

High resolution mini-gammacamera and ^{99m}Tc [HMPAO] - leukocytes for diagnosis of infection and radioguided surgery in diabetic foot

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SUMMARY: High resolution mini-gammacamera and ^{99m}Tc [HMPAO]- leukocytes for diagnosis of infection and radioguided surgery in diabetic foot.

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Discovery of osteitis may be delayed because of late appearance of X-ray signs in patients with diabetic foot. Scintigraphy with labelled leukocytes is able to detect flogosis but often misses bone involvement, due to inadequate resolution of Anger camera, the commonest detector used in nuclear medicine. Radioguided surgery and biopsy with high resolution scintigraphy (HRS) started to be studied since 2000: although this method had never been tested for planning and guiding diabetic foot surgery, in our opinion it can help early diagnosis and surgical treatment of diabetic foot.

Five patients with diabetic foot and suspected infection were studied with standard ^{99m}Tc [HMPAO]-leukocyte scan. In the same patients 2 mm spatial resolution HRS was performed 24 hours after administration of labelled WBC, using our incli² field-of-view portable mini-gammacamera. Operations were done just after the 24h scan and were guided with the portable high resolution device in the four patients who showed positive scan.

Scintigraphy with Anger camera and HRS were positive in four patients. HRS showed a bar-shaped radioactivity corresponding to small phalanges, close to the main inter-digital hot spot. The presence of osteitis on phalanges that had been shown by HRS was confirmed at surgery, that was successfully driven with the high resolution mini-camera.

In conclusion HRS is able to diagnose early osteitis of diabetic foot and to guide diabetic foot surgery.

RIASSUNTO: Mini-gammacamera ad alta risoluzione e leucociti ^{99m}Tc [HMPAO] - marcati nella diagnosi di infezione e nella chirurgia radio-guidata del piede diabetico.

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La tecnica illustrata nel presente lavoro riguarda la localizzazione di lesioni osteomielitiche nel piede diabetico mediante l'utilizzo di un nuovo dispositivo scintigrafico da impiegare in sala operatoria. In particolare, viene preventivamente eseguita una scintigrafia mediante somministrazione di leucociti marcati che evidenziano la estensione ed i limiti della lesione. Questa viene visualizzata durante l'intervento operatorio, consentendo la verifica della completa rimozione.

I casi presentati in questo studio pilota dimostrano la validità della tecnica, che necessiterà di ulteriore verifica su una più ampia casistica.

KEY WORDS: Radioguided surgery - Diabetic foot.
Chirurgia radioguidata - Piede diabetico.

Introduction

About 14% of diabetic patients are hospitalised for foot problem every year in United States, with a

mean annual inpatient stay of 6 weeks (1). Foot complications are the principal cause of morbidity, disability and mortality in these patients and the most common cause of non traumatic amputation of lower extremity (1). Mortality rates 3-5 years after amputation exceed 50% and about 1/3 of these patients have contralateral limb amputation within 3 years after initial amputation (1, 2).

Pedal ulcer represents the most relevant foot complication in the forefoot, while mid- and hind-foot is the most common site of neuropathic joint (Charcot joint)(1). Large vessel atherosclerosis,

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microangiopathy, neuropathy and dermopathy are responsible for the development of pedal ulcer which, in his turn, causes 90% of osteomyelitis (1, 3). Bone involvement is frequent and its quick and effective assessment shows capital importance for a successful surgical or medical treatment (1-3). However, the lack of clinical signs and symptoms of this involvement makes diagnosis frequently overlooked. Imaging diagnostic methods, therefore, play an important role in the evaluation of these patients.

Plain radiography show inadequate accuracy for early diagnosis of pedal osteomyelitis, nevertheless, even when non diagnostic, it provides anatomical data useful for interpretation of other studies (3, 8). magnetic resonance (MRI) and labelled-leukocyte scan are, at the moment, the most reliable methods in detection of pedal osteomyelitis underlying pedal ulcer (1, 3-5), however false positive and false negative exams do occur. Bone biopsy is useful for determining osteomyelitis and it can provide bacteriological information; on the other hand, it is invasive and potentially harmful in diabetic foot. Furthermore, cultures can be contaminated by overlying soft tissue and sometimes the histologic characteristic of osteopathy can mimic osteomyelitis (6, 7).

In the treatment of infected diabetic foot, besides the diagnosis of bone involvement, also the assessment of the extent of infection is of paramount importance, since complete surgical removal of infection themselves can delay amputation (8-10), improve wound healing (11) and probably decrease mortality. From this point of view, MRI can be considered the method of choice (1). Furthermore, both surgical and medical therapies should be followed-up by reliable diagnostic methods, in order to minimise relapses due to inadequate treatment. Currently labelled leukocyte imaging can be considered a useful method for monitoring response to medical therapy.

On the basis of the above reported data, the main still unsolved problems in this field are a more accurate diagnostic tools for detection of pedal osteomyelitis and methods able to drive surgery, that is to say able to control whether removal of infected tissues is complete or not. Spatial resolution of Anger cameras is not always able to differentiate soft tissue infection from bone involvement. On the other hand, radioguided surgery, which could be useful during operation, when performed with conventional costumer available probes, which do not provide images, does not allow to differentiate bone from soft tissues radioactivity, as well as to guide bone biopsy. Mobile, high resolution (HR) scintigraphy has already been used for radioguided surgery (12,13) and biopsy (14-16) including bone biopsy (17, 18).

Rationale of present work is to verify if radio-

guidance with ^{99m}Tc [HMPAO] - leukocytes (WBCs) and high resolution mobile detector are able to improve diagnosis and help surgery in patients with diabetic foot infections.

Materials and methods

Patients

Five patients, mean age 64 years, with diabetic forefoot ulcers and high suspicion of infection were studied with planar X-ray, MRI and labelled WBCs. Four patients were operated 24 hours after labelled WBCs with radioguided surgery.

Mobile high resolution device

Our mobile high resolution mini-gammacamera (IP-824, Li-Tech srl, Udine, Italy) has already been described (12-18). The detector is composed by an Hamamatsu H8520 C-12 position sensitive photomultiplier tube, an array of CsI crystals matched with a full tungsten, square holed collimator with 200 μ thick and 24 mm long septa, which was developed on the basis of Montecarlo simulation of radiation transport (19). Read out electronics were home-made: the electric charge coming from dinodes of position sensitive photomultiplier is converted into digital signals which are in turn used to reconstruct the image in a 64x64 pixel matrix, after having been selected for pulse height falling into an electronic window of $\pm 20\%$ around the pulse height corresponding to the 140 keV energy of the photons emitted from technetium.

Data were sent to a Compaq portable computer powered with a Pentium IV processor. Software includes on line energy channels tuning, image smoothing, change of acquisition matrix and on line smoothing (1 sec refresh).

In comparison with the first mini-camera we have presented and used (12-14), present detector is 2.5 times more sensitive, particularly thanks its new square holed collimator built with 200 μ thick full tungsten septa in place of the standard and commercially available collimators with 250 μ thick lead septa and exagonal design of holes that are generally used and had also been used by us in previous prototypes. The updated mini-camera also shows much more exact positioning of each crystal which detects radiations, thereby improving exact detection of the radiation source. This is due to the new collimator and also to the careful revision of readout electronics.

Acquisition of images

After white blood cells separation and labelling with ^{99m}Tc [HMPAO] by standard methods, labelled cells were re-injected and images were acquired with a double headed Anger camera (Millennium, GE, USA) or, at operator's judgement, with a single headed gammacamera (Starcam, GE, USA) fitted with general purpose low energy collimators. Static acquisition were carried out at 30 min, 2h and at 18-24h from cells administration, collecting 500.000 counts at 30 min and 2h, 150.000 counts at 18 to 20h. Images were acquired also with HR mini-camera just following each acquisition with Anger camera on the site where hot spots had been observed. If no hot spot was evident on Anger camera images, HR mini-camera was positioned on the site in which infection was suspected.

The patients were operated 24-30h after the administration of labelled leukocytes, thus just after the 2nd day scan with Anger camera and HR mini-camera. The high resolution mini-camera followed the patient into the operation theatre, where it was used to drive surgery. HR scintigraphy (HRS) were performed by an experienced operator during operation at surgeon's requirement. A final HRS was performed at the end of operation. Rationale of the last image was to keep surgeon sure of having taken away all the infected tissues.

TABLE 1 - LEUKOCYTE SCAN WITH ANGER AND HIGH RESOLUTION (HR) MINI-CAMERA.

	<i>Leucocyte scan negative</i>	<i>Leukocyte scan positive without bone involvement</i>	<i>Leukocyte scan positive with signs of osteitis</i>
Anger camera	1	4	0
HR mini-camera	1	2	2
Surgery (4 pts)	no infection	1	2

TABLE 2 - OVERVIEW OF THE RESULTS.

<i>Patient</i>	<i>Anger camera</i>		<i>HR mini-camera</i>		<i>Surgery</i>	<i>Usefulness of radioguide</i>
	<i>No bone inv.</i>	<i>Bone inv.</i>	<i>No bone inv.</i>	<i>Bone inv.</i>		
1	Negative		Negative		Not performed	-
2	+		+		Soft tissues infection	yes
3	+		+		Not performed	yes
4	+			+	Amputation of small phalanx, osteitis	yes
5	+			+	Bone biopsy, osteitis	yes

legenda: + positive for infection; bone inv.: bone involvement.

Image interpretation

In order to ensure blind revision, two independent datasets for each patient, containing HRS and images acquired with Anger camera, were stored on compact disks. Patients' names were changed in numbers. Data were independently reviewed by two well trained observers who were not aware of the results of operation. Images acquired during operations were not prepared for blind revision. The observers were required to answer to the following questions: 1) does purulent inflammation exist?; and, when present, 2) is the inflammation extended to bone?

Diagnostic HRS images were acquired before operation, just after scintigraphy with Anger camera, the mini-camera was positioned on the spot of the Anger camera image: thus acquisition was not independent from Anger camera. On above images questions for reviewers were: is the Anger camera hot spot confirmed? is the inflammation extended to bone? Images acquired during surgery with HR mini-gammacamera were not reviewed because the goal of these images was to guide surgery and the nuclear physician handling the camera had to give his on-site interpretation to the surgeon. Obviously the images remained stored in the portable computer memory, however any further analysis or revision after operation would have been meaningless.

Radioguiding was only evaluated with surgeon's answer at the end or each operation to the simple question: was radioguide useful? Surgeons were invited to answer only yes or not.

Statistics

No statistic test was used, due to the very limited number of patients.

Results

Results are summarized in tables I and II

Leukocytes scan was negative with both Anger and high resolution camera in one patient. This patient showed a neuropathic ulcer in which simple debridement was sufficient for obtaining complete healing. Four patients showed positive scan at Anger camera without specific signs of bone involvement. HR mini-camera showed spots of radioactivity in the same patients. In two of them part of the hot spots was bar-shaped; the bar-shaped radioactivity was in correspondence of the small phalanx. Both observers considered this bar-shaped radioactivity as a sign of osteitis.

One patient with positive leukocyte scan refused surgery on our institution. The patient with negative scan was treated with simple debridement as above mentioned. One patient with positive scan and no signs of osteitis at Anger as well as at HR camera was submitted to complete curettage of purulent inflammation with the aid of HR mini-camera during operation.

Discussion

The diagnosis of diabetic foot osteomyelitis is often difficult with clinical and standard X-ray methods, with delay of radiological signs occurrence and

difficulties in imaging interpretation. Bone biopsy is known to be, within certain limits (6, 7), the diagnosis gold standard. Repeated biopsy is not recommended and can be harmful. On the other hand not only early diagnosis of osteomyelitis but also bacterial culture are necessary to start appropriate antibiotic treatment in conjunction with conservative surgery.

Labelled leukocytes are able to diagnose purulent inflammation and presence of uptake sites can help surgeons to plan operations. Driving surgery with labelled leukocytes inside the operation theatre shows several difficulties because it is not trivial to carry a gammacamera inside the hall and to get diagnostic images with useful-for-surgery acquisition times, nor it is easy to tune a mobile probe giving no image but only acoustic signals, when radioactivity is low and background not negligible.

Present paper shows a new method for guiding surgery of diabetic foot. Our portable detector was able to show scintigraphic images during operation and helped the surgeon in 3 cases out of 5. Spatial resolution of portable device also was important: Anger camera correctly diagnosed infections whereas failed detecting early osteitis of small phalanges. High resolution scintigraphy easily and correctly showed the two bone involvements. Mobility of high resolution mini-camera allowed us to precisely detect the extent of infection before surgery as well as during operation. Diagnosis of bone infection changed surgical strategy in at least one patient.

Though our study was designed to assess usefulness of radioguided surgery for operations on diabetic foot, early assessment of osteitis that was done with high resolution mini-camera also improved diagnosis and helped medical therapy, because the presence of osteitis changes medical decision and suggests biopsy to perform antibiotic treatment after bacterial culture or, at least, with standard rifampicine plus fluoroquinolone association that is recommended for osteomyelitis in the absence of reliable antibiograms.

To our knowledge, present is the first trial in which high resolution scintigraphy has been used to improve diagnosis and to guide surgery in the field of diabetic foot. Of course our series is very short and observed data are largely preliminary; thus data here reported have to be confirmed on larger series. Operations were carried out 24-26h after i.v. administration of labelled

leukocytes, thus with very low radioactivity present on hot spots. Our group guided other orthopedic operations with HR mini-camera; these operations were mainly related to osteoid osteoma biopsy (19), that can be carried out 3-4h after the injection of 20 mCi of ^{99m}Tc -MDP, thus with similar background but much more radioactivity in comparison with present operation.

HR mini-camera was designed by us since 1997 and successively improved with continuous updating of collimators, crystal network and electronics. The mini-camera developed in 2003 and used in present study was 2,5 fold more sensitive than the similar prototype used in 2002 for biopsy of sentinel node and osteoid osteoma. The new detector and new collimators (13, 16-18) were planned on the basis of exact mathematical models (19). This detector not only is highly precise, because each hole of collimator exactly fits a crystal, but contemporaneously shows higher transmission rate than previous devices. High transmission is due to tungsten septa thinner than the exagonal shaped lead septa and to full availability of perimeter crystal detectors. In the previous mini-cameras counts from peripheral crystals were particularly lowered at the junction between the square external shield and the exagonal hole collimator, causing severe problems to readout electronics that often results in missed data.

Conclusions

In our opinion the ability of HR mini-camera to guide operation of diabetic foot opens a new way in the surgical treatment of infected diabetic foot. It is contemporaneously possible to assess if surgical removal of purulent inflammation of soft tissues is complete and to precisely guide biopsy or removal of bone when osteitis is present.

Our HR detector was able to show useful diagnostic images and to drive surgery in very difficult conditions, due to very low radioactivity present 20h after re-injection of labelled leukocytes and to mild but existing background.

Thus use of our HR device is probably mandatory when surgery of infectious diabetic foot has to be driven, but usefulness of our HR camera is more general: it can exactly drive biopsy and surgery of other organs with infection as well other pathologies, e.g. cancer-seeking radiopharmaceuticals.

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