fact that it is impossible to experimentally separate the spread of high-energy radiation from the spread of the visible light within the phosphor. In our work, we use Monte Carlo methods to investigate this particular problem for both direct and indirect portal AMFPIs.

The design constraints for portal AMFPIs are different than for diagnostic AMFPIs, and have to date not been studied. We thus use the cascade analysis formalism to explore potential benefits of the direct versus the indirect detection methods for portal imaging, and to explore the effects of detector thickness, pixel size, fill factor and electronic noise on the DQE at megavoltage energies for both indirect and direct detection techniques.

Materials and methods

We first consider the interaction of quanta with the detector, which are referred to as *analog* processes. We make the approximation that these can be divided into elementary *amplification* stages (which includes binary selection as a special case) and *dislocation* stages according to cascade analysis.[9,15] We neglect depth-dependent quantities (*i.e.* the Lubberts

effect).[16] In order to include both direct and indirect detection, we use the term *secondary quanta* to refer to optical quanta or electron-hole pairs for the case of indirect and direct detection, respectively. Similarly to Bissonnette *et al.*,[12] we use the following stages: *1)* interaction of x-rays with the detector, which is a binary selection stage with probability equal to the x-ray quantum efficiency of the detector η_x; *2)* spread of ionizing radiation within the detector, a dislocation stage which has a Modulation Transfer Function (MTF) equal to $T_{rad}(f)$; *3)* creation of secondary quanta; an amplification stage with average gain $\overline{g}_{sec}$ and variance σ^2_{sec}; *4)* spread of secondary quanta, a dislocation stage which has an MTF equal to $T_{sec}(f)$; and *5)* loss of secondary quanta, a binary selection stage with probability η_{loss}. Following these stages, the analog DQE becomes

$$DQE_a(f) = \frac{\eta_x \eta_{loss}^2 \overline{g}_{sec}^2 |T_{rad}(f)|^2 |T_{sec}(f)|^2}{\eta_{loss}^2 \left[|T_{sec}(f)|^2 (\overline{g}_{sec}^2 + \sigma_{sec}^2) + (1 - |T_{sec}(f)|^2) \overline{g}_{sec} \right] + \eta_{loss}(1 - \eta_{loss}) \overline{g}_{sec}}$$

which simplifies to

$$DQE_a(f) = \eta_x \frac{\overline{g}_{sec}^2}{\overline{g}_{sec}^2 + \sigma_{sec}^2} |T_{rad}(f)|^2 \qquad (2)$$

in the limit $\overline{g}_{sec}$ >>1 which is the case for *a*-Se and Gd_2O_2S:Tb detectors where typically ~10^4 secondary quanta are created per interacting x-ray. The analog DQE of Eq. (2) represents the intrinsic DQE of a metal/phosphor or metal/photoconductor detector at megavoltage energies. In the approximation of the cascade analysis we have used, this DQE is thus seen to be degraded only by the x-ray quantum efficiency η_x, the variance σ^2_{sec} and the spread of ionizing radiation $T_{rad}(f)$, but not the spread of secondary quanta $T_{sec}(f)$ or the loss of secondary quanta η_{loss}.

In an AMFPI, the analog signal is first integrated over the active matrix pixels, and then sampled to create a digital signal. An electronic noise component S_e is then added to the noise power spectrum (NPS) by the flat panel, leading to a digital DQE for a direct or indirect AMFPI:

$$DQE_{dig}(f) = \frac{\eta_x |T_{rad}(f)|^2 |T_{sec}(f)|^2 \mathrm{sinc}^2(af)}{\left[\left(1 + \frac{\sigma_{sec}^2}{\overline{g}_{sec}^2} \right) |T_{sec}(f)|^2 \mathrm{sinc}^2(af) \otimes \sum_{j=-\infty}^{\infty} \delta\left(f - \frac{\eta_x}{d}\right) \cdot S_e \right]}$$

where

$$S_e = \frac{S_e}{\eta_x \eta_{loss}^2 \overline{g}_{sec}^2 a^4 q_0}$$

$\overline{g}_0$ is the incident fluence, *a* is the pixel size and *d* is the pixel pitch. For perfect flat-panel characteristics, *i.e.* infinitesimally small pixels and no electronic noise, the digital DQE reduces to the analog DQE. We refer to this as the *ideal* DQE for an AMFPI detector.

In order to calculate the DQE for both direct and indirect detectors at megavoltage energies, we need the quantities, *i.e.* η_x, $\overline{g}_{sec}$, σ^2_{sec}, and $T_{rad}(f)$. These quantities depend on the incident energy spectrum, and the densities, atomic numbers, and thicknesses of the front plate and sensitive layers. We determined these quantities for metal/phosphor and metal/*a*-Se detectors by Monte Carlo methods using EGSnrc.[17] The technical details have been previously described.[18] Briefly, two different types of simulations are used. The first type of simulation scores the energy absorbed in the sensitive region of the detector in order to determine the absorbed energy distribution (AED).[19] The quantum efficiency is then given by the zeroth-moment of the AED, and the quantities $\overline{g}_{sec}$ and σ^2_{sec} can be calculated using the first and second moments, respectively. The second set of simulations determine the spatial distribution of energy deposited in the sensitive region of the detector due to an infinitesimally thin line of incident x-rays. The resulting distribution corresponds to the LSF, from which we calculate $T_{rad}(f)$ using Fourier analysis.

In our calculations, we use an incident 6 MV spectrum as given by Kubsad *et al*.[20] The detectors for the indirect detection AMFPIs are modeled with a Cu front plate and a gadolinium oxysulfide Gd_2O_2S:Tb phosphor screen with a reduced density of 3.67 g/cm^3 as described by Jaffray *et al*.[19] For direct de-

tection, the front plate is modeled in the same fashion but the phosphor layer is replaced by atomic Se with a reduced density of 4.27 g/cm^3 to match that of the amorphous state. Describing *a*-Se in this fashion is an excellent approximation for studying macroscopic energy deposition only.[21]

For the case of direct detection, we use $T_{sec}(f)$=1. For indirect detection, we need the MTF describing the spread of visible light. For this purpose, we use the experimental MTFs for phosphor screens measured by Bissonnette *et al*.[13] These total MTFs $T_{tot}(f)$ are equivalent to the product

$$T_{tot}(f)=T_{rad}(f)T_{sec}(f). \quad (3)$$

To calculate $T_{sec}(f)$, we therefore divide the total experimental MTF by the MTF due to the spread of high energy radiation obtained by Monte Carlo techniques.

We first investigate what we have defined as the *ideal* DQE, *i.e.* the intrinsic DQE of metal/phosphor or metal/*a*-Se, given by Eq. (2). We calculate the ideal DQE as a function of spatial frequency for a 1 mm Cu front plate coupled with the following sensitive detectors: four phosphors of different mass thicknesses, namely 67 mg/cm^2 (Lanex Regular), 134 mg/cm^2 (Lanex Fast Back), 358 mg/cm^2, and 721 mg/cm^2; and four *a*-Se thicknesses, namely 46 mg/cm^2 (0.2 mm), 92 mg/cm^2 (0.4 mm), 138 mg/cm^2 (0.6 mm), and 184 mg/cm^2 (0.8 mm).

Once we have explored the ideal DQE, we use the results to explore the effects of the active matrix, *i.e.* pixel size, fill factor and electronic noise, using Eq. (3). In our calculations, for *a*-Se we assume that η_{loss} is governed only by recombination and assume a recombination fraction of 0.25.[22] For the case of phosphor we assume that η_{loss} is governed only by the absorption of visible light within the phosphor, and use the values tabulated by Bissonnette *et al*.[13] We assume that there are no further losses in the coupling of the secondary quanta to the active matrix array.

In order to validate our cascade analysis for AMFPI detectors, we calculate the DQE for the indirect AMFPI detector described by Munro and Bouius,[14] which consists of a 1.5 mm Cu front plate followed by a Lanex Fast Back phosphor screen (134 mg/cm^2 $Gd_2O_2S_4$:Tb). Their detector is placed on top a glass substrate which we include in our EGSnrc simulations. This glass substrate increases the energy deposited in the phosphor due to backscatter. Their active matrix is comprised of 0.75 mm pixels with a fill factor of 54%. They have determined that their detector is quantum limited at the exposures and spatial frequencies described in their paper, and we can thus neglect electronic noise in Eq. (3) for this case (for spatial frequencies below 1 cycle/mm).

To investigate the effects of aliasing and electronic noise, we calculate the DQE as a function of pixel size and electronic noise for two fill factors: 50% and 90%, for both direct and indirect detection techniques and with the same thicknesses described above for the case of the ideal DQE (the fill factor is defined as $F_p = a^2/d^2$).

Results

In Figure 1 we show the digital DQE we have calculated for the detector described by Munro and Bouius. We show excellent agreement to their data, which shows that the approximations we have used in the calculation of the DQE are justifiable.

In Figure 2 we show the ideal DQE(f) for indirect and direct detection methods respectively. The DQE(0) for each case can be seen to increase with mass thickness. The ideal DQE for both indirect and direct detection methods are degraded with spatial frequency only by the square of the MTF due to the spread of high energy radiation. This degradation is more pronounced as the mass thickness increases, but over the spatial frequency range shown, the ideal DQE(f) is superior for a larger mass thickness.

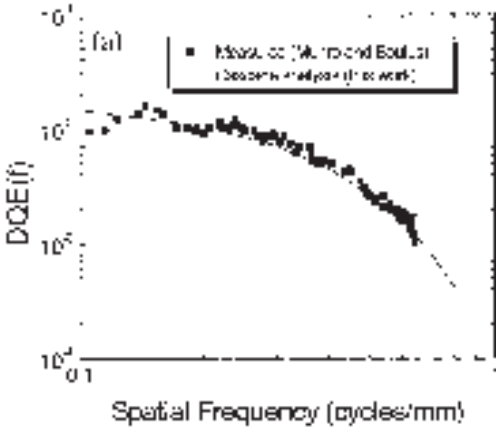

Figure 1. (a) DQE calculated from our cascade analysis for the indirect AMFPI described by Munro and Bouius, compared to their experimental data.

In order to show the effect of system noise and pixel size on the various detectors, we present our results as contour plots of the DQE normalized as a percentage of the ideal DQE. In this fashion, one can pick the appropriate design characteristics for a given detector, and visualize the corresponding degradation of the ideal DQE. The contour plots are shown at two reference spatial frequencies (0 and 1 cycles/mm) and for two fill factors (50% and 90%), for indirect detection and for direct detection AMFPIs in Figure 3 and Figure 4, respectively.

Discussion

For a given mass thickness, the ideal DQE is approximately the same for the direct and indirect methods, because as previously discussed, the NPS compensates for the degradation of the MTF. Since present practical phosphors generally have larger mass thicknesses than *a*-Se, the ideal DQEs shown are slightly greater for the indirect method. This can be overcome by increasing the thickness of *a*-Se to over 1 mm, which may however be technically difficult to attain while maintaining adequate uniformity of the *a*-Se.

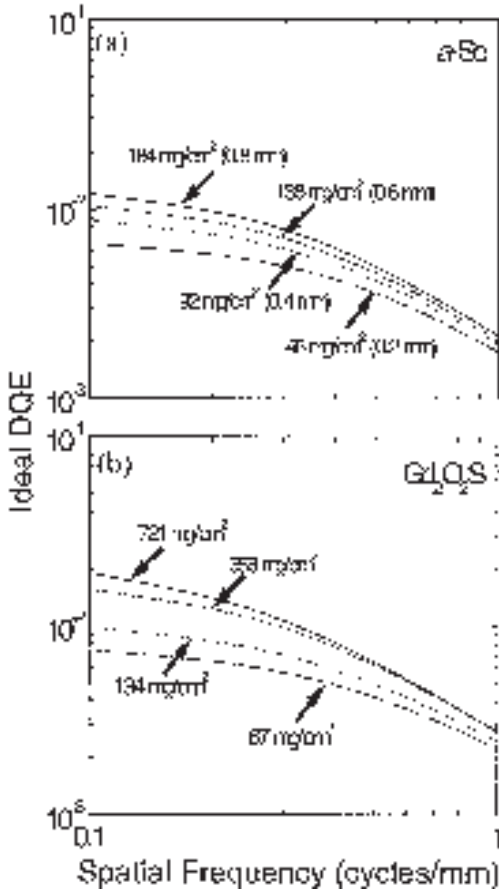

Figure 2. Ideal DQE (i.e. no system noise and no aliasing effects) for (a)direct (*a*-Se) and (b) indirect (Gd_2O_2S) AMFPIs. Theoretical calculations are for various phosphor thicknesses (a 1 mm Cu front plate and 6 MV photon beam are used).

By inspection of Figure 4, it can be seen that for indirect detection AMFPIs, the pixel size should be kept below about 0.3 mm and the electronic noise per incident fluence below about 10^5 mm^2 in order to ensure that the DQE is not significantly degraded. The fill factor is seen not to be an important factor for indirect detection detectors, as expected from the previous discussions.

For direct detection AMFPIs, the constraint on the pixel size is approximately the same as for indirect detection, but the electronic noise per incident fluence can be about

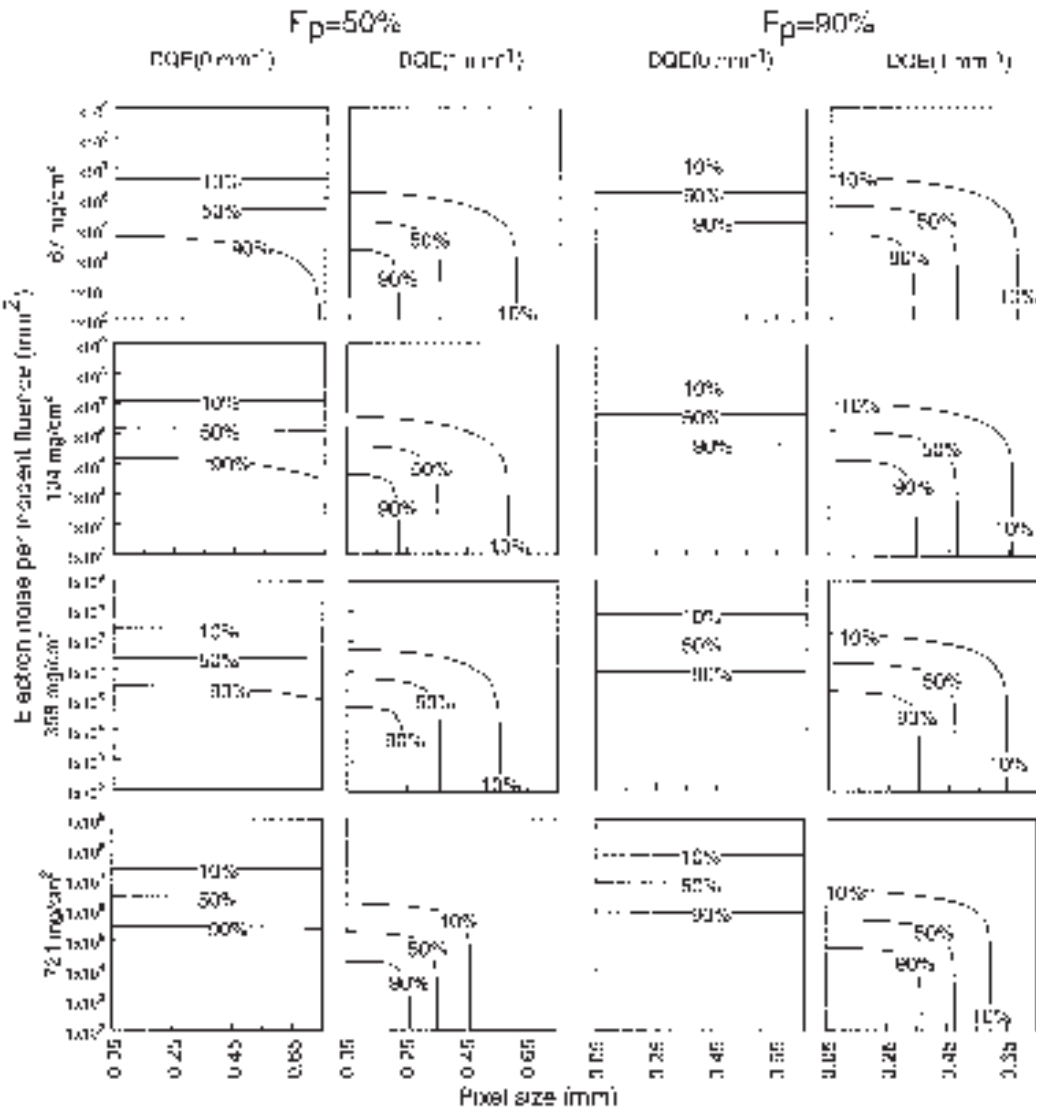

Figure 3. Contour plots of DQE at 0 and 1 cycles/mm, normalized as a percentage of the ideal DQE, for indirect AMFPIs as a function of pixel size and system noise per incident fluence. Plots are shown for both 50% and 90% fill factors, and for various phosphor thicknesses (a 1 mm Cu front plate and 6 MV photon beam are used).

two orders of magnitude greater than that for indirect detection, *i.e.* about 10^7 mm^2, before significantly degrading the DQE. It can also be seen, however, that the fill factor must be maximized for *a*-Se detectors. Several techniques have been discussed by Pang *et al.*[23] in order to increase the effective fill-factor.

The constraints on pixel size and electronic noise have been achieved in prototype detectors for diagnostic radiology, indicating that AMFPIs for portal imaging with DQEs equal to their ideal DQE can be manufactured. The AMFPI described by Munro *et al.* has been shown to be quantum limited, but

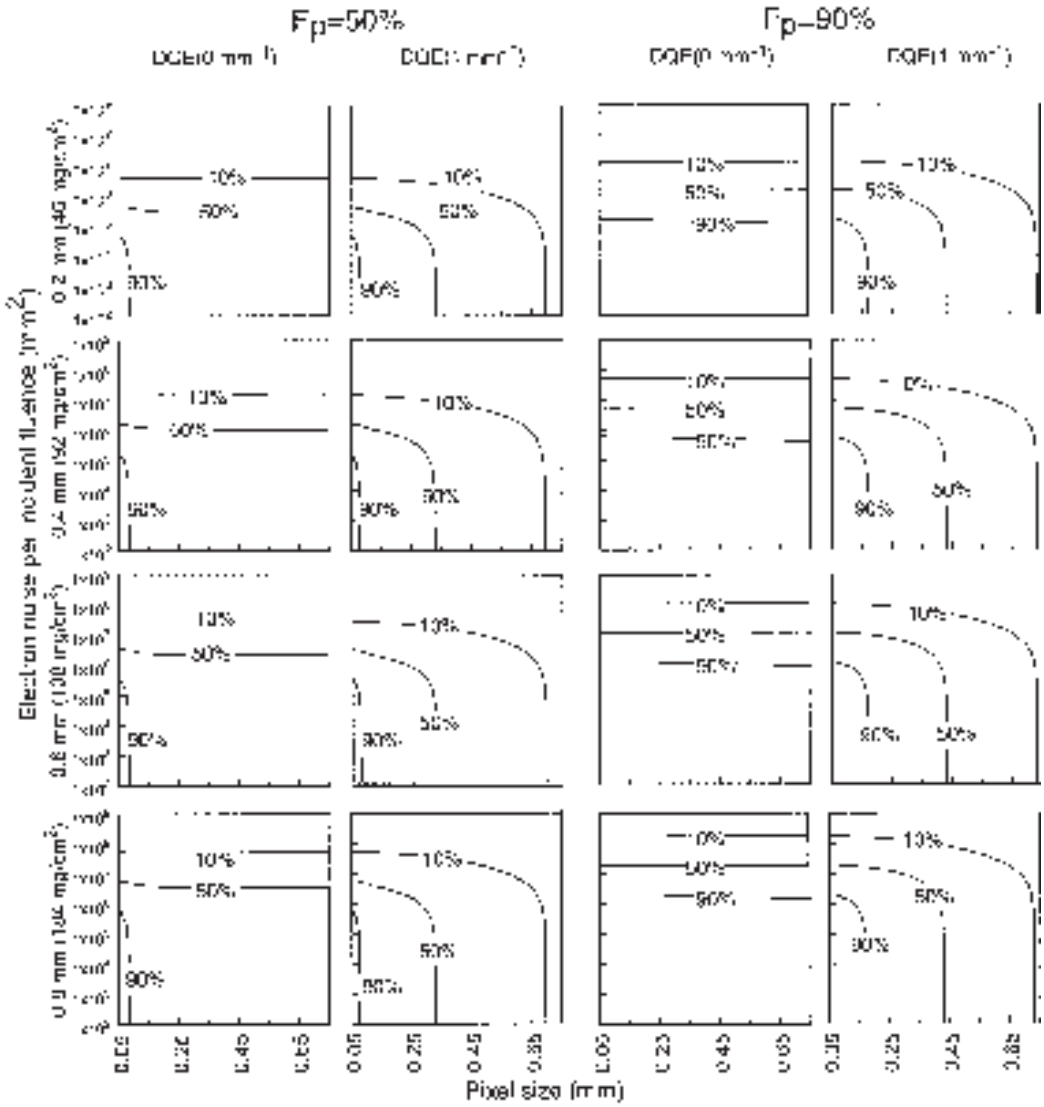

Figure 4. Contour plots of DQE at 0 and 1 cycles/mm, normalized as a percentage of the ideal DQE, for direct AMFPIs as a function of pixel size and system noise per incident fluence. Plots are shown for both 50% and 90% fill factors, and for various a-Se thicknesses (a 1 mm Cu front plate and 6 MV photon beam are used).

we have shown that its DQE could be improved if the pixel size were reduced from 0.75 mm to below 0.3 mm.

We have calculated the constraints on pixel size and electronic noise for both indirect and direct detection AMFPIs. In essence, if these constraints are satisfied, there is no significant advantage in using either the direct or indirect detection methods for megavoltage imaging. The main difference will likely be related to the manufacturing costs of building active matrices with specific pixel sizes, fill factors, and electronic noise. The cost and ease of manufacturing uniformly sensitive phosphors and *a*-Se layers must also be explored.

Conclusions

We have presented an approximation which describes the DQE of AMFPI detectors for portal imaging, for both direct and indirect detection methods. We validate our approximation with existing measurements of a prototype indirect-detection AMFPI and a metal/phosphor detector.

We calculate the ideal DQE for both direct and indirect detection AMFPIs for portal imaging. We show that although the resolution of the indirect detection method is superior to that of direct detection, the decrease in NPS compensates for this decrease in resolution.

We explore the effects of electronic noise, pixel size and fill factor for direct and indirect AMFPI detectors. We show that aliasing effects are more serious using the direct method, but that requirements on the electronic noise of the active matrix are more stringent for the indirect method. We show plots of the DQE as a function of system noise and pixel size for various detector thicknesses which should prove helpful in the design of future AMFPI detectors for portal imaging.

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Radiol Oncol 2001; 35(1): 1-10.

Stenti Z, oplaščeni s submukozo tankega črevesa v žolčnem sistemu: Rezultati preliminarne raziskave na živalskem modelu

Yamakado K, Pavčnik D, Uchida BT, Timmermans H, Corless CL, Park JW, Yamada K, Keller FS, Rösch J

Namen. Z raziskavo na svinjah smo testirali uporabnost in biološki odgovor kovinskih stentov v žolčnem sistemu, oplaščenih z submukozo tankega črevesa (SIS).

Materiali in metode. V skupni žolčevod 6 svinj smo vstavili 9 enojnih stentov Z, oplaščenih s submukozo tankega črevesa. Stente smo vstavili z laparatomijo skozi žolčni mehur in žolčnikov vod. Živali smo žrtvovali ali usmrtili 2 tedna (n=1), 4 tedne (n=2) in 10 tednov (n=2) po vstavitvi stentov. Hkrati smo izvedli tudi histološke preiskave.

Rezultati. Šestim živalim smo vgradili 9 stentov. Med pregledi po 2, 4 in 10 tednih so 3 stenti v 3 živalih ostali na svojem mestu, medtem ko se je 1 v skupnem žolčniku distalno premaknil, 5 pa se jih je obrnilo postrani. Vseh 9 stentov je bilo prehodnih. Po 10 tednih smo opazili, da se je žolčevod razširil, pretakanje žolča pa se je upočasnilo. Submukoza v tankem črevesu je ostala tudi po dveh tednih in se niti po 4 tednih niti kasneje ni histološko spremenila. Histološka preiskava ni odkrila nobenih vnetnih sprememb v žolčevodih preizkusnih živali. V 2 od 3 nepremaknjenih stentov niti po 2 niti po 10 tednih nismo opazili hiperplazije mukoze, v enem distalno premaknjenem stentu pa se je pojavila po 10 tednih. Zmerno hiperplazijo mukoze smo po 4 tednih opazili na distalnem delu nepremaknjenega stenta in po 8 in 10 tednih pri 5 premaknjenih stentih.

Zaključek. Četudi je zaradi visokega odstotka premaknjenih stentov raziskava omejena, so rezultati nepremaknjenih stentov, ki urejajo pretok žolča, potrjujejo, da stenti v tankem črevesu, oplaščeni s submukozo preprečujejo vnetje žolčevoda in hiperplazijo mukoze, ki sta pogosti pri neoplaščenih stentih. Raziskave bomo nadaljevali in jih še posebej izboljšali na stentih z ovlaženo submukozo tankega črevesa.

Radiol Oncol 2001; 35(1): 11-6.

Slikovna diagnostika hipertrofične piloriče zožitve

Frković M, Šeronja Kuhar M, Perhoč Ž, Barbarić-Babić V, Molnar M, Vuković J

Izhodišče. Rentgensko slikanje trebuha in kontrastna preiskava zgornjih prebavil sta običajni pri otrocih, kjer sumimo na hipertrofično piloriče zožitev. V zadnjem času ju dopolnjuje oziroma zamenjuje ultrazvočna preiskava. Avtorji v prispevku ocenjujejo vrednost diagnostičnega postopka pri otrocih s kirurško potrjeno hipetrofično piloriče zožitvijo.
Bolniki in metode. Avtorji so retrospektivno pregledali popise bolnikov, ki so se zdravili v zadnjih petih letih v bolnišnici Rebro zaradi hipertrofične piloriče zožitve in ugotovili, da je bilo zaradi te bolezni operiranih 14 fantov, starih od 2 (17 dni) do 10 tednov (75 dni).
Rezultati. Znak strune (string sign), znak dvojne sledi (double track sign) zdaljšanje in zožitev piloričnega kanala, znak gobe (mushroom sign), s tekočino izpolnjen želodec ter znak kljuna (beak sign) so se izkazali za značilne dignostične znake. Devet bolnkov je bilo pregledanih z ultrazvokom; pri enem je bila diagnoza napačno negativna (razlog je bila neizkušenost preiskovalca), vse ostale pa so bile pozitivne.
Zaključek. Če je klinični pregled negativen ali nejasen, je nujno potrebna še ultrazvočna preiskava, ki jo mora opraviti izkušen radiolog - specialist za ultrazvok. V primerih, ko je izvid ultrazvočne preiskave negativen, je potrebno opraviti še kontrastno preiskavo zgornjih prebavil. Kadar pa je diagnostičnih možnosti več, je kot prva na mestu kontrastna preiskava, ki opredeli bolezensko stanje.

Radiol Oncol 2001; 35(1): 17-9.

Računalniška sistema za opredeljevanje porazdelitve tlaka na kolčni sklepni površini: preizkus in rezultati

Stankovski V, Smrke D

Izhodišča. V delu sta opisana računalniška sistema *Viprecox* in *Active Contours*, ki ju uporabljamo v procesu ocenjevanja nekaterih biomehanskih parametrov kolčnega sklepa vključno z največjo vrednostjo tlaka v kolčnem sklepu p_{max}. Računalniški sistem *Active Contours* za svoje izračune uporablja standardne antero-posteriorne rentgenograme cele medenice in obeh kolkov. Aplikacija *Viprecox* v svojem jedru uporablja relativno enostaven tridimenzionalen matematični model porazdelitve tlaka na kolčni sklepni površini, ki je podrobno predstavljen drugje (npr. Iglič 1996).
Material in metode. Oba računalniška sistema smo preizkusili tako, da smo analizirali izračunane vrednosti p_{max} za 81 bolnikov (37 moških in 44 žensk).
Zaključki. Pokazali smo, da sta opisana sistema uporabna pri določanju porazdelitve kolčnega sklepnega tlaka iz standardnih anteroposteriornih AP rentgenogramov.

Radiol Oncol 2001; 35(1): 73-8.

Radiol Oncol 2001; 35(1): 21-30.

Scintigrafija skeleta v klinični praksi

Müller V, Steinhagen J, de Wit M, Bohuslavizki KH

Izhodišča. Leta 1971 so prvič izvedli scintigrafijo skeleta z ^{99m}Tc označenimi polifosfati. Od takrat je ta preiskava postala ena od najpogosteje izvajanih v nuklearni medicini. Zadnjih deset let pa so se neprestano spreminjale indikacije za obravnavano slikovno skeletno preiskavo. Predstavljamo različne indikacije, predvsem tiste, ki jih danes upoštevamo.
Zaključki. Tako kot v mnogih drugih nuklearnomedicinskih preiskavah s skeletno scintifgrafijo dosežemo veliko senzitivnost sprememb. Često ugotovimo spremembo kostnega metabolizma, preden se posledično spremeni kostna struktura, ki jo zaznamo z rentgenskim slikanjem. Na ta način lahko ugotovimo skrite kostne lezije v celotnem skeletu. Seveda pa so tako ugotovljene kostne spremembe lahko posledica zelo različnih kostnih bolezni. Kostna scintigrafija ima nizko specifičnost, zato pogosto ne moramo določiti etiologije scintigrafsko ugotovljenih kostnih sprememb. Specifičnost preiskave znatno povečamo s trifazno kostno scintigrafijo in SPECT-om.

Radiol Oncol 2001; 35(1): 31-4.

Ultrazvočno ugotavljanje pleuralnega izliva: kako majhen volumen še lahko zaznamo

Šustić A, Medved I, Kovač D, Ivaniš N, Ekl D, Šimić O

Izhodišča. Namen naše raziskave je bil določiti minimalni volumen proste tekočine v pleuralnem prostoru, ki ga je še moč ugotoviti z ultrazvokom pri kadavrih, ki so ležali vznak.
Material in metode. Raziskavo smo izvajali na 20 kadavrih (10 moških, 10 ženskih, starost 66 ±11 let; višina 172 ±9 cm; teža 75 ±12,6 kg; telesna površina 1,87 (0,2 m^2). Vsak kadaver smo punktirali obojestransko v petem ali šestem interkostalnem prostoru v medioklavikularni črti. Z venozno infuzijsko iglo smo dovajali 9% raztopino NaCl. Medtem ko je s poljubno hitrostjo vtekala tekočina, smo izvajali ultrazvočno preiskavo v predelu laterodorzalne torakalne stene tik nad pljučno bazo oz. frenikokostalnim sinusom. Ko smo zaznali tekočino med dorzalno torakalno steno in pljuči, smo prekinili dovod tekočine in ugotovili njeno količino.
Rezultati. Minimalna z ultrazvokom zaznavna tekočina v desnem pleuralnem prostoru je bila 223±52 ml in je statistično značilno korelirala s kadavrovo višino ($r = 0,69$; $p < 0,001$), težo ($r = 0,68$; $p < 0,01$) in telesno površino ($r = 0,71$; $p < 0,001$). Volumen zaznavne tekočine v levem pleuralnem prostoru je bil manjši kot na desni strani, znašal je 172±53 ml in je pravtako statistično značilno koreliral s kadavrovo višino ($r = 0,55$; $p < 0,05$), težo ($r = 0,59$; $p < 0,01$) in telesno površino ($r = 0.60$; $p < 0.01$).
Zaključki. Ugotovili smo, da najmanjši ultrazvočno zaznavni volumen intrapleuralne tekočine premosorazmerno korelira z višino, težo in telesno površino kadavrov. Izmerjena količina intraplevlarne tekočine je 223 ml na desni strani in 172 na levi.

Radiol Oncol 2001; 35(1): 35-41.

Intraoperativno obsevanje (IORT) ležišča tumorja pri karcinomu dojke

Proulx GM, Hurd T, Lee RJ, Stomper PC, Podgorsak MB, Edge SB

Izhodišča. Bolnice z zgodnjo obliko raka dojke imajo manj ponovitev bolezni, če jih postoperativno obsevamo. Takšno zdravljenje pa je dolgotrajno, zato novejše raziskave iščejo tiste skupine bolnic, ki ne bodo potrebovale postoperativnega obsevanja celotne dojke, ampak bi jih zdravili drugače. Razvili so različne oblike obsevanja, ki omogočijo enako dobre lokalne kontrole bolezni.

Bolniki in metode. Avtorji so analizirali 7 bolnic, ki so bile zdravljene z lokalnim intraoperativnim obsevanjem (IORT) ob lumpektomiji. Pri večini so tudi operativno odstranili aksilarne bezgavke. Vse bolnice so bile obsevane v času operacije na ležišče tumorja s 120 kV rentgenskimi žarki. Tumorska doza je bila od 1500 cGy do 2000 cGy. Tri bolnice so imele stadij I bolezni, dve stadij IIA in dve stadij IIB.

Rezultati. Srednja doba sledenja je bila 123 mesecev (od 86 do 139 mesecev), pri dveh od sedmih bolnic se je pojavil lokalni recidiv, ki je bil zdravljen z mastektomijo. Preživetje, ki je bilo povezano z osnovno boleznijo, je bilo 100%, celokupno preživetje pa 86%, ker je ena bolnica umrla, vendar brez zankov malignoma. Pet bolnic je bilo zadovolnjih s kozmetičnim učinkom takšnega zdravljenja. Niso zasledili zapletov, ki bi bili povezani z IORT.

Zaključki. Tudi rezultati te pilotske študije kažejo, da ni potrebno vsem bolnicam z zgodnjo obliko raka dojke postoperativno obsevati celotne dojke. Zaradi majhnega števila bolnic pa ni moč narediti zaključkov, za to so potrebne klinične študije na večjem številu bolnic.

Radiol Oncol 2001; 35(1): 43-6.

Ali naj pri ugotavljanju varovalnih bezgavk pri bolnicah z zgodnjim rakom dojke uporabljamo peritumorsko ali subareolarno iniciranje limfotropnega modrila?

Baichev G, Sergieva S, Gorchev G

Izhodišča. Biobsija varovalnih bezgavk, ki so jo razvili v novejšem času, je minimalna invazivna metoda, s katero lahko ugotovimo prizadetost aksilarnih bezgavk pri bolnicah z zgodnješo obliko raka dojke. Da bi ugotovili optimalno tehniko za lokalizacijo varovalnih bezgavk, so avtorji primerjali peritumorsko in subareolarno injiciranje modrila.
Bolniki in metode. Pri 192 od 238 bolnicah, ki so imele zgodnejšo obliko raka dojke, so uporabili peritumorsko iniciranje modrila, pri 46 pa subaereolarno iniciranje. Pri vseh je bila nato narejena biopsija varovalne bezgavke po predhodni kirurški odstranitvi aksilarnih bezgavk.
Rezultati. 80 bolnic je imelo metastatsko spremenjene aksilarne bezgavke, 69 bolnic pa je imelo metastatsko prizadete varovalne bezgavke, kar predstavlja 86,3%. Patohistološki pregled varovalne bezgavke je pravilno ocenil prizadetost aksilarnih bezgavk v 90,6%, če je bilo barvilo inicirano peritumorsko, če je bilo inicirano subareolarno, pa le v 68,8 %.
Zaključki. Izkušnje avtorjev kažejo, da je za ocenitev prizadetosti aksilarnih bezgavk primernejša peritumorska aplikacija modrila kot pa subareolarna.

Radiol Oncol 2001; 35(1): 47-52.

Kako danes gradiramo sarkome mehkih tkiv?

Golouh R, Bračko M

Namen. Večina objavljenih sistemov gradiranja sarkomov mehkih tkiv (SMT) je vsaj delno subjektivnih. Zdi se, da med strokovnjaki ni popolnega soglasja o tem, kateri od njih je najboljši. Z raziskavo smo skušali zbrati podatke med patologi iz prakse in tako vsaj delno ugotoviti, kakšna je praksa gradiranja SMT.
Anketiranci. Naključno izbranim 135 patologom smo poslali posebej prirejen vprašalnik.
Rezultati. Dobili smo 88 odgovorov patologov iz 30 dežel iz vseh petih kontinentov. Večina patologov (85%) gradira SMT, pogosteje v Evropi kot v neevropskih deželah. Oboji uporabljajo najpogosteje sistem treh stopenj, prvi v 77%, drugi 67%. V praksi so najpogostejši kriteriji FNCLCC (37.3%), NCI (24%), Brodersa (12%) in Markhedeja (1.4%). V Evropi je najbolj popularen sistem FNCLCC. Več kot pol anketirancev uporablja poleg klasičnih histoloških kriterijev tudi moderne metode. Najpogostejša je imunohistokemija, sledijo molekularni markerji in DNA pretočna citometrija.
Razprava. Rezulati raziskave kažejo, da imajo patologi histološko gradiranje SMT za koristen, čeprav ne povsem zadovoljiv kazalec bolnikovega preživetja.

Radiol Oncol 2001; 35(1): 53-61.

Nadgradnja kamer gama za države v razvoju

Fidler V, Prepadnik M, Xie Y

Izhodišča. Naredili smo nadgradnjo analognih kamer gama s sistemom osebnega računalnika. Raziskovalni projekt sta finansirala Mednarodna agencija za atomsko energijo (IAEA) in Ministrstvo za znanost in tehnologijo republike Slovenije. Projekt predstavljamo od izhodiščnih razvojnih zahtev do končnega sistema. Pri izgradnji zajemalnega vezja ter programske opreme za zajemanje in obdelavo kliničnih preiskav v nuklearni medicini je sodelovalo več nacionalnih raziskovalnih skupin (iz Kitajske, Indije, Kube ter Slovenije).
Zaključki. Kot najstabilnejši zajemalni sistem mnogih testov na mednarodnih delavnicah in na univerzitetnih klinikah se je izkazal slovensko-angleški PIP - GAMMA-PF. IAEA ga je tudi najštevilčneje dodeljevala kot tehnično pomoč državam v razvoju. V okviru projekta smo pomagali 52 državam s preko 300 kamer gama. Slovenski GAMMA-PF vsebuje izjemno stabilno rešitev za zajemanje, obdelavo preiskav s celostnim kliničnim paketom, dokumentiranjem, arhiviranjem in komuniciranjem po mrežah (MS Network, NT server, itd).

Radiol Oncol 2001; 35(1): 63-71.

Premisleki pri načrtovanju neposrednih in posrednih ravnih prikazovalnikov z aktivno matriko za portalno slikanje

Lachaine M, Fallone BG

Izhodišča. Napredek v tehnologiji tankih tranzistorskih plasti je omogočil izdelavo ravnih slikovnih prikazovalnikov z aktivno matriko, ki jih uporabljamo na različnih področjih medicinskega slikanja. Ker je načrtovanje teh prikazovalnikov še zmeraj v razvojni fazi, ni jasno, kakšne morajo biti njihove detektorske karakteristike za optimalno uporabo v portalnem slikanju.
Material in metode. Za izračun kvantnega izkoristka detektorja za neposredne in posredne prikazovalnike z aktivno matriko smo uporabili kaskadno analizo in tehnike Monte Carlo. Rezultate izračunov smo uporabili za študij optimalnih karakteristik detektorja. Svoje izračune smo potrdili z rezultati obstoječih meritev.
Rezultati. Pokazali smo, da imajo neposredne in posredne metode detekcije enak kvantni izkoristek za ravni prikazovalnik z idealnimi karakteristikami pri dani masni debelini detektorja.
Zaključki. Ustvarili smo grafe, koristne pri načrtovanju prihodnjih megavoltnih ravnih prikazovalnikov z aktivno matriko.

Radiol Oncol 2001; 35(1): 73-8.

Notices

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

Colorectal cancer

March 8-9, 2001

The ESO conference will take place in Milan, Italy.

Contact ESO Office, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 0258317850; or fax +39 0258321266; or e-mail esomi@tin.it

Radiotherapy

March 11-14, 2001

The "European Conference on Cancer Strategy and Outcomes" will take place in Edinburg, U.K.

Contact ECSO 2001, ICM Conference Associates, 4 Cavendish Square, London WiM OBX, U.K.; or call +44 207 499 0900; or fax +44 207 629 3233; or e-mail boa@icmgb.com

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Gynecological cancer

April, 2001

The ESO training course "New Developments in the Treatment of Gynecological Cancers" will be offered in Oradea, Romania.

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Breast cancer

April, 2001

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Oncology

April 1-5, 2001

The ESTRO teaching course "Molecular Oncology for Radiotherapy" will take place in Venezia, Italy.

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Rectal Cancer

April 6-7, 2001

The "2nd International Symposium on Sphincter Saving Treatment in Rectal Cancer" will take place in Lyon, France.

Contact FCSANTE@rockefeller.univ-lyon1.fr

Clinical research

April 22-26, 2001

The ESTRO teaching course "Clinical Research in Radiation Oncology" will take place in Izmir, Turkey.

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Malignant mesothelioma

April 20-21, 2001

The meeting "Malignant Mesothelioma - Therapeutic Options and Role of SV40: An Update" will take place in Chicago, USA.

Contact Conference Secretariat, S.G. Madison, 8445 Freeport Parkway, Suite 680, Irving, TX 75063, USA; or call +1 972 929 1900; or fax +1 972 929 1901; or e-mail kimp@sgmadison.com

Lung Cancer

April 26-30, 2001

The "4th International Congress on Lung Cancer" will take place in Halkidiki, Greece.

Contact FORUM International Congress Organisers, 18 Mitropoleos str., GR-54624 Thessaloniki, Greece; or call +30 31 257 128; or fax +30 31 231 849; or e-mail forup@otenet.gr; or see Internet http://www.forumcongress.gr

Cancer in elderly

April 27-30, 2001

The ESO training course "Cancer in the Elderly: New Advances and Perspectives" will be offered in St. Petersburg and Moscow, Russia.

Contact M. Vukelic, CSC Ltd., Heligenstadter Strasse 395b, 1190 Vienna, Austria; or call +43 1 369 0444; or fax +43 1 369 0444 20.

Oncology

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Prostate cancer

May 13-14, 2001

The ESTRO teaching course "Brachytherapy for Prostate Cancer" will take place in Leeds, United Kingdom.

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Radiophysics

May 20-24, 2001

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Radiology

May 22-24, 2001

The ESO training course "Interventional and Diagnostic Radiology in Clinical Oncology" will be offered in Moscow, Russia.

Contact M. Vukelic, CSC Ltd., Heligenstadter Strasse 395b, 1190 Vienna, Austria; or call +43 1 369 0444; or fax +43 1 369 0444 20.

Oncology

May 27-29, 2001

The ESO training course "Therapeutic Advances in Oncology" will be offered in Teheran, Iran.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Hyperthermic Oncology

May 31 - June 2, 2001

The "19th Annual Meeting of the European Society of Hyperthermic Oncology" (Joint with the "12th European BSD Users Conference") will take place in Verona, Italy.

Contact elmaluta@tin.it; or see Internet http://www.esho2001.com

Lung Cancer

June 3-6, 2001

The "7th Central European Lung Cancer Conference" will take place in Prague, Czech Republic.

Contact 7th CELCC, Conference Partners, Sokolska 10, 120 00 Prague 2, Czech Republic; or call/fax +420 2 2426 1371; or e-mail info@conference.cz

Radiosurgery

June 4-7, 2001

The "5th International Stereotactic Radiosurgery Society Congress" will be offered in Jerusalem, Israel Republic.

Contact 7ISRS Secretariat, c/o International Travel & Congresses Ltd., 20 Rothschild Boulevard, POB 29313, Tel Aviv 61292, Israel; or phone +972 3 795 1444; or fax +972 3 510 7716; or email congs@internationaltc.co.il; or see http://www.isrs-jerusalem.com.

Radiotherapy

June 7-9, 2001

The Annual Brachytherapy Meeting GEC/ESTRO will take place in Stresa, Italy.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see Internet http://www.estro.be

Radiobiology

June 10-12, 2001

The "1st ESTRO Workshop on Biology in Radiation Oncology" will take place in Fuglso (Aarhus), Denmark.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see Internet http://www.estro.be

Breast cancer

June 11-13, 2001

The ESO advanced course "Breast Cancer: Oncologic and Reconstructive Surgery" will be offered in Milan, Italy.

Contact ESO Office, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 0258317850; or fax +39 0258321266; or e-mail esomi@tin.it

Breast cancer

June 13-15, 2001

The ESO conference will take place in Milan, Italy.

Contact ESO Office, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 0258317850; or fax +39 0258321266; or e-mail esomi@tin.it

Chemotherapy

June 16-17, 2001

The ESO multiprofessional course "High Dose Chemotherapy with Haematological Support" will be offered in Milan, Italy.

Contact ESO Office, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 0258317850; or fax +39 0258321266; or e-mail esomi@tin.it

Oncology

June 26-28, 2001

The ESO training course "Prevention and Screening of Cancer" will be offered in Moscow, Russia.

Contact M. Vukelic, CSC Ltd., Heligenstadter Strasse 395b, 1190 Vienna, Austria; or call +43 1 369 0444; or fax +43 1 369 0444 20.

Leukemia and lymphoma

June 24-27, 2001

The ESO advanced course "Molecular Biology of Acute Leukemia and Malignant Lymphoma" will be offered in Ascona , Switzerland.

Contact ESO Office, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 0258317850; or fax +39 0258321266; or e-mail esomi@tin.it

Radiotherapy

June 24-28, 2001

The ESTRO teaching course "IMRT and Other Conformal Techniques in Practice" will take place in Amsterdam, The Netherlands.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see Internet http://www.estro.be

Radiotherapy

June 24-28, 2001

The ESTRO teaching course "Imaging for Target Volume Determination in Radiotherapy" will take place in Krakow, Poland.

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Obstetrics and gynaecology

July 10-13, 2001

The "29th British Congress of Obstetrics and Gynaecology (BCOG)" will take place in Birmingham, U.K.

Contact info@conforg.com

Radiophysics

August 26-30, 2001

The ESTRO teaching course "Physics for Clinical Radiotherapy" will take place in Leuven, Belgium.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see Internet http://www.estro.be

Brachytherapy

August 29 - September 2, 2001

The ESTRO teaching course "Modern Brachytherapy" will take place in Bratislava, Slovakia.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see Internet http://www.estro.be

Pathology

September, 2001

The ESO training course "Hot Topics in Pathology" will be offered in Alexandroupolis, Greece.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

As a service to our readers, notices of meetings or courses will be inserted free of charge.

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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education - A Report for the Fourth Quarter of 2000

The activity of the Foundation in the year 2000 and in the earlier part of 2001 represented the continuation of its well established previous pursuits. It was also agreed that it is unfortunately becoming increasingly difficult to entice individuals and other business subjects to contribute to the special type of charities, as is the activity of the "Dr. J. Cholewa" Foundation, as it was possible even some months ago. Fortunately, there are some of the donors from Slovenia and abroad who tirelessly continue to try to support it, and the members of the Foundation and its Executive and Supervisory Committees feel obliged to express their gratitude to all who understand the importance of its goals and activities to reach them.

The summary of the activities of the Foundation in the year 2000 and in the earlier part of 2001 makes a complex and interesting reading. It is planned that the Foundation will help to finance as many scientific and education events in Slovenia as possible and within its reach. Furthermore, a public invitation for research grants in the field of oncology was published in "Dnevnik" and "Večer" daily newspapers in Slovenia, in "Radiology and Oncology" international oncology journal, published in Ljubljana, Slovenia, and in "ISIS", the journal of the Medical Chamber of Slovenia, Ljubljana, Slovenia. It is planned the invitation will be publicly issued again this year with the aim to provide grants for MSc, PhD and post-doctoral studies. In addition, several grants for participation on various international congresses and symposia are to be provided for the applicants from Ljubljana and different regions of Slovenia.

The Foundation has continued to support the regular publication of "Radiology and Oncology" international scientific journal, and the regular publication of the "Challenge ESO Newsletter" in 1999, in the year 2000 and in the earlier part of 2001. Both medical journals are edited, published and printed in Ljubljana, Slovenia. In the years 1999 and 2000 the Foundation also contributed support for the publication of the Slovenian Dictionary of Medical Terminology, and for the Proceedings of two meetings organised by the Nursing Association of Slovenia, and dedicated to the problems in oncology.

The Foundation will in the year 2001 continue to strive to concentrate its activities to facilitate the access to oncology research and education to as many interested individuals and institutions in the regions of Slovenia as possible. Several new approaches and ways to achieve the enhancement of the knowledge in cancer prevention and early detection all over the country will have to be evaluated. As mentioned earlier, special attention will be given to the requests coming from the regions of Slovenia outside Ljubljana to provide grants for the participation of Slovenian oncologists and others on various educational meetings in the country and abroad.

The Foundation therefore continues to follow its objectives, as was stated before in these reports, and as was decided and outlined by its members participating in the meetings of its General assembly, its Supervisory and Executive Boards.

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

THE LITTLE KNIGHT,
FOUNDATION FOR ASSISTENCE TO YOUNG CANCER SURVIVORS

Zarnikova 3, 1000 LJUBLJANA, SLOVENIA
Phone: +386 01/306-15-87
Fax:+ 386 01/306-15-87
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THE LITTLE KNIGHT, FOUNDATION FOR ASSISTENCE TO YOUNG CANCER SURVIVORS

INTRODUCTION

The treatment of childhood cancer has markedly improved during the last three decades. We know more about the disease as well as about the damage caused by the treatment. With increased knowledge we can modify treatment in order to minimize its harmful consequences. The number of cures is increasing, from 10% to 60%. This growing group of survivors are more or less special individuals with special problems, but with common experience and memory of their fight for survival in early life. The damage is psychological, in our own studies mainly emotional, as well as somatic. These young, cured, former patients are less competitive, less ambitious and have lower self-esteem compared with their contemporaries. They have but few friends and tend to be loners. On the other hand, they appear more adult, are clearly more symphatetic and tolerant of those who differ. In Slovenia each year about 60 children get cancer. Each year the group of survivors, with all their problems, grows by about 40.

THE AIM OF THE FOUNDATION IS:

- to stimulate research of the late effects of cancer treatment in childhood in order to minimize these effects by better treatment,
- to treat and palliate the damage done, to offer technical help, to help to adequate education,
- to offer psychological and medical help and rehabilitation, also in groups, occasionally in a sanatorium, a spa and similar.

THE ORGANIZATIONAL SCHEME:

The Foundation "The little knight" is a humanitarian foundation and is a legal person according to civil law. The foundation has been founded by prof. Berta Jereb on 8.10.1996 with a legal act according to the law on Foundations (Legal Journal Slov. Rep. 60/95).

The Foundation is administered by a board, whose concern is the achieving of the aims of the foundation, all according to the law and the statute of the foundation enacted 22.1.1997. The board consists of eight members who from among them elect a president. The Foundation has a Board of control with three members, one of them elected as president. The Board of control concerns itself mainly with the economic side of the management. The Foundation is funded by the management of the founding property, by gifts and other donations, by income from activities and by the state, through subventions.

In order to inform the society about childhood cancer and its consequences the Foundation is organizing humanitarien concerts and performances. The aim is further to stimulate the young survivors to appear in public to socialize and also but not mainly colect some mony.

We have 3-4 concerts per year get support from financial different institutions and have f.i. in 1999 spend more then Sit 3,000.000.- for rehabilitation of 12 survivors in a spa and 30 in the mountains or at the beach.

The right and duties of members of the Foundation are a matter of honor. Members do not receive any compensation for their participation in the activity of the Foundation.

Berta Jereb, M.D.

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zastopa naslednja podjetja

Köttermann (Nemčija):
laboratorijsko pohištvo, varnostne omare za kisline, luge, topila, pline in strupe, ventilacijska tehnika in digestorji

DAKO (Danska):
testi za aplikacijo v imunohistokemiji, patologiji, mikrobiologiji, virologiji, mono- in poliklonalna protitelesa

SVANOVA Biotech (Švedska):
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NOVODIRECT BIOBLOCK (Francija):
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GFL (Nemčija):
laboratorijski aparati, omare in skrinje za globoko zamrzovanje

ANGELANTONI SCIENTIFICA (Italija):
hladilna tehnika in aparati za laboratorije, transfuzijo, patologijo in sodno medicino

EHRET (Nemčija):
laminar flow tehnika, inkubatorji, sušilniki, suhi sterilizatorji in oprema za laboratorijsko vzrejo živali - kletke

INTEGRA BIOSCIENCES (Švica):
laboratorijska oprema za mikrobiologijo, biologijo celic, molekularno biologijo in biotehnologijo

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EVL (Nizozemska):
diagnostični testi za uporabo v veterinarski medicini

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diagnostični testi za uporabo v veterinarski medicini

BIOMERICA (ZDA):
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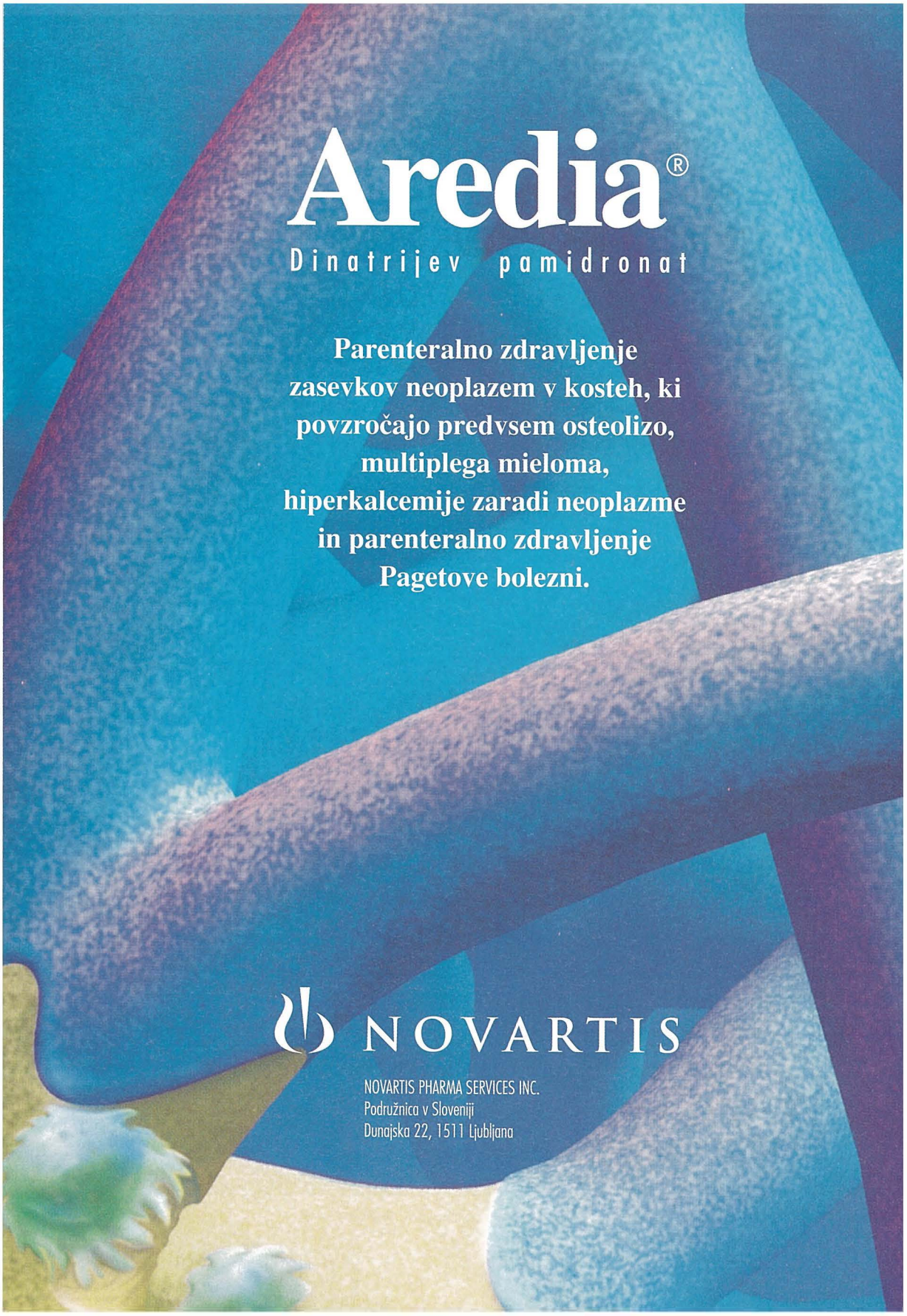
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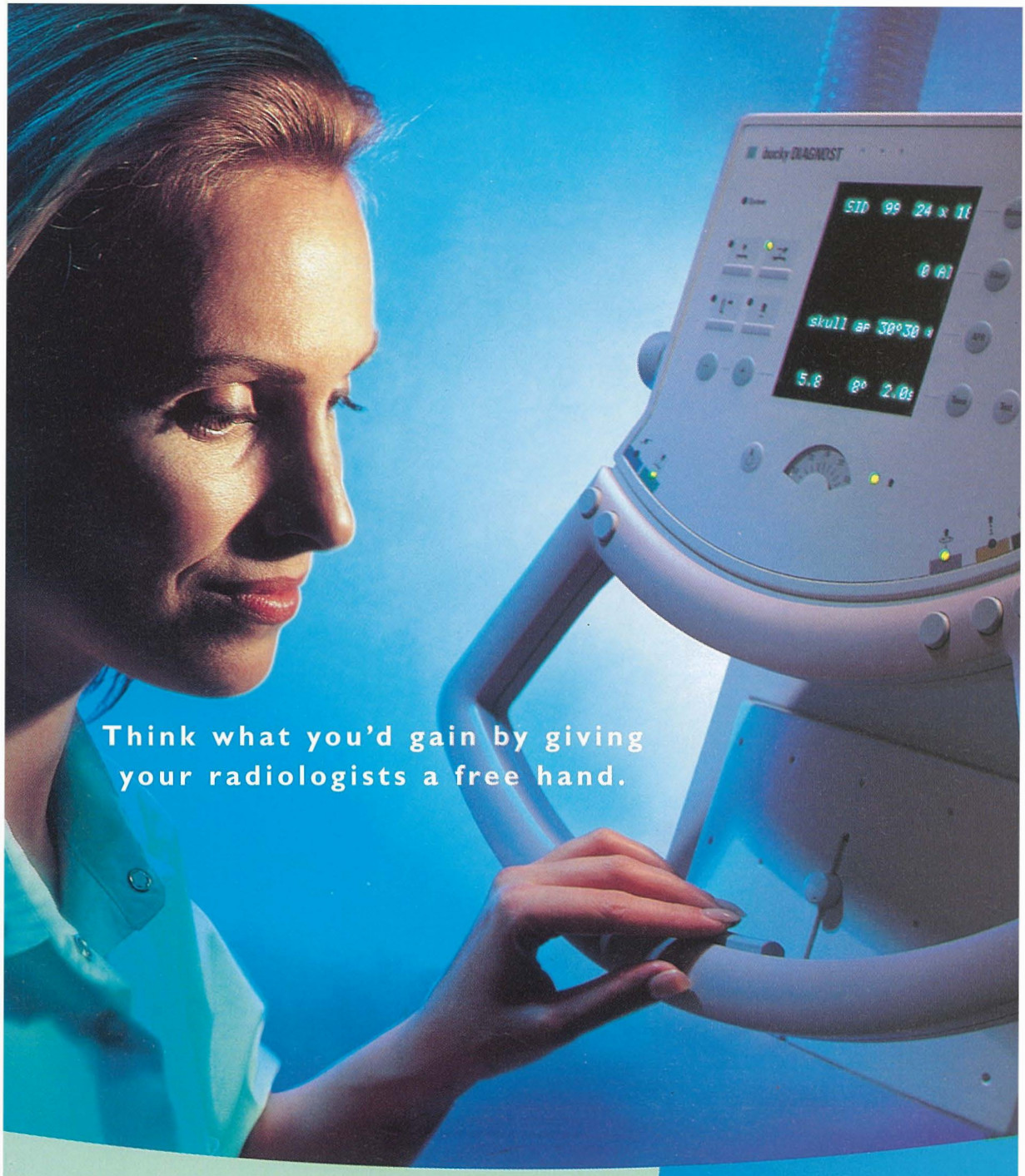

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sistemska kandidoza	*prvi dan 400 mg, nato od 200 do 400 mg na dan Največji dnevni odmerek je 800 mg.*
preprečevanje kandidoze	*50 do 400 mg na dan*
kriptokokni meningitis	*prvi dan 400 mg, nato od 200 do 400 mg na dan*
vzdrževalno zdravljenje	*200 mg na dan*

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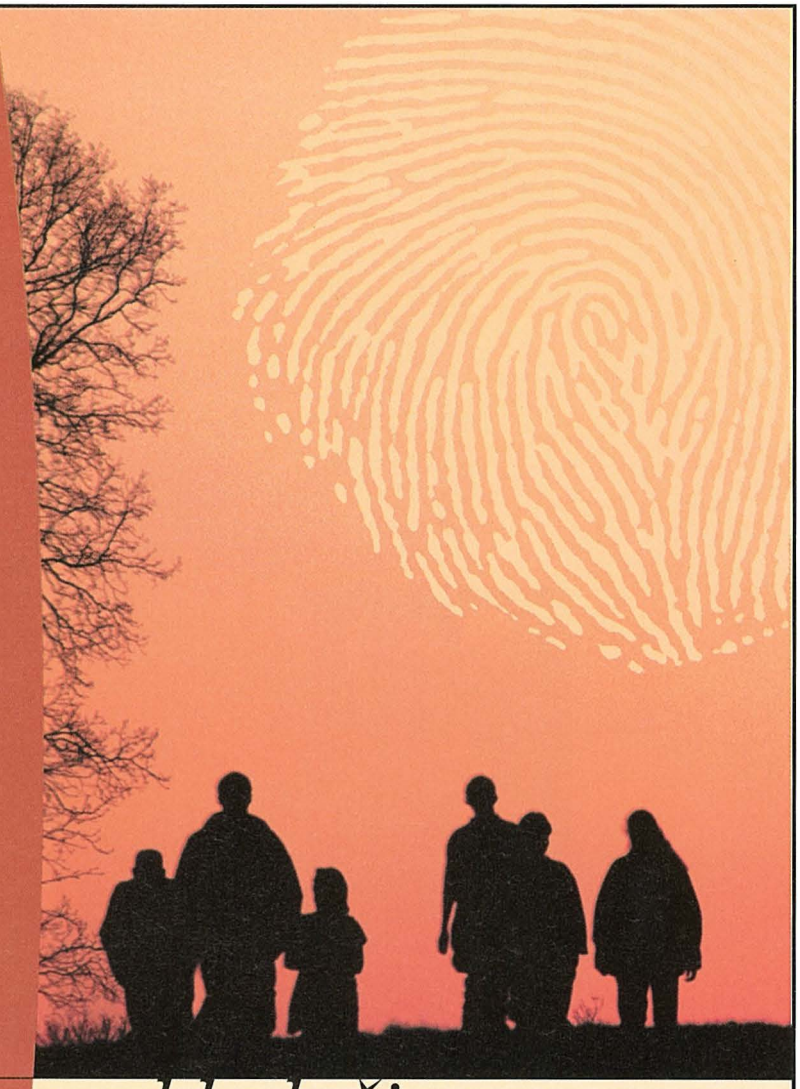

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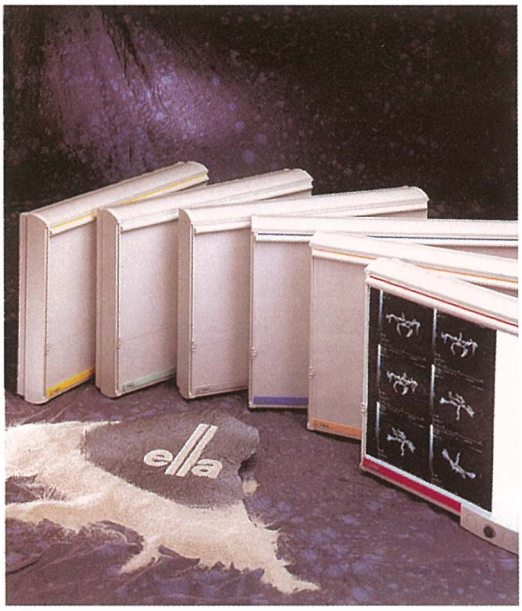

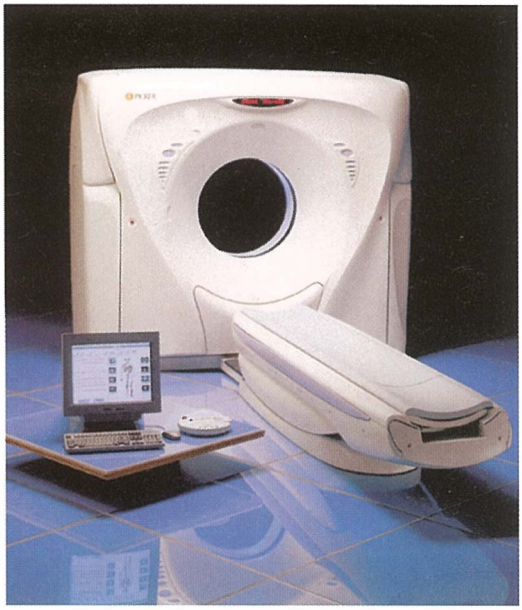

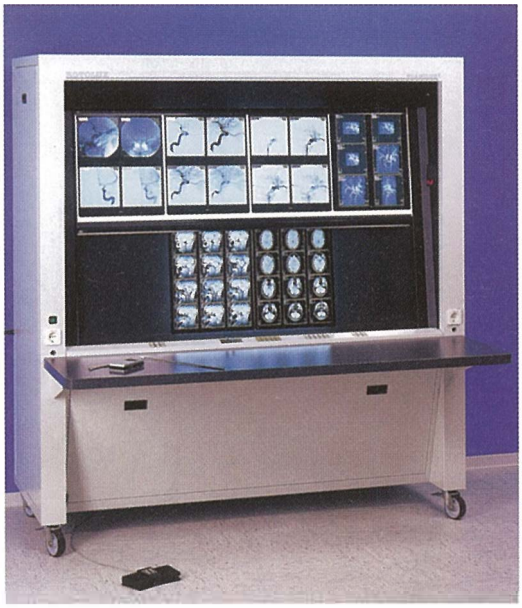

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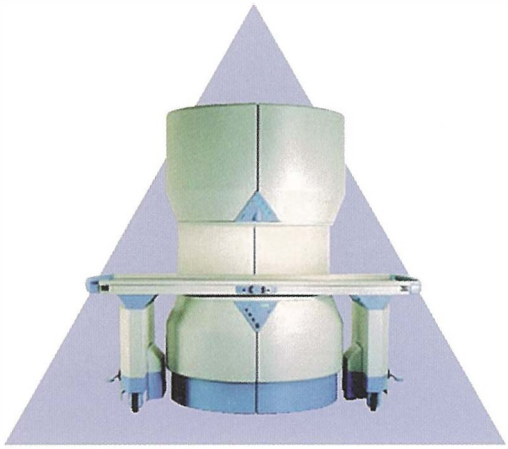

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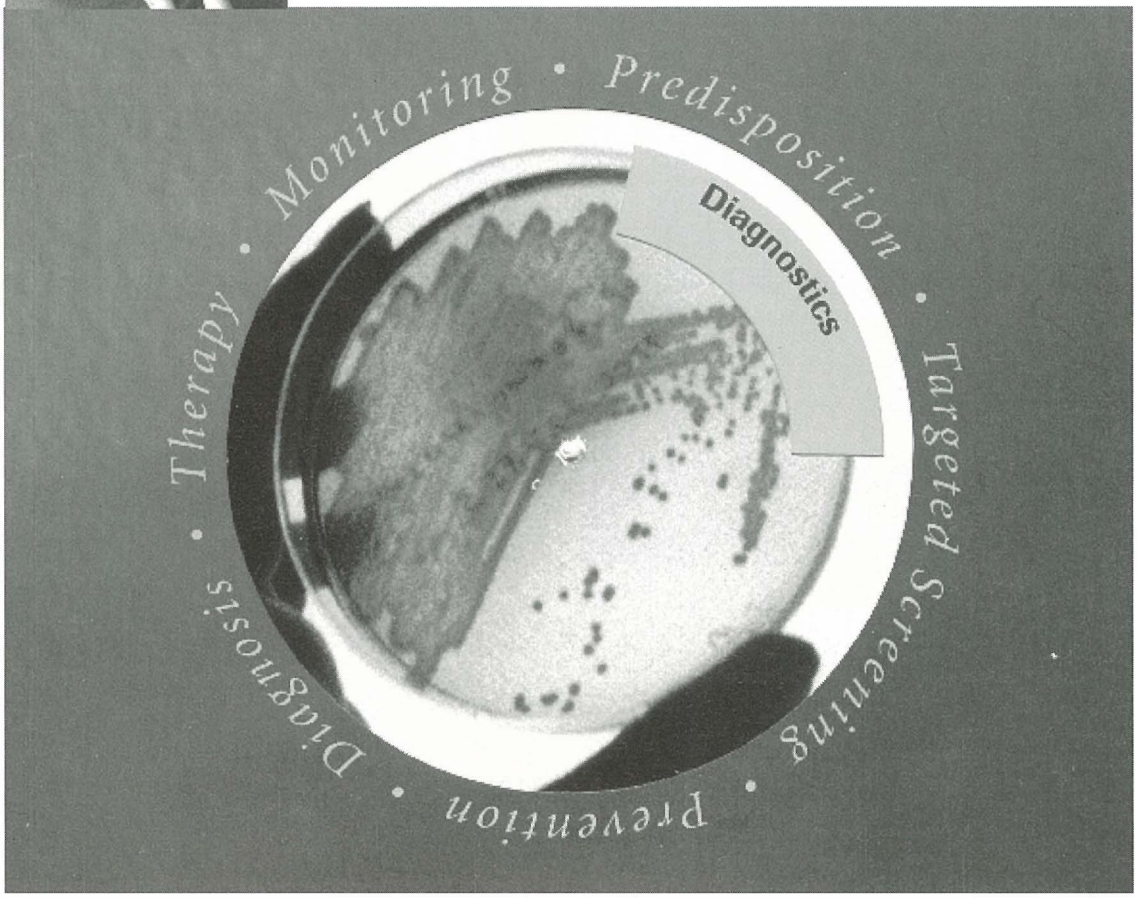

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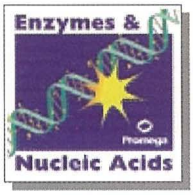

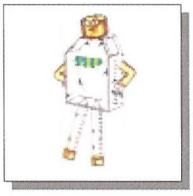

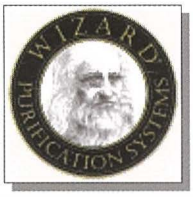

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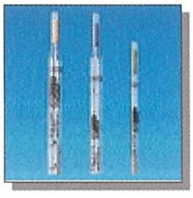

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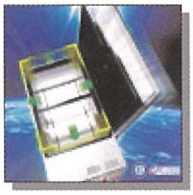

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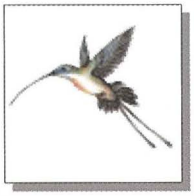

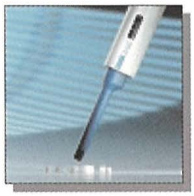

ELEKTRONSKE IN MEHANSKE AVTOMATSKE PIPETE

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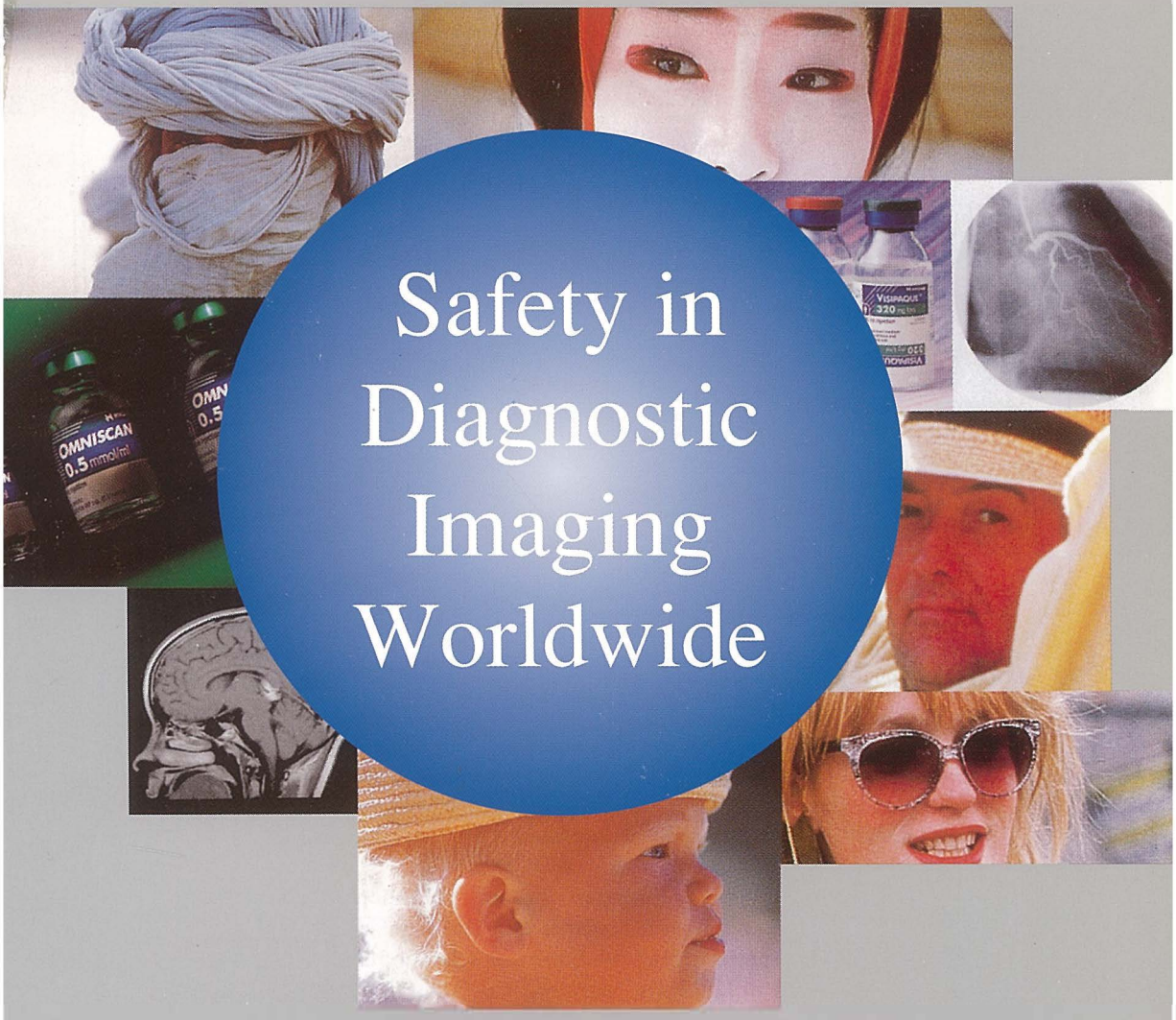

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