AN INVESTIGATION OF THE CONTRIBUTION OF SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY TO THE DIAGNOSIS OF SKELETAL METASTASES USING BONE SCAN IN THE AFRICAN CONTEXT

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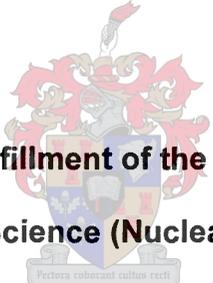
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DECLARATION

I, AHMED E. ELMADANI hereby declare that the work contained in this thesis is my own original work and has not previously in its entirety or in part, been submitted at any university for a degree.

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Summary

Planar bone scintigraphy is highly sensitive but it may not be sensitive enough to detect subtle lesions in complex bony structures such as the spine. The accurate anatomic localisation of lesions in regions such as this is also limited using planar images. Single Photon Emission Computed Tomography (SPECT) results in a higher lesion contrast resulting in an improved sensitivity for the detection of subtle lesions. SPECT also enables improved lesion localisation, often valuable in distinguishing benign from malignant disease in the spine.

A number of previous studies have demonstrated that the addition of SPECT of the spine significantly enhances the value of bone scintigraphy for the detection of bone metastases compared to planar imaging alone. These studies were however not done in the African context where patients typically present with more advanced disease.

In a retrospective study of 576 patients with known primary tumors sent to our institution for bone scintigraphy for the diagnosis of bone metastases, we evaluated 119 patients in whom both planar imaging and SPECT were obtained. The studies were graded for the probability of metastatic disease, and the number of spinal lesions was determined with and without SPECT. The influence of adding SPECT on the interpretation of the study was determined in terms of the reported probability of metastatic disease, the exclusion and

confirmation of metastatic disease, the decisiveness of interpretation, and the number of spinal lesions.

The addition of SPECT resulted in a statistically significant change in the interpretation of studies, although the actual numbers of patients affected were relatively small. SPECT resulted in a more decisive interpretation of bone scintigraphy. There was a significant increase in the number of spinal lesions detected after the addition of SPECT.

It was concluded that although the use of SPECT is ideal, acceptable results could be achieved using planar imaging alone in this patient population. This is particularly relevant in the African context, where SPECT is often unavailable or scarce and in great demand.

Opsomming

Planare beenflikkergrafie is hoogs sensitief, maar moontlik nie sensitief genoeg om subtiele letsels in ingewikkelde beenstrukture soos die werwelkolom aan te toon nie. Akkurate anatomiese lokalisasie van letsels in die genoemde strukture is beperk wanneer slegs planare beelde gebruik word. Enkelfoton-uitstraling Rekenaartomografie (EFERT) lewer 'n hoër letsel kontras, wat 'n verbeterde sensitiwiteit vir die opsporing van subtiele letsels tot gevolg het. EFERT lei ook tot verbeterde letsel lokalisasie, wat dikwels van waarde is om onderskeid tussen benigne en maligne siekte in die werwelkolom te tref.

Reeds met 'n aantal vorige studies is aangetoon dat die toevoeging van EFERT van die werwelkolom die waarde van beenflikkergrafie in die opsporing van beenmetastases beduidend verhoog bo dié van planare beelding alleenlik. Hierdie studies is egter nie in omstandighede eie aan Afrika gedoen nie, waar pasiënte kenmerkend met gevorderde siekte voordoen.

In 'n terugskouende studie van 576 pasiënte met bekende primêre tumore, wat na ons instelling verwys is vir beenflikkergrafie om beenmetastases op te spoor, het ons 119 pasiënte, wat beide planare beelding en EFERT ondergaan het, ge-evalueer. Die studies is gegradeer volgens die waarskynlikheid vir metastatiese siekte, en die hoeveelheid werwelkolom letsels, met en sonder EFERT, is bepaal. Die invloed van EFERT op die vertolking van die studie is bepaal in terme van die waarskynlikheid van metastatiese siekte, die bevestiging en uitskakeling daarvan, die beslistheid van vertolking, en die hoeveelheid werwelkolom letsels.

Die toevoeging van EFERT het tot 'n statisties beduidende verandering in die vertolking van studies gelei, alhoewel die werklike getal pasiënte wat hierdeur geraak is, relatief min was. EFERT het 'n meer besliste vertolking van beenflikkergrafie tot gevolg gehad. Daar was 'n beduidende toename in die hoeveelheid werwelkolom letsels wat opgespoor is na die toevoeging van EFERT.

Daar is tot die slotsom gekom dat, alhoewel die gebruik van EFERT wenslik is, aanvaarbare resultate met slegs die gebruik van planare beelding in hierdie pasiënt bevolkingsgroep verkry kan word. Dit is veral van belang in Afrika-omstandighede, waar EFERT dikwels onbeskikbaar of skaars is, en ook in groot aanvraag is.

DEDICATION

I would like to dedicate this thesis to my mother and my family for their continuous support and encouragement.

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Introduction

Bone scintigraphy is one of the commonest examinations in nuclear medicine and has been used extensively in the evaluation of oncology patients to detect bone metastases. By using optimised imaging techniques, it is usually possible to determine lesion characteristics that are more likely to represent malignancy. Osseous metastases occur in 80% of patients with metastatic disease [Holger *et al.*, 1998]. About 90% of these metastatic deposits are located in regions of the bones containing red marrow [Jacobson & Fogelman, 1998] and this high percentage is due to the fact that the majority of metastases that deposit in bones originate from hematogenous spread, and red marrow has a richer blood supply than yellow marrow or cortex. The accurate determination of a lesion's significance requires knowledge of the pathophysiology and other specific properties of the patient's primary tumour because some tumours metastasise preferentially to certain regions of the skeleton than others. Scan abnormalities also need to be interpreted in the light of the patient's history and physical examination.

Planar bone scintigraphy is very sensitive for the detection of osseous metastases and it is well known that it can be used to identify skeletal metastases before they are visible on radiographs [Al-janabi, 1995; Smith *et al.*, 1990]. Despite the strengths of planar bone scintigraphy, it may still not be sensitive enough to detect subtle lesions, especially in complex regions such as the spine. It has been argued that planar bone scan appearances are frequently non-specific for the diagnosis of bone metastases, since many benign bony lesions demonstrate similar tracer uptake patterns. Furthermore, planar images

have limited use for accurate anatomical localization in the evaluation of complex bony structures such as the spine.

Single Photon Emission Computed Tomography (SPECT) results in a higher lesion-to-background contrast, which results in improved sensitivity for detection of lesions [Murray, 1994; Podoloff et al., 1992]. These three-dimensional images can be displayed as tomographic slices in the transaxial, coronal and saggital planes, and as a three-dimensional reconstruction using a rotating cine display. This results in improved lesion localization, which, in turn, implies that lesions can be interpreted with more specificity [Murray, 1994]. A number of previous studies have demonstrated that the addition of SPECT of the spine significantly enhances the value of bone scintigraphy for the detection of bone metastases in comparison to planar imaging alone [Podoloff et al., 1992; Roland et al., 1995; Yueh et al., 1996].

In most African countries, a large proportion of the population is poor and has little formal education compared to those in developed countries. Furthermore there is often little awareness of the early symptoms of cancer, and screening programmes are often underdeveloped. Consequently, these patients more frequently present with cancers at advanced stages. At this point in the progression of the disease, tumour cells have often already metastasised to the skeleton. Those centers that do have gamma cameras often only have equipment capable of performing planar scintigraphy, with SPECT being unavailable. Where a gamma camera capable of performing SPECT is present, it will typically have a high workload. The author is not aware of the benefit of

SPECT having been demonstrated in a study performed in the African context, where patients often present later, with more advanced disease. The added value of SPECT for the detection of bone metastases in a population of patients such as this needs to be demonstrated. This will provide further insight into the added value of SPECT in this context, which, in turn, will assist with decision making that is more cost-effective and therefore allows for improved patient care in these countries.

Literature Review

Pathophysiology of Bone Metastases:

A metastasis is defined as a growth, separate from the primary tumour, which has arisen from detached, transported fragments of the primary tumour. Dissemination of malignant cells throughout the body, and their survival to form secondary growths, constitute a complicated process dependent on both host and tumour tissue factors [Morgan-Pakes, 1995]. Metastases are the major cause of treatment failure in cancer patients.

Once tumour cells have become detached from the primary site, their ultimate destination will depend on the route they travel. These potential pathways include haematogenous, contiguous spread, through the lymphatic system, and lastly through cerebrospinal fluid (CSF). However, cancer cells metastasise to bone almost exclusively by the haematogenous route. Bony metastases predominantly occur in areas of red marrow, because it is much richer in vascular endothelium than yellow marrow or the bone cortex. Skeletal metastases usually develop in the medulla and eventually lead to cortical damage [Galasko, 1986].

The most frequent tumours to metastasise to bones are carcinomas of the lung, breast, prostate, kidney and gastrointestinal tract [Johnston, 1970]. Metastatic neoplasms vastly outnumber primary tumours of the skeleton and generally affect multiple sites. Autopsy studies have documented skeletal metastases in

20%-70% of patients with non-osseous primary malignant neoplasms [Hendrix *et al.*, 1991]. It is not entirely clear why certain tumour cells are more often found in bone. However this can be predicted by the behaviour of cancer cells, which are closely related to the type of the primary tumour itself. The presence of a large blood supply to the skeleton with the physiologically large vascular spaces result in relative "blood stagnation" which is a suitable environment for malignant cells to thrive in bone in general [Krasnow et al., 1997]. Tumour cells, once metastasised to the skeleton, will start to multiply and invade bony structures. This invasion and the influence of substances secreted by malignant cells will normally lead to stimulation of osteoblastic activity in the bone as a reparative process. Radiologically, the skeletal metastasis of tumour cells from different tumours can lead to osteolytic, osteosclerotic, or mixed lesions. Normally, simultaneous production of new bone as well as bone destruction occurs in both osteolytic and osteosclerotic metastases. In osteolytic lesions the bone destruction predominates, resulting in the net loss of bone; in osteosclerotic metastases excessive amounts of new bone formation develop, with less bone destruction [Galasko, 1986]. Many osteolytic lesions eventually produce a partial osteosclerotic reaction, often at the periphery of the lesion and resulting in a mixed pattern.

There are situations, however, in which purely osteolytic lesions occur without an osteoblastic response. Metastases that usually produce a purely osteolytic response typically arise from carcinomas of the thyroid, kidney, bladder, melanoma, multiple myeloma and highly aggressive carcinomas. Bone formation tends not to occur with these tumours because of two known

mechanisms. The first is mediated via the osteoclasts, which are stimulated to proliferate by the secretion of osteoclast-stimulating factors by the tumour. The second is through direct bone destruction by the malignant cells, possibly because of their ability to secrete lytic and other enzymes [Galasko, 1976].

Knowledge of disease pathophysiology and other specific properties of the patient's primary tumour, along with subsequent correlation of scan abnormalities to patient history, physical examination, other tests and previous studies, is essential for determining lesion significance. Knowledge of disease pathophysiology specifically is very important because this will explain why some tumours have a greater tendency to spread preferentially to certain regions in the skeleton than others. For instance, metastases from prostate and breast carcinoma are more often located in the spine and pelvis because their malignant cells travel through what is known as Batson's plexus, whereas lung carcinoma cells move through the main venous channels and so are more often deposited in the extremities, and metastases are found in a wider variety of bones [Krasnow *et al.*, 1997].

More than 90% of metastatic bone lesions occur in the axial skeleton and the spine is the most common site of skeletal metastases (39%) because of its abundant vasculature and red bone marrow [Taoka *et al.*, 2001]. Therefore the optimal interpretation of spinal lesions is particularly important in this group of patients.

Bone metastasis is a common complication of several different cancers, and may be the first indication that the disease has spread beyond the area of the primary tumour. This normally indicates that the prognosis has worsened. Management plans of cancer patients also depend on whether a patient does or does not have bone metastasis. Bone metastasis can lead to various complications, including fractures, hypercalcemia, and bone pain, and reduced performance status and quality of life [Serafini, 2001].

Indications for Bone Scintigraphy

The indications for clinician referral of cancer patients for bone scintigraphy to detect bone metastases are many, most commonly for initial staging of disease in patients in whom carcinoma was recently diagnosed. This is applicable to cancers with a greater predilection for early metastasis to bone, such as prostate, breast, and lung cancers. Some doctors refer the patients for bone scanning to evaluate the response of bone metastases to therapy and then for routine follow up after a certain period of time, or to determine the cause of bone pain reported by the patient in order to manage that pain properly, and sometimes to reveal the cause of unexplained abnormal values of laboratory tests.

Radionuclide Bone Scan

Bone scintigraphy is the most frequently performed radionuclide examination, accounting for 40%-60% of the work in nuclear medicine departments [Holder,

1990]. Bone scanning is the primary imaging examination used to detect osseous metastases for a number of primary malignancies.

Radiopharmaceuticals

Condensed phosphate esters or polyphosphate compounds and diphosphonate compounds labelled with technetium–99m have been used for bone scintigraphy, with various diphosphonate compounds now used almost exclusively [Subramanian and McAfee, 1971]. Technetium-99m labelled methylene diphosphonate (^{99m}Tc-MDP) is taken up by chemisorption onto the phosphorous groups of calcium hydroxyapatite, the basic crystal of bone [Alazraki, 1996]. The mechanisms of abnormal ^{99m}Tc-MDP uptake demonstrated with bone scanning are complex. The factors known to accelerate deposition of ^{99m}Tc-MDP in bone are increased blood flow to abnormal bone and increased bone turnover or metabolism resulting in increased osteoblastic activity, with the latter resulting in an increased surface area of bone crystal available for binding [Saha, 1992].

Three hours after administration of the activity to a normally hydrated patient, approximately 35% of the injected dose is excreted by the kidneys, 30%-40% is associated with bone, 10%-15% is in other tissues, and 5% is in the blood [Holder, 1990]. Thus metastatic deposits that produce a vigorous osteoblastic response will be visualized as a "hot spot" on a bone scan [Krishnamurthy *et al.*, 1976]. Those lesions that generate a purely osteolytic reaction may not be detectable unless they are large enough to appear as areas of absent tracer

accumulation. Some anablastic tumours, for example, are highly aggressive and do not allow an osteoblastic response to take place. These can lead to decreased tracer uptake giving rise to a "cold spot" or a mixed lesion with a cold centre and a hot periphery [Gold *et al.*, 1990].

Strengths and Weaknesses of Bone Scintigraphy

The bone scan has many major advantages in clinical oncology. It has high sensitivity for detecting most skeletal metastases and has the capability of imaging the whole body at relatively low cost and with a low total radiation dose [Mirza *et al.*, 2001]. It is also easy to perform on almost every patient, with very few side effects [Jacobson and Fogelman, 1998]. Bone scanning has a role to play as a guide in monitoring the response to therapy. Alternative screening modalities, such as conventional radiography and CT, have been shown to be less sensitive in the detection of bone marrow metastases than skeletal scintigraphy [Olson *et al.*, 1994; Silberstein *et al.*, 1973]. Scintigraphy may reveal bone metastases up to 18 months before radiography shows them and has 50%-80% greater sensitivity [Pagani and Libshitz, 1982].

Bone scanning also has some major disadvantages, and these include the fact that a bone scan is non-specific for metastatic lesions alone and insensitive, in particular for purely osteolytic or medullary lesions. In addition, it provides limited anatomical details if compared to anatomical imaging modalities such as the CT scan and MRI. With purely intramedullary lesions, i.e. lesions without cortical involvement, the findings of bone scintigraphy are always negative

[Thrall and Ellis, 1987]. Small lesions or lesions localized away from the cortex are therefore likely to be undiagnosed on a bone scan, despite the destruction of trabecular bone [Taoka *et al.*, 2001]. Even if most of the bone marrow has been infiltrated by metastases, but the destroyed medullary bony matrix is relatively small, the uptake of radiotracers will remain low and therefore may not be easily appreciated when the uptake is contrasted with that of the normal cortex [Taoka *et al.*, 2001]. Furthermore, subtle lesions may be missed on planar images due to overlying normal bone in complex bony structures such as the spine.

Interpretation of Planar Bone Scintigraphy

Knowledge of the appearance of a normal scanned image and its variations is essential to avoid interpretive errors that may lead to a false-positive diagnosis [Gold *et al.*, 1990]. It is important clinically to recognize that an abnormally increased localization of tracer represents a similar final common pathway for all processes that disturb normal rates of osteoblastic activity. Normal structures or variants that may appear relatively hotter than the rest of the skeleton are: base of skull, costochondral junctions, external occipital protuberances, paranasal sinuses, inferior tips of the scapulae, spinous processes of vertebrae, sternum, sternoclavicular joints, sternomanubrial joints, sacroiliac joints, unfused epiphyses, [Gold *et al.*, 1990]. There are other structures that appear in a bone scan, such as thyroid gland due to free pertechnetate in the Technetium-99m labelled methylene diphosphonate dose; genitourinary system for the excretion of radioactivity; trauma and inflammation due to the increase in

the blood supply; any calcified tissue; and, lastly, in injection sites, due to extravasations of the injected radioactivity.

Features that raise suspicions about skeletal lesions as possible metastases are asymmetry; extreme variation of intensity; multiple random distribution; and occurrence being primarily in the axial skeleton [Holder, 1990]. Very widespread, diffuse metastatic disease can produce a so-called "super scan". This is an image with extraordinarily high tracer uptake throughout the skeleton, rather than individual foci. There is increased skeletal accumulation with absent renal excretion or uptake [Holder, 1990]. At least one third of solitary abnormalities detected in the bone scans of patients with known malignant disease result from benign processes or normal variations [Gold *et al.*, 1990].

When interpreting planar bone scintigraphy, knowledge of disease pathophysiology and other specific properties of the patient's primary tumour, along with the subsequent correlation of scan abnormalities to patient history, physical examination, previous studies, and other radiological examinations, is crucial for determining the true significance of lesions.

Single Photon Emission Computed Tomography (SPECT)

Frequently, differentiating between benign and malignant lesions in the vertebral column of cancer patients by using planar imaging alone is very challenging. Detecting the exact anatomical site of abnormalities of the vertebrae with planar bone scintigraphy is difficult, and the ability of planar

imaging to differentiate between malignant and benign vertebral lesions is therefore limited. SPECT is more sensitive than planar scintigraphy for detecting vertebral lesions. Bone imaging with SPECT can produce increased image contrast of deeper structures in particular [Holder, 1990]. SPECT imaging in oncology patients is most useful for the evaluation of the thoracolumbar spine, skull and pelvis. These areas have extensive surrounding soft tissue and/or complicated bony structures, and thus the superior image contrast provided by SPECT improves lesion detection [Krasnow et al., 1997].

The increasing availability of SPECT for routine nuclear medicine studies reflects the acceptance that this technology improves our ability to detect abnormalities and to assess their exact location. Because SPECT minimises the effects of overlying activity, accurate images of body sections are obtained for prescribed depths and lesion contrast consequently is improved, which improves our chances of detecting abnormalities [Delpassand et al., 1995]. An up to 6-fold increase in image contrast can be obtained with SPECT imaging techniques, compared to planar imaging, and visual interpretation of the scans benefits from this improvement in contrast [Groch and Eawin, 2000]. Subtle lesions missed when using planar imaging can therefore be detected, resulting in an increase in sensitivity.

Knowing the exact location of a lesion in the vertebra is crucial to determine its nature more specifically. SPECT improves on the specificity of planar imaging because of improved localization of abnormalities in the vertebrae [Sedonja and Budihna, 1999]. Sections or slices of the body can be displayed with SPECT in

transaxial, coronal, and sagittal views, or as a 3-dimensional image of the anatomy. This improves the interpreter's ability to locate an abnormality and, on the basis of its location, to determine whether there is a benign or a malignant process.

Indications for SPECT scanning

1. Equivocal Spinal Lesions on Planar Bone Scintigraphy

When multiple areas of increased tracer activity or a super scan consistent with bony metastases are seen on planar bone scintigraphy, SPECT examination usually adds little information to the diagnostic value of the bone scan. However, the detection of one or a few abnormal vertebrae through bone scintigraphy is a common finding in clinical practice, particularly in elderly people who have a high incidence of benign degenerative changes in the vertebral column [Evan-Sapir et al., 1993]. The detection of a solitary lesion or a few lesions in the spine by means of bone scintigraphy poses a diagnostic dilemma in patients with no other known skeletal metastases. A study undertaken by Boxer et al., (1989) found that the spine was the commonest site for both solitary (52% of cases) and multiple (87%) metastases. The differentiation between a benign and a malignant vertebral lesion is therefore an important issue, especially in patients with known cancer. The increased anatomical information provided by SPECT can assist with this.

2. Back pain

Vertebral SPECT should be performed in patients with a known malignancy, who present with back pain. This may be necessary despite normal planar

imaging, as back pain is a common presentation of bone metastases in patients with known primaries, and the overlapping of bony structures may obscure subtle lesions.

3. Suspicious findings with other imaging studies, e.g. conventional radiography or CT scan, despite a normal planar bone scintigraphy, specifically in a complex bony structure such as the spine.

Interpretation of Bone SPECT

The localization of a lesion to different vertebral parts significantly influences the likely diagnosis [Han *et al.*, 1998]. This benefit of SPECT was demonstrated in a study performed by Han *et al.*, (1998). In addition, orthogonal images are easier to correlate with other cross-sectional anatomical studies (CT and MRI). These studies can even be co-registered.

Benign lesions are more frequent when increased tracer uptake is seen in the terminal plate, lateral boundaries of the vertebral body, facet joints, and spinous process. Malignant lesions are more frequent when scan changes are in the pedicle; vertebral body with the extension to the pedicle; central parts of the entire vertebra; and in cold lesions with margins of increased uptake [Evan-Sapir *et al.*, 1993].

Evan-Sapir *et al.* (1993) found metastases in 83% of vertebrae with increased radioactivity in the entire body or part of it with extension to the pedicle,

whereas Delpassand *et al.*, (1995) found them in 96%. Sedonja and Budihna (1999) found only 53.8% of lesions that show abnormal uptake extending from the body to the pedicle in their study, but the selected population of patients with predominant osteolytic metastases in their study can explain this somehow conflicting result of their study with others. Focal uptake in the vertebral body in the study by Evan-Sapir *et al.* (1993) represented benign lesions in 96% of cases. According to Sedonja and Budihna, (1999), these lesions should be considered as possibly metastatic, especially if situated in the central part of the vertebral body.

To our knowledge, no work has been done to assess the benefit of SPECT in the diagnosis of bone metastases in a population of patients with known malignancies in Africa, where patients often present later and with more advanced disease. The added value of SPECT for the detection of bone metastases needs to be confirmed for a population of patients such as this. This will provide more insight into the added value of SPECT in this context.

Other Modalities for the Diagnosis of Bone Metastases

There are many investigative modalities used for diagnosing bone metastases. The most important are:

1- Conventional radiography.

2- Computed tomography scan (CT).

3- Magnetic resonance imaging (MRI).

4- Positron Emission Tomography (PET)

5- Bone biopsy

6- Blood biochemistry

Selection of the appropriate test from all of these modalities depends on many factors:

1- The sensitivity and specificity.

2- The cost

3- The availability

4- Its usefulness for screening the whole skeleton versus a specific region.

Conventional Radiography

Skeletal conventional radiography is not an accurate tool for the early detection of bone metastases because it cannot detect lesions until the loss of calcium in the bone is at least 30-50% [Guzzo *et al.*, 1969; Glelen *et al.*, 1976]. This explains the fact that osteoblastic or osteolytic processes need to be present for some time before resulting in osteosclerosis or osteolysis that is marked enough to be detectable. This lack of sensitivity is further compounded by the fact that the cancellous bone in the medullary canal is usually the first site of skeletal metastases [Edelstyn *et al.*, 1967].

When conventional radiography is used to examine bony structure, reduced bone density is mostly detected in cortical bone. Even small intracortical osteolytic metastases appear in high contrast to the dense compact bone surrounding them, and they are easily detected with conventional radiographs.

Thus, conventional radiographs are useful for determining integrity of cortical bone, and especially for depicting impending or early pathological fractures [Rubens, 1998].

Conventional radiography is the best modality for characterizing lesions as osteolytic, osteosclerotic, or mixed lesions and is relatively cheap and widely available [Gold, 1990]. It is normally reserved for studying limited regions of the skeleton. Although skeletal surveys can be performed with the use of conventional radiography, such use results in a relatively high radiation dose and also increases the cost. Comparison with bone scans reveals that 10 to 40% of skeletal metastases show up as normal in radiographs and as abnormal in scans, while fewer than 5% of radiographically apparent lesions are shown as normal when bone scans are used [DeNardo *et al.*, 1972].

Computed Tomography (CT) Scan

CT scan is much more sensitive than conventional radiography for the depiction of cortical involvement by metastatic bone disease and provides higher resolution images with more in-depth anatomical detail [Krasnow *et al.*, 1997]. The contrast resolution of CT is approximately ten times greater than that of conventional radiography [Gold, 1990].

Both conventional radiography and the CT scan look for a change in bone density caused by bone destruction due to bony metastases. But a CT scan can identify bone destruction earlier than conventional radiography; in addition, it can also assess extra-osseous soft tissue and intra osseous medullary spread

[Coleman, 1998]. A CT scan is therefore effective in evaluating radiographically negative areas that are symptomatic and clinically suspicious with regard to metastases. A CT scan is sensitive with regard to detecting subtle cortical invasion but it is less sensitive for detecting medullary bone or bone marrow involvement [Aitchison *et al.*, 1992].

CT scans are usually done for regions of the body such as chest, pelvis or thoraco-lumber spine and are relatively more expensive than bone scans and associated with higher radiation doses to the patients. To do a whole body CT scan is even more expensive, but a whole body CT scan is not practical because of the high level of radiation of the patient.

Magnetic Resonance (MR) Imaging

MRI provides images with exceptional anatomical detail, and substantial information on bone and bone marrow pathology as well as soft tissue and solid organ disease can be discerned with the use of various pulse sequences and intravenous contrast materials. It offers the best direct evaluation of bone marrow [Gold, 1990].

A number of studies have shown MRI to be superior to bone scintigraphy for the demonstration of spinal metastases [Haulbold-Reuter *et al.*, 1993; Gosfield et al. 1993; Frank *et al.*, 1990]. CT is even more sensitive than MR imaging for the detection of cortical disruption, but MR imaging is more sensitive than CT for detecting bone marrow involvement [Krasnow *et al.*, 1997]. Nevertheless the

choice between CT and MR imaging in the diagnosis of bone metastases may mostly depend on their relative availability [Gold, 1990].

There are several circumstances in which MR imaging may have a significant impact on the management of the patient with suspected osseous metastatic bone disease. These include the detection of metastases in symptomatic patients in whom radiographs and radionuclide bone scans are equivocal or negative, and the asymptomatic patient with regard to whom there is serious suspicion of metastatic bone disease, especially when both the radiograph and the bone scan provide negative results [Jones *et al.*, 1990].

MR imaging may also be useful for determining the cause of vertebral collapse in elderly patients with a known primary malignancy. In this case the secondary osteoblastic reaction detected with bone scanning can be due to a fracture only or may also be caused by metastases [Yuh *et al.*, 1989]. In addition, specificity is higher for MRI because there are fewer abnormalities that will have a similar appearance to bony metastatic disease [Traill *et al.*, 1995]. However, one study utilizing SPECT imaging found similar results to MR imaging [Kosuda *et al.*, 1996]. Although whole body MRI techniques are available, they are difficult to perform, expensive and time-consuming [Krasnow *et al.*, 1997]. Due to the cost of MRI machine itself the availability in African countries is doubtful, and even if found it would be costly and not accessible to huge sector of population because of poverty.

Positron Emission Tomography (PET)

PET using ^{18}F-fluoro-deoxyglucose (FDG) images the whole body and can play a major role not only in the diagnosis but also in the staging, treatment planning and monitoring of patients with cancer [Wagner *et al.*, 1998]. With FDG PET it is possible to obtain a whole body image giving a whole body distribution of glucose metabolism rather than only of the skeleton, and in the absence of disease, there is virtually no bone visualization. PET has a higher resolution in comparison to other nuclear medicine methods [Holle *et al.*, 1996]. It is very expensive and only available in well-developed countries, and even there it is not normally available for day-to-day clinical practice. It is not available anywhere in Africa at present.

FDG PET has been reported to have high sensitivity and specificity (> 90 %) for the detection of malignant lesions [Martin *et al.*, 1996]. New imaging techniques such as MR imaging and Positron Emission Tomography (PET) can identify bone metastases at an earlier stage of growth than other procedures, before host reactions of the osteoblasts occur, and both have been reported to provide a sensitivity approaching 100% for detecting bone metastases [Daldrup-Link *et al.*, 2001].

Bone Biopsy

Bone biopsy provides a rapid, accurate, and relatively safe means of obtaining proof that a lesion detected by means of conventional radiography, radionuclide bone scanning, CT, or MR imaging is a metastasis [Gold, 1990]. The decision to

do a biopsy of a skeletal lesion is usually made after roentgenograms and appropriate laboratory work have provided a differential diagnosis. At this stage the method for obtaining the tissue sample is influenced by the location of a lesion, its surgical accessibility and the strength of presumptive diagnosis. All the advantages of needle biopsy will be nullified without a close working relationship between the surgeon and the pathologist [Johnston, 1970]. The surgeon, in particular, needs to know if he has missed the lesion or whether his biopsy is adequate. His concern naturally is shared by the radiologist and the pathologist. Open surgery is utilized only when needle biopsy is diagnostically inconclusive [Johnston, 1970]. Bone biopsy is an invasive procedure, after all, and still associated with the risk of complication, especially in the case of suspected vertebral lesions in the elderly [Aitchison *et al.*, 1992]. Bone biopsy will not be done routinely for every patient with suspected bone metastases, but can be of use if there is a solitary bone lesion with high a possibility of being metastatic.

Blood biochemistry

Markers of bone remodelling could help the clinician in the diagnosis and follow-up of bone metastases. A common feature of both types of bone metastases (lytic and sclerotic) is an alternation of bone remodelling activity. The rate of formation or degradation of the bone matrix can be assessed either by measuring a prominent enzymatic activity of the bone-forming or -resorbing cells or by measuring bone matrix components released into the circulation during formation or resorption [Fontana and Delmas, 2000]. They have been separated into markers of formation and resorption, but when both events are

coupled and in balance, either of these markers will reflect the overall rate of bone turnover. These markers are of unequal specificity and sensitivity, and some of them have not been fully investigated for bone metastases yet. None of these markers is disease specific [Fontana and Delmas, 2000]. They are used mainly for excluding metastatic disease rather than for confirming its presence. Normal serum values of these markers indicate a very low probability of metastases. In a study undertaken by Freitas *et al.*, (1991) it was found that a Prostate Specific Antigen (PSA) value of ≤8 ng/ml excluded bone metastases with a negative predictive value of 98.5%. Others have shown that in prostatic cancer patients with normal Alkaline Phosphatase and no pain will have a positive scan in less than 1% of cases [Gerber and Chodak, 1991].

Aim of the Study

The aim of this research is to investigate the added benefit of performing spinal SPECT, compared to planar bone scintigraphy alone, for the diagnosis of bone metastases in African patients with known primary malignancies.

The objectives:

1. To compare the interpretation of bone scintigraphy for planar imaging alone with planar imaging with SPECT with regard to:

   a. Overall interpretation of the bone scans

   b. Thresholds for considering metastatic disease to be likely, exclusion of metastatic disease and confirmation of metastatic disease

   c. The influence of SPECT on the decisiveness of interpretation

   d. The number of spinal lesions detected.

2. To compare these results with those described in the literature and form an opinion on the contribution of spinal SPECT for the detection of metastatic disease in this group of patients.

Materials and Methods

Patient Population

Planar and SPECT studies of bone scans of patients were obtained from departmental archives. The study was restricted to patients with known primary malignancies who underwent both planar bone scintigraphy and SPECT to diagnose bony metastases in our institution during the year 2000. In our institution, patients were initially imaged with planar scintigraphy of the entire skeleton, and SPECT of the spine was then performed in cases reporting back pain, equivocal spinal lesions on the planar images, or documented spinal lesions on previous radiological imaging. In the event of the same patient undergoing planar bone scintigraphy with SPECT more than once in the same year, only the first study was used.

Bone Scanning

Seven hundred and forty MBq (20mCi) of technetium-99m methylene diphosphonate was injected intravenously. Planar imaging was performed three hours later with a high-resolution low-energy, parallel hole collimator and at least 500 kilo counts per image were obtained, using Elscint Helix, Elscint SP-4, Elscint 409 and GE Starcam gamma cameras (GE Medical Systems, USA). SPECT imaging was performed immediately after planar imaging, using Elscint Helix and Elscint SP-4 gamma cameras.

SPECT data acquisition was performed with the Elscint Helix gamma camera using a 180-degree oval orbit, step and shoot mode and 3-degree steps

counted for 20 seconds. For the Elscint SP-4 camera it was performed over 360 degrees with 6-degree steps and counting for 40 seconds per frame. Transaxial, Coronal and Saggital slices were reconstructed using filtered back-projection with a Butterworth filter of cut-off frequency of 0.3 and a power factor of 10. Slice thickness was 4.4 mm. Planar images and SPECT slices were then recorded onto X-ray film.

Interpretation of scans

Three experienced Nuclear Medicine physicians interpreted the bone scans. The interpreters had access to clinical information such as the primary malignancy and any symptoms experienced by the patient. Decisions were reached by consensus.

Firstly the planar images of the whole skeleton were examined in isolation, with the interpreters blinded to the SPECT study. A decision was made as to the likelihood of bony metastasis for the whole skeleton, which was scored on a four-point scale or graded as 1 = "no metastases" ($p < 0.2$), 2 = "probably no metastases" ($0.2 < p < 0.5$), 3 = "probably metastases" ($0.5 < p < 0.8$) or 4 = "metastases" ($p > 0.8$), with p being equal to the probability of metastatic disease for the entire skeleton. A decision was also reached as to the number of spinal lesions present.

Immediately following this, the planar and SPECT images were interpreted together. Again, a decision was made as to the likelihood of bony metastasis for the whole skeleton, which was scored using the same four-point scale. A

decision was again reached as to the number of spinal lesions present, and the lesions were localized to one or more of the following regions: osteophyte, vertebral body, pedicle, facet joint, lamina and spinous process. A spinal lesion was considered metastatic when it involved the pedicle or vertebral body, whereas lesions not involving these structures were considered to be benign.

Data Analysis

All these data were entered into a spreadsheet for analysis. The results of all statistical tests were considered significant for $P < 0.05$.

The grading of the planar imaging alone was then compared with the grading of the combined planar and SPECT studies. Attention was given to the effect of adding SPECT to the different planar gradings in particular. Scan gradings were compared using a pairwise nonparametric method (Wilcoxon matched pairs test) to test for statistical difference between the grading of planar imaging alone and the grading after addition of SPECT for all patients, breast cancer patients and prostate cancer patients.

In order to compare the results, these grades were regrouped into two categories, using four different classifications. Mosteller's exact test was used to compare proportions of different groups after each re-classification. However, if no patients had not undergone upgrading or downgrading as a result of the addition of SPECT, Mosteller's exact test was not applicable. In this case McNemar's test was used, on the condition that a total of at least 10 patients had undergone upgrading and downgrading.

The following four classifications were used:

"Metastases" versus "No Metastases"

Firstly, grades of 1 or 2 were considered to indicate the absence of disease ("No Metastases"), while grades of 3 or 4 were considered to indicate the presence of disease ("Metastases"). The influence that adding SPECT exerted on changing the interpretation of the bone scan in such a way that this threshold was crossed, was then evaluated.

The relative sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of planar scintigraphy alone with regard to predicting the result of planar imaging with SPECT were then calculated for the all patients in the study. The interpretation of the planar studies alone was defined as negative for bone metastases for grades of 1 or 2, and positive for bone metastases for grades of 3 or 4. Similarly, for the interpretation of the combined planar and SPECT studies, grades of 1 and 2 were considered to indicate the absence of disease, while grades of 3 and 4 were considered to indicate the presence of disease.

The following formulae were used:

$$\text{Sensitivity} = \frac{TP}{TP + FN} \tag{1}$$

$$\text{Specificity} = \frac{TN}{TN + FP} \tag{2}$$

$$\text{PPV} = \frac{TP}{TP + FP} \tag{3}$$

$$\text{NPV} = \frac{TN}{TN + FN} \tag{4}$$

$$\text{Accuracy} = \frac{TN + TP}{\text{Total Studies}} \tag{5}$$

Where: TP is the number of true positive studies

FP is the number of false positive studies

TN is the number of true negative studies

FN is the number of false negative studies

"Metastases excluded" versus "Not excluded "

Secondly, grade 1 only was considered to exclude metastases ("Metastases Excluded"), while grades of 2, 3 and 4 were considered to not exclude metastases ("Metastases not excluded"). The influence that the addition of SPECT had on changing the interpretation of the bone scan in such a way that this threshold was crossed was then evaluated.

The relative sensitivity, specificity, accuracy and positive and negative predictive values of planar scintigraphy alone, with regard to predicting the result of planar imaging with SPECT, were then calculated for the all patients in the study, using formulae (1) to (5). The interpretation of the planar studies alone was defined as negative for grade 1 only, and positive for grades 2, 3 and 4. Similarly, in interpreting the combined planar and SPECT studies, grade 1 was considered to indicate the absence of disease, while grades 2, 3 and 4 were considered to indicate disease.

"Metastases confirmed" versus "Not confirmed "

Thirdly, grade 4 only was considered to confirm metastases ("Metastases Confirmed"), while grades of 1, 2 and 3 were considered to not confirm metastases ("Metastases not confirmed"). The influence that adding SPECT had on changing the interpretation of the bone scan in such a way that this threshold was crossed was then evaluated.

The relative sensitivity, specificity, accuracy and positive and negative predictive values of planar scintigraphy alone, with regard to predicting the

result of planar imaging with SPECT, were then calculated for all the patients in the study, using formulae (1) to (5). The interpretation of the planar studies alone was defined as positive for grade 4 only, and negative for grades of 1, 2 and 3. Similarly, for the interpretation of the combined planar and SPECT studies, grade 4 was considered to indicate disease, while grades 1, 2 and 3 were considered to not indicate disease.

"Decisive" versus "Equivocal"

Grades of 1 and 4 were considered to represent "Decisive" diagnoses, while grades of 2 and 3 were considered to represent "Equivocal" diagnoses. The influence that adding SPECT had on changing the relative numbers of patients falling into each of these categories was evaluated.

Number of Spinal Lesions

The total number of spinal lesions detected when using planar imaging alone was compared with the number of spinal lesions detected after the addition of SPECT imaging. The number of lesions detected per patient was also compared for planar imaging alone and after the addition of SPECT; using the Wilcoxon matched pairs test.

Results

Patient Population

A total of 576 patients with known primary malignancies had bone scans performed by our institution for the diagnosis of bone metastases during 2000. Of these, 119 patients had planar and SPECT studies performed. These 119 patients consisted of 45 males and 74 females. Their ages ranged from 11 to 89 years, with a median age of 62 years. In this group of patients, breast carcinoma and prostate carcinoma were present in the majority of cases. Breast carcinoma (n = 55) and prostate carcinoma (n = 29) together represented more than seventy percent of the total number of patients, while other malignancies were represented in small numbers. A breakdown of the number of patients for each primary malignancy is given in Table 1. Sixty-four patients (53.8%) were documented as having symptoms of back pain, and 55 patients (46.2%) had no documented symptoms of back pain.

Grading of Studies

Grading of the planar whole body scans for the probability of bone metastases resulted in 57 patients being graded as grade 1 (no metastases), 42 as grade 2 (probably no metastases), 13 as grade 3 (probably metastases) and seven as grade 4 (metastases). After the addition of SPECT, 64 patients were graded as grade 1, 21 as grade 2, 21 as grade 3 and 13 as grade 4. It can be noted from these figures that the number of cases in grade 2 ("probably not metastases") halved with the addition of SPECT, whereas the number of cases increased equally in the other three grades. A list of the various patients' primary tumours,

grading and number of lesions, for both planar imaging and combined planar and SPECT imaging is given in Table 2.

A more detailed analysis of the effect on the grading of scans when SPECT was added revealed that grading was unchanged in 84 patients (70.6%). A total of 24 patients (20.2%) were "upgraded" (i.e. metastases more likely); 22 of these were upgraded by 1 grade and two by 2 grades. Of these 24 patients, 16 were graded as grade 2, four were grade 1 and four were grade 3 when planar images were used alone. A total of 11 patients (9.2%) were "downgraded" (i.e. metastases less likely), with nine of them downgraded by 1 grade and two by 2 grades. Of these 11 patients, nine were grade 2 and two were grade 3 when planar imaging was used alone. It can therefore be noted that the grading of a total of 35 patients (29.4%) was altered by the addition of SPECT, while 25 of these patients were rated as grade 2 ("probably not metastases") when planar images were used alone.

Of the 57 patients graded as grade 1 by planar imaging alone, only four (7 %) were re-graded after the addition of SPECT, and all were upgraded to grade 2. Of the 42 patients graded as grade 2 by planar imaging alone, 25 (60 %) were re-graded after the addition of SPECT. Of the 25, nine were downgraded to grade 1, 14 were upgraded to grade 3 and two were upgraded to grade 4. Of the 13 patients graded as grade 3 by planar imaging alone, six (46 %) were re-graded after the addition of SPECT. Of these six, two were downgraded to grade 1 and four were upgraded to grade 4. No change was made in seven cases graded as grade 4 after the addition of SPECT (Figure 1).

When applying a Wilcoxon matched pairs test to all patients and the subgroups of patients with breast cancer and prostate cancer, no significant difference was found between the grading obtained by planar imaging alone and that obtained after the addition of SPECT. These results are shown in Table 3.

"Metastases" versus "Not Metastases"

This classification was unaffected by the addition of SPECT in 101 patients (84.9%). Eighteen patients (15.1%) were placed in a different group after the addition of SPECT. Of these 18 patients, sixteen (13.4%) who were grouped as not having metastases when using planar imaging alone were regrouped as having metastases after the addition of SPECT; all of these patients were graded as grade 2 ("probably not metastases") when planar imaging was used alone. The remaining two patients (1.7%) were grouped as having metastases when planar imaging was used alone and were regrouped as not having metastases after the addition of SPECT. Both of these patients were graded as grade 3 ("probably metastases") when using planar imaging alone.

Mosteller's exact test, which was performed for the all patients, found SPECT to make a significant difference (P = 0.0001), as shown in Table 4. In the breast cancer subgroup (Table 5) and prostate cancer subgroup (Table 6), the differences were also found be significant (P = 0.0078 & 0.0313 respectively). Relative to planar imaging and SPECT, planar imaging alone was found to have a sensitivity of 53%, a specificity of 98%, an accuracy of 85%, a PPV of 90%, and a NPV of 84%.

"Metastases Excluded" versus "Metastases Not Excluded"

In 104 patients (87.4%), this classification was unaffected by the addition of SPECT. Fifteen patients (12.6%) were placed in a different group after the addition of SPECT. Of these 15 patients, 11 patients (9.2%) were grouped as not having excluded metastases when using planar imaging alone and they were regrouped as having excluded metastases after the addition of SPECT. Nine of these patients were graded as grade 2 ("probably not metastases") when using planar imaging alone. Four patients (3.4%) grouped as having excluded metastases using when planar imaging alone were regrouped as not having excluded metastases after the addition of SPECT.

Mosteller's exact test, performed for all patients found SPECT to make a significant difference (P = 0.0352) as shown in Table 7. In the breast cancer subgroup (Table 8) and prostate cancer subgroup (Table 9), the differences were also found be significant (P = 0.0156 & 0.0313 respectively).

Relative to planar imaging and SPECT, planar imaging alone was found to have a sensitivity of 93%, a specificity of 83%, an accuracy of 87%, a PPV of 82%, and a NPV of 93% for the exclusion of metastasis.

Disease Confirmed versus Not Confirmed

This classification was unaffected by the addition of SPECT in 113 patients (95.0%). Six patients (5.0%) who were grouped as not having confirmed metastases when using planar imaging alone were regrouped as having confirmed metastases after the addition of SPECT. Of these patients, four were

graded as grade 3 ("probably metastases") and two were graded as grade 2 ("probably not metastases") when planar imaging alone was used. No patients grouped as having confirmed metastases using planar imaging alone were regrouped as having not confirmed metastases after the addition of SPECT.

It was not valid to apply Mosteller's exact test due to the fact that there were no patients reclassified from metastases confirmed to metastases not confirmed after the addition of SPECT. A McNemar's test was therefore applied to the group consisting of all patients. The difference was found to be statistically significant (P = 0.0412), as shown in Table 10. A McNemar's test could not be used for the breast cancer and prostate cancer subgroups due to the small number of patients undergoing reclassification.

Relative to using planar imaging and SPECT, planar imaging alone was found to have a sensitivity of 54%, a specificity of 100%, an accuracy of 95%, a PPV of 100%, and a NPV of 95% for the confirmation of metastasis.

Decisive versus Equivocal Diagnosis

In 98 patients (82.4%) this grouping was unaffected by the addition of SPECT. Therefore 21 (17.6%) of the total group of patients were reclassified after the addition of SPECT. Seventeen patients (14.3%) grouped as equivocal when using planar imaging alone were regrouped as decisive after the addition of SPECT. Eleven of these patients were graded as grade 2 ("probably not metastases") and six were graded as grade 3 ("probably metastases") when using planar imaging alone. Four patients (3.4%) were grouped as decisive

using planar imaging alone and were regrouped as equivocal after the addition of SPECT. All of these patients were graded as grade 1 ("no metastases") when using planar imaging alone.

Mosteller's exact test, performed for all patients, found SPECT to make a significant difference (P = 0.0015), as shown in Table 11. In the breast cancer subgroup (Table 12) and the prostate cancer subgroup (Table 13) the differences were also found to be significant (P = 0.0020 & 0.0313 respectively).

Number of Lesions

The total number of lesions detected by using planar imaging alone was 137, while 170 lesions were detected when planar and SPECT imagings were used. Therefore the number of lesions detected by planar imaging alone was 19% less than the number detected using planar imaging with SPECT. The median number of lesions per patient was one, with a first quartile of zero (no lesions) and a third quartile of two lesions for both planar imaging alone and after the addition of SPECT.

The number of lesions detected for each patient when using planar imaging alone and after the addition of SPECT is shown in Table 2.

Using planar imaging alone, 40 patients had no lesion, 44 patients had one lesion, 21 patients had two lesions, eight patients had three lesions, four patients had four lesions, one patient had five lesions and one patient had six lesions. After the addition of SPECT, 35 patients had no lesion, 36 patients had

1 lesion, 22 patients had two lesions, 16 patients had three lesions, eight patients had four lesions and two patients had five lesions (Figure 2).

The number of detected lesions remained unchanged after adding SPECT in 66 patients (55.5%). In 37 patients (31.1%), the number of lesions increased, whereas the number of lesions decreased in 16 patients (13.4%). As mentioned above, in 40 patients planar imaging detected no lesions but after the addition of SPECT lesions were detected in 11 of them, five patients were shown to have one lesion, three patients had two lesions and three patients had three lesions.

A Wilcoxon matched pairs test was used to determine the significance of the difference in the number of lesions detected by planar imaging alone and after the addition of SPECT. The difference was found to be statistically significant (P = 0.00675), as shown in Table 14.

Table 1: Demographic characteristics of the study population.

Characteristic	N (%)
Age [median $(Q_1,Q_3)]^{\P}$	62 (50-74)
Gender	
Female	74 (62)
Male	45 (38)
Primary Ca	
Breast	55 (46.2)
Prostate	29 (24.4)
Gynaecological tumours	10 (8.4)
Gastrointestinal tumours	8 (6.7)
Genitourinary tumours	8 (6.7)
Bronchus	3 (2.5)
Lymphoma	3 (2.5)
Melanoma	2 (1.7)
Leukaemia	1 (0.8)
Clinical history	
Back pain documented	64 (53.8)
No back pain documented	55 (46.2)

$\P Q_1,Q_3$ First and third inter-quartile range.

Table 2: Patients' clinical information, grading and number of lesions: by Planar imaging alone and after adding SPECT.

No.	Age	Sex	Primary Ca.	No. of Lesions by Planar	Grading by Planar	No. of Lesions by SPECT	Grading by SPECT
1	81	F	Breast	0	2	3	2
2	77	F	Breast	1	2	1	2
3	48	F	Breast	0	1	0	1
4	49	F	Breast	1	2	3	3
5	81	F	Breast	2	1	0	1
6	64	F	Breast	6	1	4	2
7	47	F	Breast	0	1	0	1
8	56	F	Breast	1	1	0	1
9	67	F	Breast	2	2	0	1
10	46	F	Breast	0	1	0	1
11	54	F	Breast	0	1	0	1
12	34	F	Breast	0	1	0	1
13	59	F	Breast	1	4	4	4
14	62	F	Breast	2	1	2	1
15	69	F	Breast	2	2	1	3
16	55	F	Breast	0	1	0	1
17	76	F	Breast	1	1	0	1
18	46	F	Breast	0	1	0	1
19	48	F	Breast	2	2	1	3
20	62	F	Breast	1	2	1	1
21	70	F	Breast	1	2	1	1
22	89	F	Breast	1	2	3	3
23	47	F	Breast	0	1	0	1
24	49	F	Breast	1	3	3	3
25	35	F	Breast	1	4	1	4
26	51	F	Breast	0	1	0	1
27	53	F	Breast	0	1	0	1
28	55	F	Breast	1	2	1	3
29	35	F	Breast	1	2	0	1
30	60	F	Breast	1	2	1	1
31	41	F	Breast	0	1	0	1
32	63	F	Breast	0	1	1	1
33	65	F	Breast	2	3	1	1
34	70	F	Breast	2	3	2	3
35	58	F	Breast	1	2	2	2
36	80	F	Breast	1	1	2	1
37	86	F	Breast	2	1	3	1
38	77	F	Breast	3	3	3	4
39	59	F	Breast	2	2	1	2
40	82	F	Breast	2	2	1	2

41	62	F	Breast	4	2	4	2
42	51	F	Breast	2	3	3	3
43	58	F	Breast	2	3	4	4
44	56	M	Breast	1	2	2	4
45	76	F	Breast	2	1	2	1
46	53	F	Breast	0	1	0	1
47	51	F	Breast	1	1	1	1
48	74	F	Breast	2	1	2	1
49	67	F	Breast	3	4	3	4
50	75	F	Breast	3	4	2	4
51	60	F	Breast	0	1	0	1
52	54	F	Breast	0	1	0	1
53	60	F	Breast	1	3	1	3
54	50	F	Breast	1	1	2	1
55	37	F	Breast	1	2	2	3
56	71	M	Prostate	0	1	0	1
57	65	M	Prostate	0	1	2	1
58	60	M	Prostate	1	1	1	1
59	69	M	Prostate	1	2	1	3
60	75	M	Prostate	3	2	4	1
61	67	M	Prostate	3	4	4	4
62	82	M	Prostate	1	1	1	2
63	73	M	Prostate	1	3	1	1
64	75	M	Prostate	1	2	1	2
65	74	M	Prostate	4	1	2	1
66	69	M	Prostate	1	2	2	2
67	69	M	Prostate	0	1	0	1
68	72	M	Prostate	2	2	3	3
69	68	M	Prostate	0	1	1	1
70	76	M	Prostate	1	2	2	1
71	74	M	Prostate	2	2	5	3
72	70	M	Prostate	2	2	2	3
73	74	M	Prostate	1	1	1	1
74	75	M	Prostate	3	2	3	2
75	64	M	Prostate	3	1	3	1
76	82	M	Prostate	2	2	3	1
77	74	M	Prostate	4	2	4	2
78	80	M	Prostate	1	2	2	2
79	75	M	Prostate	1	2	1	2
80	73	M	Prostate	4	2	0	1
81	76	M	Prostate	3	2	4	2
82	75	M	Prostate	2	3	1	3
83	64	M	Prostate	0	1	3	1
84	80	M	Prostate	0	2	1	3
85	38	F	Cervix	0	1	1	1
86	23	F	Cervix	0	1	0	1
87	59	F	Cervix	1	1	1	1
88	47	F	Cervix	1	2	1	2

89	49	F	Cervix	1	2	2	2
90	42	F	Cervix	1	2	1	3
91	36	F	Cervix	0	1	1	2
92	69	F	Endometrial	0	3	0	3
93	66	F	Ovary	1	3	1	4
94	50	F	Bartholine gland	1	2	1	4
95	72	F	Colon	1	1	2	1
96	18	M	Colon	1	2	1	3
97	60	F	Colon	0	1	2	1
98	37	M	Colorectal	0	1	0	1
99	77	F	Stomach	1	1	3	1
100	75	M	Stomach	0	1	0	1
101	60	F	Oesophagus	0	2	0	2
102	52	M	Oesophagus	1	4	1	4
103	39	M	Bladder	0	1	0	1
104	70	F	Bladder	1	1	2	1
105	72	M	Bladder	2	2	2	3
106	38	F	Renal cell	0	1	0	1
107	18	M	Renal cell	1	3	1	4
108	40	M	Seminoma	0	1	0	1
109	17	M	Testis	0	1	0	1
110	80	F	Urethral	5	1	5	2
111	59	F	Bronchus	2	4	1	4
112	64	M	Bronchus	0	1	0	1
113	50	M	Bronchus	1	2	1	2
114	67	M	Lymphoma	0	3	2	3
115	54	F	Lymphoma	0	1	3	1
116	49	M	Lymphoma	1	1	3	1
117	58	F	Melanoma	0	1	0	1
118	68	M	Melanoma	0	1	0	1
119	11	M	Leukaemia	0	1	0	1

Table 3: Wilcoxon Matched Pairs Test: comparing the grading of planar imaging alone to the grading after the addition of SPECT for all cancers, breast cancer and prostate cancer

Pair of Variables	Valid N	T	Z	P-level
All cancers	119	211.0000	1.703431	0.088488
Breast cancer	55	53.0000	0.775632	0.423690
Prostate cancer	29	33.0000	0.00	1.000000

Table 4: Mosteller's exact test for "metastasis" versus "not metastasis": All cases as classified by planar imaging alone and after the addition of SPECT.

Planar alone			
After SPECT	Not metastasis	Metastasis	P-value
Not metastasis	83	2	
Metastasis	16	18	0.0001

Table 5: Mosteller's exact test for "metastasis" versus "not metastasis": Breast cancer cases as classified by planar imaging alone and after the addition of SPECT.

Planar alone			
After SPECT	Not metastasis	Metastasis	P-value
Not metastasis	37	1	
Metastasis	7	10	0.0078

Table 6: Mosteller's exact test for "metastasis" versus "not metastasis": Prostate cancer cases as classified by planar imaging alone and after the addition of SPECT.

Planar alone			
After SPECT	Not metastasis	Metastasis	P-value
Not metastasis	21	1	
Metastasis	5	2	0.0313

Table 7: Mosteller's exact test for "metastasis excluded" versus "metastasis not excluded": All cases as classified by planar imaging alone and after the addition of SPECT.

After SPECT	Planar alone		
	Excluded	Not excluded	P-value
Excluded	53	11	
Not excluded	4	51	0.0352

Table 8: Mosteller's exact test for "metastasis excluded" versus "metastasis not excluded": Breast cancer cases as classified by planar imaging alone and after the addition of SPECT.

After SPECT	Planar alone		
	Excluded	Not excluded	P-value
Excluded	25	6	
Not excluded	1	23	0.0156

Table 9: Mosteller's exact test for "metastasis excluded" versus "metastasis not excluded": Prostate cancer cases as classified by planar imaging alone and after the addition of SPECT.

After SPECT	Planar alone		
	Excluded	Not excluded	P-value
Excluded	9	5	
Not excluded	1	14	0.0313

Table 10: McNemar's test for "metastasis confirmed" versus "metastasis not confirmed": All cases as classified by planar imaging alone and after the addition of SPECT.

| After SPECT	Planar alone		
	Confirmed	Not confirmed	P-value
Confirmed	7	6	
Not confirmed	0	106	0.0412

Table 11: Mosteller's exact test for "decisive" versus "equivocal": All cases as classified by planar imaging alone and after the addition of SPECT.

Planar alone			
After SPECT	Decisive	Equivocal	P-value
Decisive	60	17	
Equivocal	4	38	0.0015

Table 12: Mosteller's exact test for "decisive" versus "equivocal": Breast cancer cases as classified by planar imaging alone and after the addition of SPECT.

Planar alone			
After SPECT	Decisive	Equivocal	P-value
Decisive	29	9	
Equivocal	1	16	0.0020

Table 13: Mosteller's exact test for "decisive" versus "equivocal": Prostate cancer cases as classified by planar imaging alone and after the addition of SPECT.

Planar alone			
After SPECT	Decisive	Equivocal	P-value
Decisive	10	5	
Equivocal	1	13	0.0313

Table 14: Wilcoxon Matched Pairs test for all cancers comparing the number of lesions detected by planar imaging alone to those detected after the addition of SPECT.

Pair of Variables	Valid N	T	Z	P-level
Number of lesions by Planar alone and lesions by SPECT of all cancers	119	409.5000	2.708946	0.006750

Figure 1: change in planar grading after the addition of SPECT
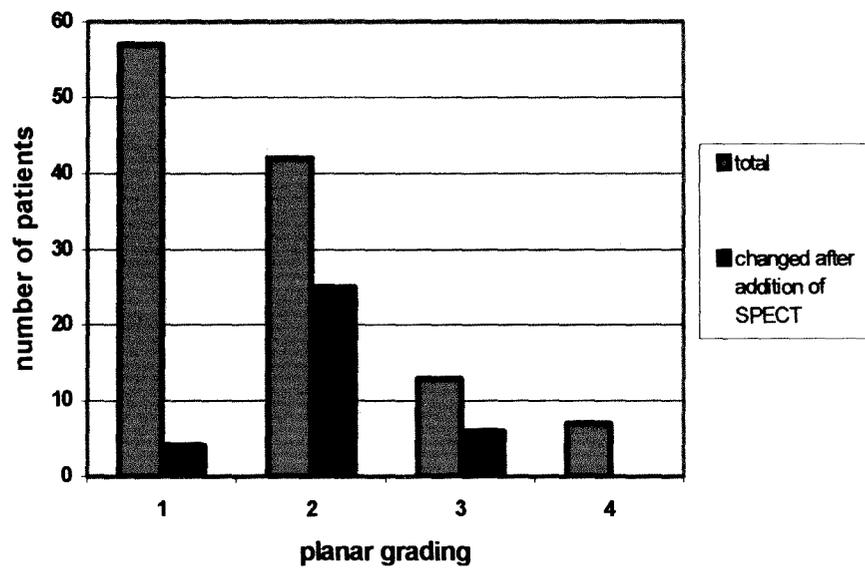
Figure 2: Number of patients classified according to the number of lesions detected by planar imaging alone and after the addition of SPECT
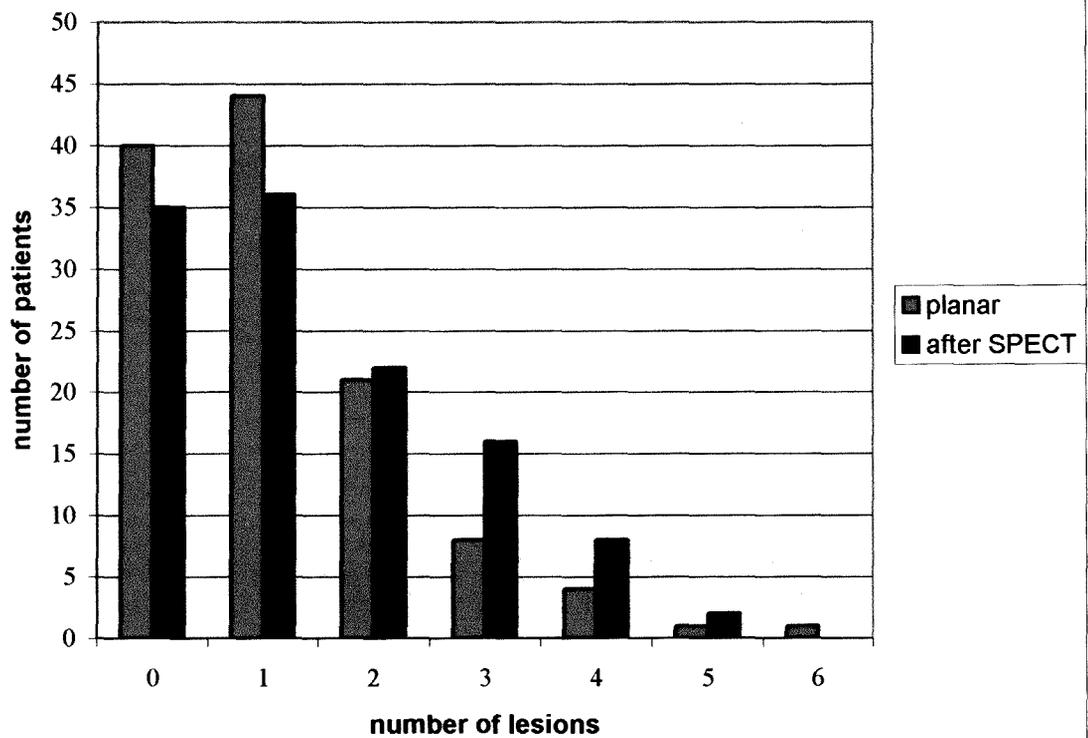
Discussion

Bone scintigraphy is one of the commonest examinations in nuclear medicine and has been used extensively in the evaluation of oncology patients for detecting bone metastases. No imaging modality is more sensitive in screening the whole body for skeletal metastases than a bone scan [Delpassand *et al.*, 1995]. It can detect many types of lesions, but all of them are not necessarily malignant. It is sometimes difficult to differentiate between benign and malignant lesions in the spines of cancer patients, especially in elderly patients who are more likely to have co-morbid conditions, such as degenerative disease. It is difficult to detect the exact anatomical site of abnormalities of the vertebrae using only planar bone scanning. Addition of SPECT to bone scanning in the spine improves the ability to detect abnormalities and to assess their exact anatomical location. Because SPECT minimizes the activity superimposed on structures by overlying and underlying structures, accurate images of body sections are obtained for prescribed depths and lesion contrast consequently is improved, which improves our chances of detecting subtle abnormalities. In addition, our ability to locate an abnormality is improved because sections or slices of the body can be imaged with SPECT in transaxial, coronal and sagittal views. On the basis of its location, it is possible to determine with more certainty whether the observed abnormality is a benign or malignant process. SPECT provides better contrast and it localizes the lesions anatomically better than planar imaging alone. It can detect new lesions not seen with planar imaging alone because of better contrast, which may result in upgrading, or it can localize a lesion which was thought to be degenerative on planar imaging to a pedicle and/or vertebral body, with improved localization

possibly leading to upgrading. However, improved localization may also lead to downgrading; a lesion may be thought to be metastatic on planar imaging, for instance, but SPECT could localize it to a facet joint consistent with degenerative disease. Sometimes, there is suspicion of a lesion on planar imaging, which is not seen with SPECT. This leads to fewer lesions being recorded after the addition of SPECT, due to better contrast, and that, too, may lead to downgrading. Both upgrading and downgrading may make a significant alteration to patient management, but this is not necessarily true always, especially if grading is moved from one equivocal grade to another, for instance from grade 2 to 3 or vice versa. Even in this situation, the consequent increase or decrease in the level of suspicion may alter the decided approach to the problem, with follow up times being altered or extra tests being used.

SPECT has certain disadvantages, for instance the prolonged imaging time. This may also lead to patient discomfort, with the potential of motion artifacts. All these factors will lead to a lower throughput of patients per camera, which can be a problem, especially if resources are limited. These problems, however, have been partially solved by the development of multihead gamma cameras, which greatly reduce the scanning time, thereby improving patient throughput and easing department workload considerably.

SPECT is technically more demanding than planar imaging, as it requires careful quality control and accurate patient set-up. Further, reconstruction and processing of the images require specialized knowledge [Gates, 1988].

There were 576 patients with documented primary malignancies who had planar bone scans for the diagnosis of bone metastasis at our institution during the year 2000. Of these patients, 119 were examined with both planar imaging and SPECT. In accordance with our inclusion criteria, this study was limited to them. Breast and prostate cancers are among the most common tumours known to spread to the bone, and these cancers involved more than 70% of our patients. In the other 457 patients only planar bone scans were performed because it was considered that there was no need for performing SPECT, as it was believed that this would have little impact on the outcome seeing that the scans were clearly normal or of a metastatic pattern. It is widely accepted that, for clearly normal or typical metastatic disease, SPECT adds little to the planar bone scan. SPECT was needed as an adjunct for clarification of the planar bone scan for the 119 patients in our study. This study, in which we compared the use of planar imaging alone to planar imaging combined with SPECT was limited to these 119 "difficult" patients. Based on previous literature, one would expect SPECT to contribute significantly in this group [Han *et al.*, 1998; Jacobson and Fogelman, 1998].

Despite the absence of a gold standard we approached our data in different ways in order to compare the results of planar imaging alone to those obtained after the addition of SPECT. We started by comparing the overall grading of all patients by planar imaging alone and the grading after the addition of SPECT. Then we regrouped the four grades into two groups, using three different classifications. These classifications were "metastases/not metastases", "metastases excluded/not excluded" and "metastases confirmed/not confirmed".

We made these classifications in an attempt to predict the clinical implication of adding SPECT to planar imaging by looking at the effects of adding SPECT on proportions of patients in each classification. To determine the capability of planar imaging alone for predicting the same results as after the addition of SPECT, relative sensitivity, specificity, PPV, NPV and accuracy were calculated in each classification. We examined the overall number and percentage of patients that were actually affected after the addition of SPECT for each classification. We assessed how SPECT could place significantly more patients into "decisive" grades, if added to planar imaging. We investigated the impact of adding SPECT to the number of lesions detected in these patients.

When we inspected those patients whose grading was altered after the addition of SPECT, a total of 35 patients (29.4%) out of the 119 patients were involved. Twenty-four patients (20.2%) had their grading upgraded after the addition of SPECT, compared to 11 patients (9.2%) who were downgraded. This implies that SPECT may upgrade more than it downgrades. Of the 24 patients who were upgraded, 16 (66.7%) initially diagnosed as grade 2, while four (16.7%) initially were grade 1 and four (16.7%) initially were grade 3. Of the 11 downgraded patients, nine (81.8%) were initially diagnosed as grade 2, whereas only two (18.2%) were initially grade 3. This data indicates that SPECT has the greatest impact for patients with grade 2 scans on planar imaging, whether it leads to upgrading or downgrading.

Comparing the overall grading using planar imaging alone to grading after the addition of SPECT, the difference was not statistically significant (P = 0.0884).

There are many reasons for this discrepancy. First, probably most importantly, the change of grading occurred in two directions resulting in the upgrading of one patient cancelling out the downgrading of another and vice versa. Second, only 35/119 patients were affected and the situation of the majority (31/35) changed by one grade only. Lastly, the determined P value is close to significant, i.e. there was an 8% likelihood that this was due to chance.

SPECT was shown to add little to planar imaging when there is a close to normal or clearly abnormal planar scan. Our study showed that only 4 (7%) out of 57 patients who were graded as grade 1 by planar imaging alone were re-graded after the addition of SPECT. Interestingly, two of these had documented back pain while the other two did not have back pain, but had suspicious vertebral lesions without any other skeletal lesions. There were 53 (93%) out of 57 patients in whom grading was retained as grade 1 even after the addition of SPECT. Thirty-one out of 53 did have documented information on back pain. It is notable that, amongst the grade 1 patients on whom planar imaging was performed, those who were later upgraded after the addition of SPECT were no more likely to have documented back pain than those whose grading remained unchanged. The prime concern of clinicians regarding cancer patients with back pain is whether it is caused by metastasis. In a study undertaken by Schutte, (1979), it was concluded that, in the assessment of malignancies, bone pain is a good indication for bone scanning, although osteoblastic lesions do not often present with pain. Bone pain, if metastatic, is attributed to cortical and periosteal irritation and reactions as seen in lytic processes and fractures [Schutte, 1979]. In breast and prostate cancers one may expect osteoblastic metastases. Back

pain in cancer patients could be due to any cause other than metastases and breast and prostate cancer in fact represented more than 70% of our patients. Previous studies have concluded that SPECT is indicated to determine the underlying cause of back pain even if planar imaging is normal [Han *et al.*, 1998].

There was no change in the grading of seven patients who were graded as grade 4 by planar imaging alone after the addition of SPECT. This is in stark contrast to the 42 patients who were graded as grade 2 by planar imaging alone, of whom 25 (60%) were re-graded after the addition of SPECT, and to the 13 patients who were graded as grade 3 by planar imaging alone, of whom seven (46%) were re-graded after the addition of SPECT, as shown in Figure 1. Grades 2 and 3 correspond with more equivocal diagnoses, and SPECT clearly makes a much greater contribution here than for grades 1 and 4.

The ultimate goal of any investigation report is to be of help to the clinician with regard to patient management. This partly involves producing a report that is as decisive as possible. In reality the report has to be stated in terms of probabilities. Generally speaking, SPECT will be added to planar imaging to decrease the uncertainty of certain unclear cases in skeletal scintigraphy. In other words, the addition of SPECT increases the diagnostic usefulness of the study. The nuclear medicine physician will be able to classify many of these cases as more normal or more abnormal. Using percentage probabilities as thresholds for our grades, we arranged them into three different classifications, as metastases versus not metastases (greater than or less than 50%),

exclusion of disease (less than 20%) and confirmation of metastases (greater than 80%). These classifications were made in order to predict the impact of a change in grading on clinical management. To assess the impact of adding SPECT to planar grading, we looked at the change in the proportions of patients in each of these categories before and after the addition of SPECT in each classification. This method does not follow individual cases but rather looks at proportions; therefore there is a risk of significant changes not being detected if there is equal movement between the groups in both directions. This could result in statistical tests being negative despite SPECT having a significant impact. However, with this data the movement that took place was normally in both directions but not equal, resulting in all of these tests being significant.

Firstly, to assess movement across a threshold corresponding to a 50% probability of metastatic disease being present, grades 1 and 2 were classified as "metastases" and grades 3 and 4 as "not metastases". SPECT was found to have a statistically significant impact on this classification, when classifying all patients, including breast cancer patients and prostate cancer patients (P = 0.0001, 0.0078 and 0.0313 respectively). It can be argued, however, that this distinction is of limited value in the context of clinical decision-making, and will have little impact on patient management. However, it is also to be expected that a patient seen as having about 70% probability of metastatic disease will be investigated and followed up more closely than a patient with about 30% probability, even though disease has not been excluded or confirmed in either case.

Secondly, to assess a threshold corresponding to a 20% probability of metastatic disease being present, we classified grade 1 as "metastases excluded" and all other grades as "metastases not excluded". SPECT was found to make a statistically significant impact on this classification, when classifying all breast cancer patients and prostate cancer patients (P = 0.0352, 0.0156 and 0.0313 respectively). It can be argued that the effective exclusion of metastatic disease is an indicator of a clinically important difference between using planar imaging alone and using it with the addition of SPECT. If metastasis can be confidently excluded, the patient may, for example, need no treatment but only follow up. In another patient in whom metastases cannot be excluded, this may necessitate the need for further investigations and/or more frequent follow up.

Thirdly, to assess a threshold corresponding to an 80% probability of metastatic disease being present, grade 4 was classified as "metastases confirmed" and all the other grades as "metastases not confirmed". This resulted in a statistically significant difference occurring in this classification of all patients after the addition of SPECT (P = 0.0412). A report that confirms the presence of metastases is also of major clinical benefit to the physician who can then start treatment, as opposed to going on to perform further investigations and/or follow up as in the case of metastases not being confirmed.

SPECT made a statistically significant difference to all three classifications. According to our knowledge, there is no documented comparison that uses the same method of analysis as we did. Hence there are no comparable results

from the literature. Our findings, however, are consistent with the view in the literature that SPECT makes a significant contribution in a group of patients such as those that we have investigated.

As mentioned above, no gold standard was available for this data, and hence we could not work out the sensitivity, specificity, PPV, NPV and accuracy of planar imaging with and without SPECT for comparison. Instead we calculated values for planar imaging alone, relative to the performance of planar imaging with SPECT. These values must not be confused with absolute values and cannot be compared with absolute values found in the literature. These values do, however, quantify the performance of planar imaging alone with regard to the performance after the addition of SPECT for the diagnosis of bone metastases. We applied the calculations to the three different classifications described above.

For the "metastases" versus "not metastases" classification, relative to planar imaging with SPECT, planar imaging alone had a sensitivity of 53%, specificity of 98%, PPV of 90%, NPV of 84%, and an accuracy of 85%. The low sensitivity means planar imaging alone detected a high number of false negative cases. This is due to the fact that 16 patients thought to have a probability of metastatic disease of < 50% on planar imaging alone were considered to have a probability of > 50% after the addition of SPECT. It is therefore clear that planar imaging substantially underestimates the presence of metastatic disease in a significant proportion of those in whom it is regarded as being present with the aid of SPECT. These patients are therefore not likely to receive necessary

further investigations or adequate close follow up. It must be borne in mind that the patient population consisted of the 119 "difficult" cases only. This low sensitivity supports the use of SPECT amongst this group of patients. The high specificity of the planar imaging alone here means that there were very few patients classified as false positive. This is due to the fact that only two patients thought to have a probability of metastatic disease of > 50% on planar imaging alone were considered to have a probability of < 50% after the addition of SPECT. Consequently, the use of planar imaging alone would result in unnecessary investigations or excessively close follow up in a small number of cases only. The relatively good PPV, NPV and accuracy show that overall for this population of patients; planar imaging alone classified most patients similarly before and after the addition of SPECT. Its performance for patients considered to have a probability of disease of > 50% with the aid of SPECT, was however poor, with almost half of these being "undergraded" when using planar imaging alone. It can therefore be concluded that the addition of SPECT has relatively little impact in cases found to have a probability of metastatic disease of greater than 50% when using planar imaging. In cases found to have a probability of less that 50%, the need for performing SPECT is far greater.

For the classification of "metastases excluded" versus "not excluded", planar imaging alone was found, relative to planar imaging with SPECT, to have a sensitivity of 83%, specificity of 93%, accuracy of 87%, positive predictive value of 93% and negative predictive value of 82%. It is clear from this data that planar imaging alone classifies the majority of patients similarly to when SPECT is added. In particular, it is effective in predicting those regarded as "not excluded" with the aid of SPECT. This implies that planar imaging can be used

alone with a high degree of certainty for the exclusion of metastatic disease. Using this classification, planar imaging alone does relatively well (sensitivity and specificity more than 80%) to approach the result of planar imaging combined with SPECT. The relatively good PPV, NPV and accuracy show that overall, for this population of patients, planar imaging alone classified most patients similarly before and after the addition of SPECT. Therefore it could be argued that it is reasonable to not perform SPECT in cases where metastatic disease is excluded on the basis of planar imaging alone if resources are limited. In cases not found to have excluded metastases when using planar imaging, SPECT should still be performed, as it has a far greater impact for these patients.

Lastly, for the classification of patients with "metastases confirmed" versus "not confirmed" gradings, planar imaging alone was found relative to planar imaging with SPECT to have a sensitivity of 54%, specificity of 100%, PPV of 100%, NPV of 95%, and accuracy of 95%. The low sensitivity demonstrates the fact that only seven of 13 patients considered to have disease confirmed through planar imaging combined with SPECT, were detected when using planar imaging alone. It is likely that the sensitivity would have been considerably higher if the patient population had not consisted of the "difficult" 119 cases only, but rather included all 576 cases. This low sensitivity strongly supports the use of SPECT in addition to planar imaging to confirm the presence of metastasis. The high specificity in this classification was due to the fact that planar imaging did not classify any patient as a false positive. This again demonstrates that SPECT makes little contribution in cases already considered

to have confirmed disease using planar imaging alone. For many of these patients planar grading of 4 was based on the presence of metastatic lesions in the rest of the skeleton. Therefore SPECT will not make much difference to the planar classification when the scan is abnormal due to other skeletal lesions with or without vertebral lesions, and in this case planar imaging will be sufficient if used alone. However, in these patients, SPECT may still be of benefit if used to determine an underlying cause of a back pain, even if there is no lesion seen in the spine by planar imaging alone. Also SPECT may be used if there are lesions in the spine but it is unclear if they are metastatic or not and also to determine the extent of lesions for planning radiotherapy. Of the seven patients who were graded as grade 4 by planar imaging alone, four had clear metastatic lesions outside the spine and the other three had very intense vertebral lesions. Interestingly, six out the seven had documented back pain, which might explain the indication for performing SPECT. The relatively good PPV, NPV and accuracy show that overall for this population of patients, planar imaging alone classified most patients similarly before and after the addition of SPECT. Therefore cases confirmed as having metastases using planar imaging benefit little from the addition of SPECT. In cases where the presence of metastases is not confirmed, SPECT makes a contribution and should be performed if at all possible.

The overall numbers of patients affected

Despite the statistically significant difference in all the three classifications, the actual numbers of patients involved were small. There were only 18 patients out of 119 (15%) for whom the final diagnosis changed concerning the

"metastases/not metastases" classification. As one sees here, this percentage is small when seen as out of 119 and it gets even smaller (3%) if the entire number of 576 patients is considered. It was assumed that SPECT would make no contribution to planar diagnosis in cases considered as clearly normal or abnormal. This demonstrates that, although SPECT has a major impact on some, it has little impact on the majority of patients. Therefore patients should be carefully selected for SPECT scanning, rather than performing SPECT routinely on every patient.

Interestingly, when using the "metastases excluded/not excluded" classification, only 15 patients (12.6% of the 119 undergoing SPECT) were reclassified and only four of them were upgraded, which means metastases would have been incorrectly excluded in a very small number of patients only if only planar bone scanning were used. Although this may be important for the individuals concerned, this proportion becomes even smaller if we consider the entire 576 patients, where less than 3% of the total group is affected. This indicates that SPECT will not make a contribution in the vast majority of patients when the scan is used to exclude metastasis and the planar scan is close to normal. It could therefore be argued that the planar bone scan would be sufficient if used alone in these circumstances, if this results in improved utilization of limited resources.

Using the "metastases confirmed/not confirmed" classification, only 6/119 (5%) patients had their classification changed and all of them were upgraded. This percentage becomes even smaller (1%) if taken from the total 576 patients.

This again confirmed that SPECT only makes an impact on a limited population of patients, so one has to make sure that these patients are carefully selected for have SPECT rather than perform SPECT routinely on every patient.

Decisive versus Equivocal Results

In this study, 17 patients were reclassified from equivocal results with planar imaging alone (grades 2 and 3), to decisive results using planar imaging with SPECT (grades 1 and 4). In comparison, only four patients were reclassified to equivocal grades after initially being in decisive grades. In this case, a total of 21 (18%) patients had their classification altered after the addition of SPECT. Comparing the sizes of the decisive and equivocal groups before and after the addition of SPECT for the whole group of 119 patients, as well as the groups of patients with breast and prostate carcinoma, there was statistically significant difference in the performance of planar imaging alone and after the addition of SPECT (P = 0.0015, 0.0020, and 0.0313 respectively). This implies that the addition of SPECT leads to more decisive results than planar imaging alone. This is also consistent with the observation elsewhere in this study where SPECT is seen as having its main impact on patients graded as 2 or 3 after planar imaging. The main purpose for adding SPECT to planar imaging is to attempt to make more precise diagnoses in these unclear cases. If the referring doctor receives more reports with decisive diagnoses, the clinician's confidence while making decisions when managing patients is improved.

Number of lesions detected

SPECT is more sensitive than planar scintigraphy in detecting vertebral lesions. It is probably also more specific because of its improved localization of abnormalities in the vertebrae. Consequently, bone SPECT is particularly valuable in the spine when only one or a few lesions are detected by planar scintigraphy. When the number of lesions detected through using planar imaging alone and after the addition of SPECT was compared, the difference was statistically significant (P = 0.007). In our study, planar bone scanning detected 137 lesions in the spine compared to 170 lesions detected after the addition of SPECT. The overall number was therefore 19% lower with planar imaging alone. This is consistent with a result reported by Gates, (1988) which reported 17% of lesions detected by SPECT only, and also with a study undertaken by Han *et al.*, (1998) who reported that 20.1% of the lesions were not seen on planar imaging.

Interestingly, the number of recorded lesions decreased in some patients after the addition of SPECT. Therefore not all the lesions seen with planar imaging were not seen with SPECT. A possible reason for the decrease in the number of lesions after the addition of SPECT may be that under- or overlying activity is actually interpreted as spinal lesions when using planar imaging. The advantage of the better localization with SPECT makes it possible to determine the exact location of the activity with greater ease. However, lateral and oblique planar views may to some extent also be able to differentiate between spinal lesions and other activity. Subtle "lesions" that are suspected with planar imaging may also not be found using SPECT.

To some extent the greater the number of spinal lesions the more confident the physician is that these are due to metastases. This therefore has importance clinically. The detection of extra lesions also has clinical implications in terms of patient management using radiotherapy, for example, in which radiation fields may need to be adjusted following the detection of additional or fewer lesions as a result of the addition of SPECT.

Our study contains a number of shortcomings. Firstly, and most importantly, the retrospective nature of our study prevented us from working to a gold standard. To measure the impact of SPECT in diagnosing bony metastases one ideally has to have an absolute gold standard such as histo-pathological analysis of tissue samples removed at surgery, biopsy, or autopsy. But this not possible for the daily clinical practice. Instead, one can use a combination of other imaging modalities such as X-rays, CT, MRI, FDG-PET imaging, a follow-up bone scan and clinical follow-up of the patient. This information was not available for our study. This made comparison with the results of previous studies from the literature impossible. Figures of sensitivity, specificity, accuracy, positive and negative predictive values were calculated for planar imaging relative to the results of planar imaging and SPECT. If a gold standard had been available, it would have been possible to calculate the true sensitivities and specificities for SPECT and planar imaging alone. Receiver Operating Characteristic curves would then enable comparison between planar imaging alone and planar imaging with SPECT, and allow the statistical significance of the difference between them to be calculated.

Secondly, the system used for grading the studies into four grades was not based on clear criteria, but rather on the experience of the physicians concerned, which may have affected the reproducibility of these results in other hands. This, however, reflects the situation in routine clinical work. It does take into account the fact that reports are not just positive, or negative, but also have results that reflect an intermediate probability of disease. An attempt was made to reflect this using a four-point scale.

Thirdly, retrospective documentation of back pain based on referral forms was probably unreliable and this should therefore be used with caution in further analysis. The images were however re-examined prospectively by the same physicians, which should enhance the consistency of their interpretation.

Conclusions

1. In this group of patients, the performance of SPECT was shown to be significantly different to planar imaging alone in all classifications. Although there were no comparable results or figures from the literature, this was consistent with the view expressed in the literature, namely that SPECT usually makes a significant contribution in a group of patients such as those included in this study. Despite the statistically significant difference, the actual number of patients involved was small, which demonstrates that although SPECT can have a major impact on some patients, this is not the case for the majority. This implies that the patients who will undergo SPECT have to be selected as carefully as possible, rather than performing SPECT routinely on all patients. In the vast majority of cancer patients planar imaging alone performs similarly to cases for which SPECT is performed for the diagnosis of bony metastases. This is encouraging, especially as limited resources make SPECT unavailable in most African countries.

2. This study also showed that the performance of planar imaging alone for the exclusion of metastases approached that of SPECT and hence planar imaging can be used alone with a high degree of certainty (relative sensitivity, specificity, PPV, NPV and accuracy all over 80%). For the confirmation of metastases, however, planar imaging showed relatively poor sensitivity. When planar imaging shows a metastatic pattern due to other skeletal lesions with or without vertebral lesions, SPECT makes little difference to the planar classification, however,

SPECT can still be beneficial if used to determine the underlying cause of a back pain or for radiotherapy planning.

3. Statistically it has been shown that the addition of SPECT resulted in a tendency for interpretation to be more decisive because of clearer anatomical localization of lesions. This is very important clinically for the physicians to manage a patient with more certainty of the diagnosis.

4. After the addition of SPECT, more lesions were detected than those detected by planar imaging alone and this was statistically significant. This is clinically relevant because more lesions imply a higher possibility of malignancy. This increases the certainty and confidence of the nuclear medicine physician in reporting the scans. It may also have an impact on individual patient management.

Recommendations

1. This study provides evidence to support the use of SPECT as adjunct to planar bone scan imaging for the detection of bone metastases, under circumstances where SPECT is available.

2. This study should be followed up by a prospective study using a reliable gold standard based on bone biopsy, radiological imaging and adequate clinical follow-up to better evaluate those cases that resulted in a discrepancy between the interpretation of planar imaging alone and planar imaging with SPECT.

3. An important point to note is that planar imaging is still clinically useful and that SPECT provides no additional information in a large percentage of cases. Planar imaging can continue to be used on its own with a great deal of confidence in countries where no SPECT facilities are present, as in most African countries.

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