THE ADDED VALUE OF SPECT/CT IN THE EVALUATION OF EQUIVOCAL SKELETAL LESIONS IN PATIENTS WITH KNOWN MALIGNANT DISEASE

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DECLARATION

I, XOLANI NDLOVU 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

Introduction: Bone scintigraphy is used extensively in evaluating metastatic disease. There are currently no clear recommendations for the use of SPECT/CT in metastatic bone disease. Existing procedural guidelines from the Society of Nuclear Medicine (SNM) for SPECT/CT do not provide specific indications for use of SPECT/CT in bone scintigraphy, and there are currently no other guidelines for the use of SPECT/CT in bone scintigraphy that the author is aware of. The aim of this study was to investigate the additional value of SPECT/CT, and to identify the clinical indications for which SPECT/CT is most useful in patients with suspected bone metastases.

Subjects and Methods: Forty-two patients with equivocal lesions on planar scintigraphy were prospectively recruited and planar imaging, SPECT, and SPECT/CT done on all patients. On reading of SPECT and then SPECT/CT, patients and individual lesions were classified as malignant, benign or equivocal. Radiological studies and available clinical information were also used during reading of scans. Review of clinical information, radiological studies and/or follow-up bone scans were used as gold standard. The results of the SPECT and SPECT/CT were compared in terms of proportion of equivocal findings and accuracy.

Results: Forty-two patients with 189 skeletal lesions were examined. There was a diverse variety of primary tumours, although the majority had breast (n=22) or prostate cancer (n=8). Overall, SPECT/CT resulted in a significant reduction in the proportion of equivocal findings on both a patient-wise ($p=0.0015$) and lesion-wise basis ($p<0.0001$). The overall accuracy of SPECT/CT was significantly higher than that of SPECT on both a patient-wise ($p=0.0026$) and lesion-wise basis ($p<0.0001$). Generally SPECT/CT decreased the proportion of equivocal findings and increased the accuracy independent of the presence of bone pain, type of primary tumour, or skeletal region involved. SPECT/CT did not significantly improve the diagnostic confidence of readers in equivocal lumbar lesions although accuracy was significantly improved in this region.

Conclusion: SPECT/CT performs significantly better than SPECT alone for the interpretation of equivocal planar lesions. There is no evidence that the benefit of SPECT/CT is dependent on the type of primary tumour or the presence of bone pain. Where resources are limited, SPECT/CT is indicated only in those patients in whom correct classification of the lesions in question is expected to alter the patient's management. SPECT/CT images should be interpreted with the aid of a diagnostic radiologist or nuclear medicine physicians should acquire sufficient experience in Computed Tomographic image interpretation in order to optimise diagnostic benefit from SPECT/CT.

OPSOMMING

Inleiding: Beenflikkergrafie word wyd vir die evaluering van metastatiese siekte gebruik. Daar bestaan tans geen duidelike aanbevelings vir die gebruik van Enkelfotonemissie rekenaartomografie gekombineer met rekenaartomografie (EFERT/RT, Engels SPECT/CT) in metastatiese beensiekte nie. Bestaande riglyne van die Amerikaanse *Society of Nuclear Medicine* (SNM) vir EFERT/RT gee nie spesifieke indikasies vir die gebruik van EFERT/RT in beenflikkergrafie nie, en daar is tans geen ander riglyne waarvan die outeur bewus is nie. Die doel van hierdie studie was om die bykomende waarde van EFERT/RT te ondersoek, en om dié kliniese indikasies waar EFERT/RT in pasiënte met vermoedelike beenmetastases mees nuttig sal wees, te identifiseer.

Pasiënte en Metodes: Twee en veertig pasiënte met twyfelagtige letsels op planare skeletflikkergrafie is prospektief geselekteer en planare beelding, EFERT en EFERT/RT is op alle pasiënte gedoen. Tydens beoordeling van EFERT en daarna EFERT/RT beelde is pasiënte en individuele letsels as maligne, benigne of twyfelagtig geklassifiseer. Radiologiese studies en beskikbare kliniese inligting is ook tydens interpretasie van flikkergramme gebruik. Kliniese inligting, radiologiese studies en/of opvolg beenflikkergramme is as goue standaard gebruik. Die resultate van EFERT en EFERT/RT is ten opsigte van die aantal twyfelagtige bevindings en akkuraatheid vergelyk.

Resultate: Twee en veertig pasiënte met 189 skeletale letsels is ondersoek. Daar was ‘n verskeidenheid van primêre tumore, maar die meerderheid van pasiënte het bors-

(n=22) of prostaatkanker (n=8) gehad. Die gebruik van EFERT/RT het gelei tot ‘n betekenisvolle afname in die aantal twyfelagtige bevindings, beide op ‘n pasiënt- en ‘n letselbasis ($p=0.0015$ en $p<0.0001$ onderskeidelik). Die algehele akkuraatheid van EFERT/RT was betekenisvol hoër as die van EFERT alleen, beide op pasiënt- en op letselbasis ($p=0.0026$ en $p<0.0001$ onderskeidelik). Oor die algemeen het EFERT/RT die aantal twyfelagtige letsels verminder en die akkuraatheid verhoog, ongeag die teenwoordigheid van beenpyn, die tipe primêre tumor of die area van die skelet wat betrokke was. In twyfelagtige lumbale letsels het EFERT/RT nie die diagnostiese vertroue van beoordelaars van flikkergramme verhoog nie, alhoewel die akkuraatheid vir hierdie gebied wel betekenisvol toegeneem het.

Gevolgtrekking: EFERT/RT vaar betekenisvol beter as EFERT in die beoordeling van twyfelagtige letsels op planare beenflikkergramme. Daar is geen bewys dat die voordeel van EFERT/RT afhanklik is van die tipe primêre tumor of die teenwoordigheid van beenpyn nie. Waar hulpbronne beperk is, is EFERT/RT slegs aangedui in dié pasiënte waar verwag word dat korrekte klassifikasie van die betrokke letsel behandeling sal beïnvloed. EFERT/RT beelde behoort met die hulp van ‘n diagnostiese radioloog beoordeel te word, of kerngeneeskundiges moet genoegsame ondervinding in die interpretasie van rekenaartomografiebeelde hê om die diagnostiese voordeel van EFERT/RT optimaal te kan benut.

DEDICATION

THIS BOOK IS DEDICATED TO THE ALMIGHTY GOD THROUGH WHOM ALL THINGS ARE POSSIBLE, MY LOVING WIFE AND SON, AND TO MY UNCLE WHO HAS SUPPORTED ME THROUGH HARD TIMES.

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CHAPTER 1

INTRODUCTION

Bone scintigraphy is one of the most commonly performed nuclear medicine procedures in most nuclear medicine departments, with an average of 24 bone scans performed per week at Tygerberg Hospital. Indications for bone scans include the detection of skeletal metastatic deposits, and the evaluation of other bone and joint diseases. Data obtained from a recent study at Tygerberg Hospital showed that 75% of patients undergoing a bone scan were investigated for metastasis, and of these, 51% of patients had breast cancer.[1] Fifty eight percent of patients were positive for skeletal involvement, while the results of bone scans in 11% of patients investigated for skeletal metastasis were equivocal with no definitive diagnosis.

The skeleton is the third most common localisation site of malignant tumours after the lungs and liver, with solid tumours exhibiting a relatively high rate of metastasis in the skeletal system depending on the primary tumour.[2] Bone metastases are the most common bone tumour, occurring in 30-70% of all cancer patients, with breast cancer being the leading cause in women and prostate cancer in men, followed by lung cancer.[3] About 75% of patients with malignancy and pain have been shown to have abnormal bone scan findings, and 25-45% of asymptomatic patients with malignancy were shown to have scintigraphic evidence of bone metastasis.[4]

With metastases constituting the major cause of treatment failure in cancer patients, the early detection of bone and bone marrow metastases is important as it allows for a rapid initiation of appropriate therapy and a reduction in morbidity. The initial localisation of metastases in the bone of patients with solid tumours has a relatively good prognosis in comparison with visceral metastasisation.[5] Visceral metastases are more likely to be fatal, with long-term survival falling from 90 to around 5%.[6] In contrast, patients with only metastases to bone can survive up to 10 years or more.[7,8,9,10]

Bone scintigraphy has been shown to be very sensitive in detecting skeletal metastatic lesions.[11] Its main purpose is to identify bone metastases as early as possible, to determine the full extent of the disease, to predict complications of malignant bone involvement (pathologic fractures, spinal cord compression etc), to monitor response to therapy, and sometimes to guide biopsies.[12]

More than 90% of metastatic bone lesions occur in the axial skeleton and the spine is the most common site of skeletal metastases (39%).[13-14] Therefore, the optimal interpretation of skeletal lesions is particularly important in this region of the skeleton. With a large proportion of skeletal metastasis being found in the vertebral column, it is very important that benign lesions be distinguished from those that are malignant. Bone metastases indicate a poorer prognosis, and patient management plans depend on whether or not skeletal metastases are present. They may also lead to various complications, including fractures, hypercalcaemia, and bone pain, and a reduced

performance status and quality of life.[15] Isolated lesions in the rest of the skeleton are often also equivocal with metastasis being difficult to distinguish from other causes of osteoblastic activity such as trauma, arthritis etc.

There is growing evidence that the fusion of images between separate modalities can be of considerable help in guiding patient care in many circumstances.[16] Computed Tomography (CT) is commonly used in side-by-side visual comparison with SPECT slices. In the 1980s images were fused with software that used external or internal markers identifiable on both anatomical (CT) and functional (SPECT) studies.[17] Success of this co-registration method was seen mainly with studies of the brain because of its rigid structure. Corresponding techniques for other regions of the body did not achieve the same widespread clinical use. Image co-registration in the chest or abdomen is more difficult because most alignment algorithms rely on the presence of mutual information between the two sets of images and in the abdomen the functional image may contain little correlative anatomical information. A confounding issue is the fact that the SPECT and CT data is usually acquired on different days, on different systems, and using unrelated protocols by different operators. The chest and abdomen are not rigid structures and differences in patient positioning, movement of internal organs, and respiratory motion make it difficult to align anatomical and functional images obtained during separate acquisition sessions.

In recent years the integration of anatomical imaging techniques and SPECT has undergone significant growth. The first commercial SPECT/CT system was the GE

Hawkeye™ (GE Health Care, Haifa Israel) which was developed in 1999.[18] This system integrates a variable-angle gamma camera with a low-dose single-slice CT scanner within the same gantry. The CT component in this system is used mainly for attenuation correction and localisation, rather than diagnostic radiology. Its design offers advantages over side-by-side visual analysis and software co-registration as this equipment enables the patient to be imaged on the same bed, in the same position with a minimal delay between SPECT and CT image acquisition.

SPECT/CT hybrid scanners have been reported to show improved diagnostic accuracy over SPECT alone in conditions such as lymphoma,[19] infection,[20] bone disease,[21] neuroendocrine tumours,[22-23] parathyroid adenomas,[24-25] thyroid cancer,[26-27] adrenal tumours,[28] cavernous haemangiomas,[29-30] and lymphoscintigraphy,[31-32] Its use in the evaluation of possible skeletal metastases is still evolving. It is clear that fused images are not required for all imaging studies, hence in order to optimise the utilisation of this new technology, there is a need to identify the clinical indications for which image fusion is most useful in influencing patient care and outcome.[16] There are currently no clear recommendations for the use of SPECT/CT for these patients. Existing procedure guidelines from the Society for Nuclear Medicine (SNM) for SPECT/CT do not provide specific indications for use of SPECT/CT in bone scintigraphy. There are currently no other guidelines for the use of SPECT/CT in bone scintigraphy that the author is aware of.

CHAPTER 2

LITERATURE REVIEW

PATHOPHYSIOLOGY OF SKELETAL METASTASES

A metastatic deposit can be defined as a growth of malignant cells separate from the primary tumour which arises from detached fragments of the primary tumour. The histological features of the metastatic cells are similar to those of the primary tumour.

The development of skeletal metastases involves two main stages[33]: (1) penetration of cells from the primary tumour into the blood vessels or lymphatic system, release of tumour emboli into the circulation, arrest of emboli in small vascular channels, and infiltration into the adjacent tissue; and (2) growth into a metastatic tumour. Metastatic cell deposits are in turn susceptible to spread, resulting in further metastases.

The dissemination, growth and survival of malignant cells are determined by both host and tumour tissue factors.[34] Pathways for the spread of tumour cells include haematogenous, lymphatic, direct infiltration and cerebrospinal fluid. Invasiveness is a fundamental and distinguishing characteristic of malignant tumour cells, enabling them to penetrate into lymphatics, blood vessels, and surrounding tissues.[33] Vascular penetration plays a more important role than lymphatic infiltration in the development of

skeletal metastases. Prostate, kidney, breast, lung and thyroid cancers account for 80% of skeletal metastases and about 20-50% of solitary spinal lesions are due to metastatic spread.[3,35] A large proportion (about 90%) of metastatic deposits in bone are located in regions containing red marrow due to the higher vascularity of red marrow compared to yellow marrow or bone cortex,[11] and due to the fact that the majority of tumours metastasising to bone spread by the haematogenous route. Consequently, metastases do not affect all the bones with the same pattern and frequency, but generally prefer the spine and pelvis. Evidence of venous connection between the peri-prostatic and lumbar plexuses was first described by Batson *et al* in 1940.[36] The authors evidenced the existence of a network of longitudinal, valveless vessels, running parallel to the vertebral column and forming countless anastomoses to the sinusoidal structure of the vertebral marrow. As metastases enlarge within marrow, surrounding bone undergoes osteoclastic and osteoblastic reactive changes. Skeletal metastases usually begin in the medulla of bone and ultimately lead to cortical damage.[37]

There is a limited fashion in which bone can react to the presence of metastatic deposits. There can be either bone resorption (lytic bone metastases), or bone formation (sclerotic/blastic metastases); however, the most common pattern of bone response is a mixture of formation and resorption. A lytic or blastic response may predominate in any given patient.[38] Thyroid and renal carcinomas frequently produce lytic lesions, and prostatic carcinoma is typically associated with blastic metastases. Lung and breast cancer often produce mixed lytic and blastic deposits.

Based on the balance between the osteoclastic (lytic) and osteoblastic (sclerotic) processes, the radiographic appearance of bone metastases may be lytic, sclerotic or mixed. The difference, however, in the basic pathologic processes is minor.[39] This is because a simultaneous process of bone formation and destruction occurs in the majority of metastases. Where bone formation predominates, the lesion appears sclerotic, and where bone destruction predominates the lesion appears lytic. Mixed lesions demonstrate a combination of both bone formation and bone destruction.

New bone formation in a metastatic lesion appears to occur by two main mechanisms, namely stromal and reactive bone formation, both mediated by osteoblasts.[40] Stromal bone formation consists of the development of intramembranous ossification within fibrous stroma that develops around the tumour. Reactive bone formation occurs as a response to bone destruction and plays a more important role than stromal bone formation in bone metastases. The new bone may be similar to the callus that develops in fracture healing and is laid down in response to stress on the weakened bone. Reactive bone formation is seen in most metastases with the exception of highly anaplastic rapidly growing tumours, myeloma, lymphoma, and leukaemia, in which reactive bone formation is rare. Sclerosis may also be a sign of repair after treatment of bone malignancy.

At least two main mechanisms are attributed to bone destruction (osteolysis) that occurs in skeletal metastases, the more important being osteoclast-mediated destruction.[28] Osteoclast proliferation occurs in most skeletal metastases in the vicinity of the tumour

and is believed to be mediated by osteoclast stimulating factors secreted by the tumour. The tumour continues to grow and destroy bone until a late stage when multinucleate osteoclasts disappear and there is no new bone formation. At this stage the tumour cells are directly responsible for the bone destruction possibly due to their secretion of lytic enzymes. Non-malignant macrophages are also believed to play a role.

INVESTIGATIONS FOR SKELETAL METASTASES

A patient with a malignant bone tumour, whether primary or metastatic, may seek treatment for various reasons which include pain in the lesion, pathological fracture, or an incidental finding on imaging. Back pain occurs frequently and is the most common symptom to bring a patient to an orthopaedic clinic as the spine is the most common site of metastatic involvement.[41] It is important to differentiate pain secondary to malignant disease from that due to a benign cause. Many patients with bone metastases are asymptomatic and metastases are detected incidentally on routine screening or when a cause for rising tumour marker is looked for. For patients with known or presumed skeletal metastases, the clinical circumstances will determine the manner in which various imaging modalities will be used.[42,43,44]

There are various imaging modalities available for the investigation of skeletal metastases which include conventional radiography, bone scintigraphy, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET). According to the American college of Radiology, the first line of

imaging should be radiography as it is relatively inexpensive and the differential diagnoses of most primary tumours can be made based on radiographic features.[45] This is probably true if there is bone pain and in cases of primary bone tumours. In the case of whole body staging for asymptomatic cases, bone scintigraphy is the logical first line imaging modality as it is more sensitive and subjects the patient to less radiation. Non-imaging investigations include biopsy (which may be done under image guidance) and biochemistry. Each modality of investigating bone metastases has its inherent advantages and limitations.

SKELETAL SCINTIGRAPHY

INDICATIONS

Technetium-99m Methylene Diphosphonate (^{99m}Tc-MDP) skeletal scintigraphy remains the most common method for the whole body assessment of bone metastases.[38] It is the initial staging modality in cancer patients who are at high risk for skeletal metastases. Referral for bone scintigraphy may also be made in order to evaluate the response of known bone metastases to therapy, for routine follow-up to monitor progress of disease, or to determine the cause of bone pain. It provides a sensitive, cost-effective, rapid means of identifying skeletal metastases.

Schirrmeister and co-workers published data indicating that 14% to 22% of patients with non-small-cell lung carcinoma would have undergone futile thoracotomy or neoadjuvant chemotherapy if asymptomatic patients were denied a bone scan.[46] ^{18}F-PET-CT has been shown to have significant impact in this regard as its sensitivity is greater than that of bone scintigraphy in the diagnosis of bone metastases from lung cancer.[83] The cost-effectiveness of bone scintigraphy was also described in a cohort of patients with varying types of primary tumours being investigated for skeletal metastases.[47]

RADIOPHARMACEUTICALS

The radiopharmaceuticals commonly used for bone scintigraphy are the ^{99m}Tc-labelled Diphosphonate compounds, Hydroxy-methylene Diphosphonate (HDP or HMDP), and Methylene Diphosphonate (MDP) with the general consensus being that they exhibit similar behaviour in vivo.[48] Other radiopharmaceuticals such as ^{99m}Tc-labelled pyrophosphate have been used for bone scintigraphy but have largely been replaced by the Diphosphonates which are more stable in vivo. This stability is explained by the fact that the P-O-P bond in phosphates is easily broken down by phosphatase enzymes whereas the P-C-P bond of diphosphonates is not.[49]

The factors that influence the uptake of diphosphonates by bone are the regional bone blood flow, the rate of bone formation governed by osteoblastic activity, and the

extraction efficiency. The higher the rate of blood flow and bone formation, the greater the uptake of tracer by bone. There are two hypotheses on the bone uptake mechanism of phosphonate compounds, namely hydroxyapatite uptake and collagen uptake.[48] It has been suggested that in the hydroxyapatite uptake theory that hydroxyapatite crystal removes the phosphonate component from ^{99m}Tc-phosphonate complexes, setting free reduced technetium-99m to bind independently to hydroxyapatite at another binding site. Hydroxyapatite constitutes the inorganic matrix of bone and is primarily composed of calcium phosphate, and to some extent calcium carbonate and calcium hydroxide. The collagen uptake theory suggests that ^{99m}Tc-phosphonate complexes localise in both inorganic and organic matrices of bone, the latter uptake depending on the amount of immature collagen present.[48]

After intravenous injection, about 50% of the activity accumulates in bone. Maximum bone activity is reached at one hour after injection and remains constant for up to 72 hours.[50] About 3% of injected activity remains in the blood stream three hours after injection. More than 30% of unbound ^{99m}Tc-MDP is cleared by glomerular filtration in one hour in patients with normal renal function, with about 60% being cleared in six hours.

Metastatic deposits which exhibit an osteoblastic response will be visualised as an area of high count density or a “hot spot” on the bone scan, while those with a purely osteolytic reaction may not be detectable unless they are large enough to be seen as areas of reduced count density or a “cold spot”. Some tumours are so highly aggressive

that they do not allow an osteoblastic response to take place, leading to such a scintigraphic appearance.[42]

SCINTIGRAPHIC IMAGE INTERPRETATION

Despite its high sensitivity for detecting skeletal metastases, skeletal scintigraphy has low specificity and should not be interpreted in isolation. Rather, scintigraphic images should be read together with the clinical history and any available radiological modalities that may have been carried out in order to reduce the incidence of false-positives.[37] After an abnormality has been detected by a bone scan, selected radiographs should be performed to permit evaluation of scan-positive areas and should be interpreted in conjunction with the scan.[51] Detection of a solitary or few bone lesions on bone scan often indicates the need for further assessment of the lesions, most common correlation being with plain radiographs or Computed Tomography (CT).[52,53] In some cases, however, disseminated metastases often show a pattern that is typical of skeletal metastatic disease and hence specific. Proliferative changes in the axial skeleton in association with spondylosis or osteoarthritis and articular erosions from inflammatory arthritis may produce confusing patterns on scintigraphy. Thus, when correlative radiographs are not already available, they should be performed for those areas that have equivocal or suspicious scintigraphic findings.[54] In most cases, however, degenerative disease can be identified on SPECT and even planar scintigraphy in other joints e.g. knees, ankles, shoulders.

Bone scintigraphy may be done in the form of planar images in which anterior and posterior views are acquired with the gamma camera. Abnormal areas on the skeleton may be seen as areas of either increased or decreased tracer uptake. It is important, however, to note that there are normal areas within the skeleton which may show relatively high tracer uptake. These include the base of the skull, the costochondral junctions, external occipital protuberances, paranasal sinuses, inferior tips of the scapulae, spinous processes of vertebrae, sternum, sternoclavicular joints, sternomanubrial joints, sacroiliac joints and unfused epiphyses in growing children and adolescents.[42] Some non-osseous structures may also be visualised on the bone scan such as the genitourinary system (due to excretion of radiopharmaceutical), trauma and inflammation, and the injection site. Soft tissue calcifications may also be seen on a bone scan.

There are various scintigraphic features that suggest that skeletal abnormalities are possibly metastatic. These include asymmetry, multiple random distribution, extreme variation in intensity, and occurrence of the abnormality being primarily in the skeleton.[55] If metastases are widespread and diffuse, they may produce what is described as a “super scan”, in which there is high skeletal uptake of tracer with absent or very minimal renal excretion or uptake.[46]

In the interpretation of planar scintigrams, it is important to know the pathophysiology and specific characteristics of the primary tumour in order to determine the significance of any scan abnormalities as accurately as possible. The scan findings must be

correlated with the patient's clinical history, physical examination findings, previous scan results, and the results of other imaging modalities that may have been performed.

When it is not possible to differentiate between benign and malignant lesions on planar scintigraphy alone, single photon emission computed tomography (SPECT) may be performed in order to improve the diagnostic accuracy for detecting malignant bone involvement. This is especially applicable to lesions in the spine where the complex structure of the vertebrae makes it difficult to localise an abnormality accurately. SPECT also allows for a direct comparison with other tomographic-based imaging techniques such as Computed Tomography and Magnetic Resonance Imaging. Other indications for performing SPECT include back pain in a patient with known malignancy, and suspicious findings on other imaging studies, despite a normal planar bone scan.

The overall sensitivity of bone SPECT (Single Photon Emission Computed Tomography) is between 87% and 92% with a specificity of nearly 91%.[3] It has been found to be superior to planar scintigraphy in the detection and localisation of lesions in the axial skeleton.[56] SPECT detects 20%-50% more lesions in the spine than planar scintigraphy.[57] The pattern of uptake in the vertebrae allows malignant disease to be distinguished from more benign pathology with SPECT imaging. It has been demonstrated that increased uptake in the body of the vertebrae on SPECT imaging has a positive predictive value of 83-95% for malignancy.[58,59] Uptake in the anterolateral and posterolateral aspects of the vertebrae (including facet joints) sparing the substance of the vertebral body was shown generally to be due to benign disease.

Some lesions, however, will remain indistinguishable on SPECT and may require further workup in order to elucidate their significance.

Bone scintigraphy is commonly used as a means of follow-up in patients receiving therapy for previously diagnosed bone metastases. Post-therapy, healing may be indicated by a decrease in the intensity of tracer uptake or disappearance of lesions that had been detected on a baseline study. Bone repair is commonly associated with transiently increased osteoblastic activity, and a bone scan may not be able to accurately differentiate between ongoing disease and the "flare phenomenon".[60,61] In addition, lytic lesions previously overlooked pre-therapy may later present as "new" sites of increased uptake and may be misinterpreted as indicating disease progression. Flare phenomenon usually occurs during the first 3 months after initiation of therapy with a gradual decrease in intensity of uptake after 6 months.

STRENGTHS AND LIMITATIONS OF SKELETAL SCINTIGRAPHY

Skeletal scintigraphy is highly sensitive for the detection of most bone metastases with the ability to image the whole body at relatively low cost and low radiation dose.[62] It may be used as a tool to guide biopsy for tissue diagnosis.[12] Skeletal scintigraphy is able to demonstrate bone metastases several months before they are radiographically

identifiable, with a 5%-10% change in ratio of lesion to normal bone required to detect an abnormality.[63,64]

The major advantages of skeletal scintigraphy can be summarised as: (1) high sensitivity for the detection of skeletal metastases; (2) whole body imaging capability; (3) relatively low cost; (4) ease of performance on almost any patient; (5) absence of significant toxicity or side effects; (6) relatively low total body radiation dose; (7) value as a guide for monitoring response to therapy, including palliative radionuclide therapy.[11]

The disadvantages include low specificity and anatomical imprecision. Bone scintigrams may be negative in patients without cortical bone involvement, despite trabecular bone involvement.[13] Small purely osteolytic lesions may also be missed on bone scans.

SPECT-CT

A SPECT/CT hybrid system acquires SPECT (Single Photon Emission Computed Tomography) images and CT images in one session in order to minimise misregistration.

Some work has been done with the aim of evaluating the use of this hybrid system in bone disease. Römer and co-workers were able to clarify more than 90% of lesions previously classified as indeterminate on SPECT in a study using a SPECT/CT system

with a dual-head gamma camera and a dual-slice spiral CT component mounted within the same gantry.[65] Improved localisation of skeletal lesions has been found to be especially useful in the spine, with better differentiation of vertebral abnormalities and better definition of the exact vertebra, or part of the vertebra affected.[66] In addition, final scan interpretation is significantly altered in 23% of patients after SPECT/CT with impact being less in the appendicular skeleton. The impact also seems to be greater for patients being investigated for infection than for skeletal metastases, probably due to better demarcation between soft tissue and bone involvement.

Utsunomiya and co-workers retrospectively studied the additional diagnostic value of fused SPECT and CT images in assessing possible skeletal metastases using separately acquired SPECT and CT images.[67] They concluded that there was increased diagnostic confidence obtained with fused SPECT/CT images compared with separate sets of scintigraphic and CT images in differentiating malignant from benign lesions. The system used in this study was designed by the investigators and consisted of a dual-head, gantry-free gamma camera with a multi-detector row (diagnostic) CT system. Software co-registration algorithms were used for image fusion, using internal anatomical structures common to both modalities as reference points. The systems using diagnostic CT provide superior image resolution and allow separate assessment of bony structures. This however is at the cost of high radiation dose to the patient, with the radiation dose to a patient having a chest CT estimated at about 8mSv. [68] Potential for image misregistration arose in this study as fusion was done manually with successful co-registration confirmed by consensus of two radiologists.

SPECT/CT with a Millennium VG® Hawkeye™ system (GE Healthcare) has been shown to be a feasible technique yielding co-registered dual-modality images, allowing more precise interpretation of scintigraphic studies in various clinical situations.[69] This same system has been evaluated in a study by Horger and co-workers to assess whether it could improve the differentiation between benign and malignant skeletal lesions.[21] They concluded that combining SPECT and CT improved the diagnostic accuracy of bone scintigraphy significantly by identifying benign bone abnormalities. Eighty one percent of lesions that had initially been classified as indeterminate on SPECT were correctly diagnosed on SPECT/CT. The sensitivity of SPECT/CT for skeletal metastases in this study was not significantly higher than that of SPECT (98% vs. 94% p=0.63), whereas the specificity of SPECT/CT was significantly higher (81% vs. 19% p=0.001). It would have been interesting if the data in this study had also been analysed on a patient-wise basis, in addition to the lesion-wise basis, so as to get an overall picture of how SPECT/CT influenced each patient's diagnosis and probable subsequent management. This system is more widely available and the patient is subjected to a lower radiation dose as the CT component is single slice, with the trade-off being lower image spatial resolution and increased noise.

CONVENTIONAL RADIOGRAPHY

This modality has been the first line of investigation for metastatic disease for many years. It is still used for assessing clinically symptomatic areas and for areas identified as abnormal on bone scintigraphy. In this situation radiography assists in differentiating between a benign or malignant cause of symptoms or scintigraphic findings. X-rays are appropriate for imaging abnormalities of cortical and trabecular bone by detecting lytic, sclerotic and mixed-type lesions. Conventional radiography is useful in assessing the integrity of cortical bone and is able to depict early pathological fractures.[70] Its advantage is that it is relatively affordable and readily accessible compared to other imaging modalities such as scintigraphy, Computed Tomography, and Magnetic Resonance Imaging.

Conventional radiography, however, suffers from low sensitivity as there should be 30-50% bone demineralisation in a lesion for it to be detected.[45] Moreover, its use for an overall metastatic bone survey to identify foci of skeletal metastases has not been found to be cost-effective and is relatively insensitive for the detection of asymptomatic metastatic disease.[38] Serial surveys are still being used for the assessment of progression of metastatic disease, although a survey limited to previously demonstrated areas of disease is probably more cost-effective.

COMPUTED TOMOGRAPHY (CT)

CT is commonly used for further assessment of equivocal lesions suggested by bone scan and has an important role in identifying complications that may accompany malignant bone involvement. It has the advantage of providing information about metastatic deposits such as soft tissue extension, intraspinal spread of vertebral metastases, spinal canal compromise, and risk of pathological fracture. It is widely used for the investigation of malignancy due to its good anatomic resolution, soft tissue contrast, and detailed morphology. Both cortical and trabecular bone components can be well defined and the sensitivity of CT for detecting bone metastases ranges between 71% and 100%.[52] The sensitivity of CT is superior to that of conventional radiography for the depiction of cortical bone involvement with a contrast resolution approximately ten times that of conventional radiography.[42] CT is able to detect skeletal metastases before they are apparent on conventional radiography. Because it is able to provide good cross-sectional anatomic images, use of CT is beneficial when examining complex structures such as vertebrae.

However, because considerable cortical destruction is required for visualisation of a metastasis by CT, the sensitivity in detecting early malignant bone involvement is still relatively low.[71] Cortical destruction may be more difficult to determine in the presence of severe osteoporotic or degenerative changes.[72] CT is not commonly used as a routine imaging modality for the survey of metastatic bone involvement, but is usually used for further assessment of equivocal lesions suggested by bone scintigraphy. The

sensitivity for assessment of malignant bone marrow infiltration is limited. Computed Tomography is also relatively expensive compared to conventional radiography and scintigraphy and delivers a high radiation dose to the patient. The effective dose equivalent to a patient undergoing conventional chest radiography is between 0.02-0.05mSv while that to a patient undergoing chest CT is about 8mSv, up to four hundred times the dose from chest x-ray.[68] The effective dose equivalent for a patient receiving ^{99m}Tc-Methylene Diphosphonate (MDP) is 0.006mSv/MBq (4.4mSv for an adult dose of 740MBq).[73] It is also because of the magnitude of the radiation dose that a whole body skeletal survey for metastases is not normally done.

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) has been shown to be superior to skeletal scintigraphy for in the evaluation of metastatic disease of bone marrow.[44,74] The possible explanation for this is that haematogenously seeded intramedullary metastases produce detectable lesions by bone marrow replacement before intrinsic or reactive metabolic changes in cancellous and cortical bone can be detectable scintigraphically or radiographically.[75] It has been found to have a sensitivity of up to 100% for the detection of bone marrow metastases.[76] MRI is particularly useful for depicting spinal and pelvic metastases as well as providing additional information on extension of the tumour outside of the bony margins and evaluating the integrity of the spinal canal.

MRI is, however, relatively expensive and is not widely available. Computed Tomography is more sensitive than MRI in evaluating cortical bone destruction, although MRI is more sensitive than CT for detecting bone marrow involvement.[77] Whole body MRI techniques are difficult to perform and are time-consuming, thereby making scintigraphy the preferred screening test for skeletal metastases as it examines the entire skeleton, and is less expensive.[75] Although MRI is currently the best imaging technique for detecting marrow-based disease and for delineating the osseous and soft tissue extent of a bone tumour, it is not as useful as conventional radiography for characterising the aggressiveness of most bone lesions.[78] The reason for this is that on both T1 and T2-weighted sequences on MRI, cortical bone appears black and thus cannot be adequately assessed with this modality.[79]

POSITRON EMISSION TOMOGRAPHY (PET)

Positron Emission Tomography is a nuclear medicine imaging modality characterised by high contrast resolution, whole body tomographic data acquisition and the ability to perform quantitation of tracer uptake. Some functional changes that occur in bone marrow and bone due to malignant infiltration may precede any structural changes that are required to visualise the presence of malignant bone involvement by morphologic imaging modalities. The PET tracers mostly used for assessment of malignant bone involvement are ^{18}F-Fluoride and ^{18}F-fluorodeoxyglucose (^{18}F-FDG).

^{18}F-FLUORIDE

^{18}F-Fluoride was first introduced as a bone imaging agent in 1962.[80] The mechanism of uptake is similar to that of Methylene Diphosphonate. After diffusion into bone extracellular fluid, fluoride ions exchange with –OH groups in the hydroxyapatite crystal to form Fluoroapatite, which is deposited mainly at the surface where bone remodelling and turnover are greatest. Uptake reflects increased regional blood flow and is higher than that of MDP (up to a factor of 2). ^{18}F-Fluoride has minimal protein binding and hence higher capillary permeability and faster blood clearance leading to better target-background ratio. The regional plasma clearance is reported to be 3 to 10 times higher in bone metastases compared to normal bone.[64,81,82]

Increased ^{18}F-Fluoride uptake may be detected in both sclerotic (osteoblastic) and lytic lesions, demonstrating higher sensitivity than MDP for detection of lytic lesions. Schirrmeister and co-workers reported that ^{18}F-Fluoride PET detected bone metastases overlooked by bone scan in patients with lung cancer, as well as all metastatic lesions diagnosed by MRI.[83] It is, however, not a routine imaging modality for detecting malignant bone involvement, with use primarily suggested in patients at high risk for metastatic bone disease where bone metastases are suspected but bone scan is negative. ^{18}F-Fluoride PET is also indicated in patients with a tumour type that has predominantly lytic bone lesions such as multiple myeloma.[64,60,83]

^{18}F-Fluoride PET has the drawback of limited specificity because uptake of the Fluoride is also demonstrated in benign bone pathology. It is prone to a higher incidence of false-positive sites of uptake than bone scan with MDP.[81] Lesions detected may require correlation with CT or MRI for further validation. The use of hybrid systems e.g. PET/CT may improve the specificity of ^{18}F-Fluoride PET by determining the morphology of the scintigraphic lesion on the CT data of the study.[84]

^{18}F-FLUORODEOXYGLUCOSE (FDG)

Fluorodeoxyglucose (FDG) is an analogue of glucose which is taken up avidly by highly metabolic tissue, including some malignancies. FDG is taken up into cells by glucose membrane transporter proteins that are over-expressed in many tumour cells. It undergoes the first step of phosphorylation but is not metabolised further, resulting in its intracellular accumulation. It has been successfully used in combination with CT as a functional, morphological examination method in the routine clinical evaluation of some oncological patients.[5]

^{18}F-FDG PET is used in the staging of malignant tumours and in monitoring tumour response to therapy. Normal red marrow usually demonstrates low-intensity FDG uptake, thereby assisting in detecting increased uptake in early marrow involvement before an identifiable bone reaction.[85] A study by Ohta and co-workers found ^{18}F-FDG PET to be statistically superior in specificity to bone scintigraphy in the diagnosis of bony metastases from breast carcinoma, concluding that it was a powerful tool in the

diagnosis of bony metastases in such patients.[86] It also has the advantage of detecting both soft-tissue and skeletal disease. Some data suggests that ^{18}F-FDG PET is more sensitive in detecting lytic metastases than sclerotic lesions.[87] Sclerotic metastases show uptake of lower intensity compared with lytic lesions, sometimes no increased uptake at all. Bone scintigraphy appears to have a complementary role to that of ^{18}F-FDG PET as most lesions that are non-^{18}F-FDG-avid (mostly blastic) will show uptake on bone scintigraphy while those that do not show uptake on bone scintigraphy (mostly lytic) will show uptake on ^{18}F-FDG PET. If the primary tumour is not FDG avid, ^{18}F-FDG PET is not considered a suitable modality for staging but rather bone scintigraphy. Failure to detect metastases in these cases may be unrelated to their localisation in bone or their sclerotic nature but to reflect the non-FDG avidity of the individual tumour.[12] Other studies have shown that ^{18}F-FDG PET is less sensitive than skeletal scintigraphy in detection of bone metastases in cases of prostate cancer and osteosarcoma.[88,89]

^{18}F-FDG may also accumulate in non-malignant sites such as areas of infection, leading to false-positive findings. Significant problems also arise in patients on bone marrow stimulating medication in which there will be areas of increased ^{18}F-FDG uptake even without tumour involvement. PET services are relatively expensive to run and are not readily available, thereby limiting the use of ^{18}F-FDG PET as a routine investigation tool for skeletal metastases.

AIM OF THE STUDY

The aim of this research is to investigate the added value of SPECT/CT imaging in the evaluation of equivocal skeletal lesions in patients known to have primary malignant disease.

OBLECTIVES

1. To assess the added value of SPECT/CT over SPECT alone on
    a. Lesion-wise and
    b. Patient-wise basis in the evaluation of equivocal lesions.

2. To establish the appropriate clinical indications for skeletal SPECT/CT imaging in patients with known malignant disease.

CHAPTER 3

SUBJECTS AND METHODS

PATIENT SELECTION

Forty two patients were included in the study prospectively between April 2007 and April 2008. Participant recruitment was carried out from the day to day referrals of patients with known malignant disease, undergoing routine bone scanning for screening or follow-up, regardless of primary tumour location or histological type. Patients who showed skeletal lesions on planar scintigraphy that could not be confidently classified as either malignant or benign were included in the study. No individual patient had more than one study included in the study.

The study was approved by the Stellenbosch University Faculty of Health Sciences Ethics Committee for Human research and written informed consent was obtained from each patient before inclusion in the study.

IMAGE ACQUISITION

Planar scans were obtained 3 hours after intravenous injection of 740MBq of ^{99m}Tc-Methylene Diphosphonate (^{99m}Tc-MDP). Planar imaging was done using one of six gamma cameras, two single head cameras (GE Starcam™ and Elscint SP4™) and four dual-head gamma cameras (two Elscint Helix™ and two GE Infinia cameras, one of which is the Hawkeye™), each equipped with high-resolution, low-energy collimators. Whole body planar images on the single head cameras were acquired in the form of multiple static images over different regions of the body. A 256×256 matrix was used with 700 000 counts being counted per image in the axial skeleton and 300 000 to 500 000 counts per image in the appendicular skeleton. On the dual head Elscint Helix™ cameras, a step-and-shoot mode was used and counting done for 200 seconds per step on a 512×256 matrix. The number of steps depended on the patient's height. Whole body planar imaging on the GE Infinia cameras was done in a continuous mode at a rate of 10cm per minute on a 512×256 acquisition matrix.

One or more SPECT/CT volumes were chosen following a visual assessment of the whole body planar scan. Volumes were selected to include all equivocal planar lesions in the field of view, irrespective of the location of the lesions in the skeleton. SPECT imaging was done on the two Elscint Helix dual head cameras using a 128×128 matrix

and a 6º step-and-shoot mode with counting done at 20 seconds per step. Each head was set to rotate through 180º for a total 360º SPECT acquisition. The CT component of the SPECT/CT acquired on the GE Infinia Hawkeye™ was done with an X-Ray tube mounted within the same gantry on a 256×256 matrix, voltage 140kV and current 2.5mA. Acquisition slice thickness was 10mm with rotation velocity set at 2.6rpm.

Processing of SPECT and SPECT/CT images was done on the Xeleris™ and Hermes™ workstations by iterative reconstruction and fusion of SPECT and CT images was done automatically on the same workstations. The Butterworth filter was used for SPECT images while a Hann filter with a cut-off frequency of 1.0 was applied to the CT data.

DATA/IMAGE ANALYSIS

Nuclear Medicine images (planar images and SPECT) were evaluated by two Nuclear Medicine Physicians with interpretations by consensus. All lesions noted within the SPECT/CT volume(s) were interpreted, including any new lesions only visible on SPECT. The planar images were initially used to determine the volume(s) that would be assessed using SPECT/CT. The Nuclear Medicine Physicians then evaluated the planar and SPECT images blinded to the CT study. Lesions were classified as benign, malignant or equivocal. Lesions were classified as equivocal if they could not be confidently assigned as being either malignant or benign. Similarly a classification of benign, malignant, or equivocal, was made for the patient's overall status for bone

metastases. This scoring was done in the light of all available clinical information, including a brief history of each patient, laboratory results, primary tumour, and any treatment given to the patient to date.

SPECT/CT images were then re-evaluated by the nuclear medicine physicians together with an experienced diagnostic radiologist. All lesions and patients were then reclassified using the same system. The CT images obtained from the SPECT/CT were also analysed for any additional abnormalities at sites other than those identified on the bone scan.

VALIDATION OF SPECT AND SPECT/CT INTERPRETATION

A final decision as to the true status of lesions was made after consideration of the clinical information, including a follow up period of 6-9months. When available, additional radiological studies (CT, Radiographs, and MRI) performed within 3months of the bone scan, were used to reach the overall decision, as well as follow-up bone scan in some patients. Change in character and/or size on radiological studies was considered to indicate malignancy, whereas a lesion was considered benign if there was no change. Lesions which showed increase in size and/or intensity of ^{99m}Tc-MDP uptake on follow-up bone scan were considered to be malignant. Those which remained unchanged over at least 9months without therapy were considered benign. A lesion that decreased or increased in size and/or intensity on cytotoxic therapy was considered to be malignant.

STATISTICAL ANALYSIS

The proportion of equivocal interpretations on SPECT and SPECT/CT, as well as the accuracy of each were compared on both a patient-wise and lesion-wise basis. In order to calculate the accuracy of SPECT and SPECT/CT, equivocal lesions were considered to indicate malignancy. Ninety five percent confidence intervals (CIs) were used in the estimations and comparison was done using McNemar Chi-square test for matched pairs, and Mosteller's Chi-square test for small samples when $n<20$. SPECT and SPECT/CT results were each compared to the gold standard in order to compare the performance of each.

CHAPTER 4

RESULTS

SPECT and SPECT/CT were performed on 42 patients all with histologically confirmed malignant disease. Twenty-eight of these patients were women, and 14 were men, ranging in age between 28 years and 79 years (mean age 58 years). The primary malignancies included in this sample were 22 breast (52%), 8 prostate (19%), four bronchus, and one each of bladder, oesophageal, chordoma, chondrosarcoma, osteosarcoma, nasopharyngeal, colorectal, and vulva cancer (Table 1). There were twenty-nine patients included in the study who described having bone pain at the time of the bone scan.

Table 1: Frequency Table of Tumour type

Tumour Type	Count	Percent
Breast Ca	22	52.4%
Prostate Ca	8	19.0%
Bronchial Ca	4	9.5%
Osteosarcoma	1	2.4%
Oesophageal Ca	1	2.4%
Chondrosarcoma	1	2.4%
Bladder Ca	1	2.4%
Chordoma	1	2.4%
Colorectal Ca	1	2.4%
Vulva Ca	1	2.4%
Nasopharyngeal Ca	1	2.4%
TOTAL	**42**	**100%**

Diagnostic radiology (X-Rays, CT, or MRI) was available for all patients at the time of review of records, which was done between six and nine months after SPECT/CT acquisition. None of the participants had biopsy of equivocal lesions. Three patients had MRI of the regions containing equivocal lesions, three had repeat bone scans, seven had Computed Tomography (CT), and 29 had X-Rays. The final decision as to whether the patient had malignant or benign disease at the sites demonstrated on the bone scan was made after reviewing this information, as well as clinical information that included laboratory results such as rising serum calcium levels. This was then used to make a final decision regarding the status of lesions which was then used as a gold standard for this study. Based on this 24 patients were diagnosed as having benign bone disease (57%) while 18 had malignant bone disease (43%) (Table 2).

Table 2: SPECT, SPECT/CT interpretation, and Gold Standard, patient-wise

Pt	Tumour Type	Age(Yrs)	Sex	SPECT	SPECT/CT	G S	Bone Pain
1	Osteosarcoma	53	M	M	M	M	Y
2	Bronchial Ca	69	M	E	B	B	Y
3	Breast Ca	52	F	B	B	B	Y
4	Breast Ca	64	F	E	B	B	N
5	Breast Ca	65	F	E	E	B	N
6	Breast Ca	52	F	M	M	M	Y
7	Breast Ca	75	F	M	M	M	N
8	Oesophageal Ca	72	M	M	M	M	Y
9	Prostate Ca	63	M	M	M	M	Y
10	Breast Ca	77	F	E	B	B	N
11	Breast Ca	54	F	E	M	M	N
12	Breast Ca	55	F	M	M	M	Y
13	Breast Ca	48	F	M	M	M	N
14	Prostate Ca	55	M	E	E	B	Y
15	Breast Ca	67	F	E	E	B	N
16	Breast Ca	69	F	E	B	B	N
17	Breast Ca	63	F	B	B	B	Y
18	Prostate Ca	55	M	E	B	B	Y
19	Prostate Ca	65	M	M	M	M	Y

20	Prostate Ca	59	M	M	M	B	Y
21	Breast Ca	55	F	M	M	M	Y
22	Prostate Ca	73	M	E	M	B	N
23	Chondrosarcoma	39	F	M	M	M	Y
24	Bladder Ca	56	F	M	M	M	Y
25	Chordoma	56	F	B	B	B	Y
26	Breast Ca	47	F	M	M	B	N
27	Bronchial Ca	59	M	B	B	B	Y
28	Breast Ca	55	F	E	B	B	Y
29	Breast Ca	39	F	E	M	M	N
30	Breast Ca	48	F	E	B	B	Y
31	Breast Ca	49	F	E	B	B	N
32	Breast Ca	43	F	B	B	B	N
33	Breast Ca	58	F	B	M	M	Y
34	Colorectal Ca	62	F	M	M	M	Y
35	Prostate Ca	69	M	E	B	B	Y
36	Prostate Ca	82	M	E	E	B	Y
37	Breast Ca	57	F	E	E	B	Y
38	Vulva Ca	64	F	E	M	M	Y
39	Nasopharyngeal	28	M	M	E	B	Y
40	Breast Ca	43	F	M	M	M	Y
41	Bronchial Ca	62	F	E	M	M	Y
42	Bronchial Ca	59	M	E	B	B	Y

M-Malignant B-Benign E-Equivocal Y-Yes N-No GS-Gold Standard

PATIENT-WISE ANALYSIS

SPECT

Using SPECT on a patient-by-patient basis, six patients were interpreted as having benign bone disease, 16 as having malignant bone disease, and 20 patients (47%) were equivocal (Table 2). Three of the patients described as having malignant disease on SPECT were found to have benign disease based on the gold standard. One of the patients described as having benign disease was found to have malignant disease based on the gold standard. Of the 20 patients described as being equivocal on SPECT, 16 were found to be benign, and 4 were found to be malignant based on the gold standard.

SPECT/CT

Fifteen patients were interpreted as having benign bone disease on SPECT/CT while 21 were malignant and 6 (14%) had equivocal diagnoses (Table 2). There were three patients who had malignant diagnoses on SPECT/CT found to be benign based on the gold standard, while no patient was upgraded from benign to malignant. All of the equivocal patients on SPECT/CT were found to have benign disease.

Table 3: Patient-wise proportion of equivocal interpretations for SPECT versus SPECT/CT:

		SPECT		SPECT/CT			
	n	**Equivocal**	**%**	**Equivocal**	**%**	**Statistical Test**	**p-value**
Total	42	20	48	6	14	McNemar X^2	0.00115
Bone Pain	29	11	38	4	14	McNemar X^2	0.04550
No Bone Pain	13	9	69	2	15	Mosteller's	<0.0001
Breast Ca	22	11	50	3	14	McNemar X^2	0.01333
Prostate Ca	8	5	63	2	25	Mosteller's	<0.0001

For all patients SPECT-CT was found to result in significantly fewer equivocal patient studies compared to SPECT alone (p=0.00115) (Table 3). This was also true for subgroups with and without bone pain, and those with breast and prostate carcinoma. Compared to SPECT, SPECT-CT was found to alter the interpretation of 17 patients (40%). Equivocal interpretations on SPECT in 10 patients were altered to benign on SPECT/CT, all of which were found to be benign based on the gold standard. In 5 patients equivocal interpretations were altered to malignant, 4 of which were found to be malignant and one found to be benign based on the gold standard. In another patient a benign interpretation was altered to malignant, which was found to be malignant based on the gold standard. A malignant interpretation was altered to equivocal in a single patient, which was found to be benign based on the gold standard.

Table 4: <u>Patient-wise accuracy for SPECT versus SPECT/CT:</u>

		SPECT		SPECT/CT			
	n	**Correct**	**%**	**Correct**	**%**	**Statistical Test**	**p-Value**
Total	42	22	52	33	79	McNemar X^2	**0.0026**
Bone Pain	29	17	59	24	83	McNemar X^2	**0.0233**
No Bone Pain	13	5	38	9	69	Mosteller's	**<0.0001**
Breast Ca	22	11	50	18	82	McNemar X^2	**0.0233**
Prostate Ca	8	2	25	4	50	Mosteller's	**<0.0001**

When equivocal studies on both SPECT and SPECT/CT were taken to indicate malignancy, the accuracy of SPECT/CT (79%) was significantly greater than that of SPECT (52%) (p=0.0026) (Table 4). This was also true for subgroups with and without bone pain, and those with breast and prostate carcinoma.

In three patients there were lytic lesions detected on SPECT/CT that were not seen on SPECT. In one case, the patient was reclassified as having malignant disease on SPECT/CT and gold standard after being classified as having benign disease on SPECT. In the other two patients there was no alteration in the overall diagnoses as there were other malignant osteoblastic lesions detected.

LESION-WISE ANALYSIS

SPECT

The forty-two patients who underwent imaging had 189 lesions detected on planar scintigraphy and on SPECT alone (Table5). Eighty-six lesions were interpreted as benign on SPECT while 45 were malignant and 58 (31%) were equivocal. Of the 58 equivocal lesions, forty-eight were diagnosed as benign and ten as malignant on gold standard. Eight of the 45 lesions that were interpreted as malignant on SPECT were found to be benign on gold standard while 4 of the 86 that were interpreted as benign were found to be malignant.

Table 5: SPECT interpretation, and Gold Standard, lesion-wise

SPECT Interpretation		**Gold Standard Interpretation**	
		Benign	**Malignant**
Benign	86	82	4
Malignant	45	8	37
Equivocal	58	48	10
Total	189	138	51

SPECT/CT

On SPECT/CT, forty-six lesions were interpreted as malignant and 126 as benign while 17 (9%) remained equivocal (Table 6). Twelve of the equivocal lesions were found to be benign on gold standard while 5 were malignant. Forty-four of the 46 malignant lesions on SPECT/CT were also found to be malignant on gold standard with two being downgraded to benign. Only one of the 126 lesions interpreted as benign on SPECT/CT was found to be malignant on gold standard. The diagnosis was not altered in the other 125 benign lesions. The skeletal region with the greatest proportion of equivocal lesions on both SPECT and SPECT/CT was the vertebral column (62% and 53% of equivocal lesions respectively).

Table 6: SPECT interpretation, and Gold Standard, lesion-wise

SPECT/CT Interpretation		**Gold Standard Interpretation**	
		Benign	**Malignant**
Benign	126	125	1
Malignant	46	2	44
Equivocal	17	12	5
Total	189	139	50

For all lesions taken together SPECT/CT led to a significant reduction in the number of equivocal lesions when compared to SPECT alone ($p<0.0001$), altering the interpretation of 56 lesions (30%) (Table 7). The reduction in the number of equivocal

lesions was also significant for all regions of the skeleton except the lumbar spine (p=0.22067). However, the reduction was significant when the entire vertebral column was considered as a single region (p<0.0001).

Table 7: Lesion-wise proportion equivocal

		SPECT		SPECT/CT			
	n	**Equivocal**	**%**	**Equivocal**	**%**	**Statistical Test**	**p-Value**
Total	189	58	31	17	9	McNemar X^2	<0.0001
Skull	5	1	2	0	0	Mosteller's	<0.0001
Chest Wall	38	15	39	5	13	McNemar X^2	0.00938
Cervical Spine	16	7	44	0	0	Mosteller's	<0.0001
Thoracic Spine	63	15	24	2	3	McNemar X^2	0.00195
Lumbar Spine	37	9	24	5	14	McNemar X^2	0.22067
Sacrum	13	5	38	2	15	Mosteller's	<0.0001
Vertebral Column	129	36	28	9	7	McNemar X^2	<0.0001
Pelvis	6	2	33	1	17	Mosteller's	<0.0001
Extremities	11	4	36	1	9	Mosteller's	<0.0001

For all lesions taken together the accuracy of SPECT/CT was found to be significantly higher than that of SPECT when equivocal lesions were interpreted as indicating

malignancy ($p<0.0001$) (Table 8). This also applied to all other regions of the skeleton except the skull where statistical analysis was not applied since there was no difference between the accuracy of SPECT and SPECT/CT in this region.

Table 8: <u>Lesion-wise accuracy for SPECT versus SPECT/CT:</u>

		SPECT		SPECT/CT			
	n	**Correct**	**%**	**Correct**	**%**	**Statistical Test**	**P-Value**
Total	189	126	67	174	92	McNemar X^2	**<0.0001**
Skull	5	4	80	4	80	Not Done	
Chest Wall	38	25	66	34	89	McNemar X^2	**0.0077**
Cervical Spine	16	9	56	15	94	Mosteller's	**<0.0001**
Thoracic Spine	63	43	68	61	97	McNemar X^2	**<0.0001**
Lumbar Spine	37	28	76	35	95	McNemar X^2	**0.0233**
Sacrum	13	6	46	10	77	Mosteller's	**<0.0001**
Vertebral Column	129	86	67	121	94	McNemar X^2	**<0.0001**
Pelvis	6	4	67	5	83	Mosteller's	**<0.0001**
Extremities	11	7	64	10	91	Mosteller's	**<0.0001**

CHAPTER 5

DISCUSSION

In this study, we found that SPECT/CT results in fewer equivocal diagnoses and increased accuracy compared to SPECT on both a patient-wise and lesion-wise basis. Where SPECT/CT resulted in a change in a patient's diagnosis, most of the time it was downgrading rather than upgrading the diagnosis. We found that SPECT/CT has a high negative predictive value for skeletal metastases, although further investigations may be required in order to reduce the number of false-positive diagnoses. It was also shown that SPECT/CT increases the proportion of correct diagnoses compared to SPECT and that its benefit seems to be independent of the presence of bone pain or the type of primary tumour. The addition of the CT component in SPECT/CT in the lumbar spine does not improve the diagnostic confidence in equivocal lumbar lesions significantly, however it does improve accuracy in this region. As far as the author is aware this is the first study addressing in impact of SPECT/CT in bone metastases on a patient-wise basis, as well as studying different regions of the skeleton separately.

On SPECT/CT, there was a decrease in the number of patients diagnosed as having malignant or equivocal bone disease which were benign on gold standard, with 9 patients on SPECT/CT as opposed to 19 patients with SPECT being downgraded to

benign on gold standard. This result indicates that, while the results are better than SPECT, further investigations may be required in order to further reduce the number of false-positive diagnoses in patients with malignant bone disease based on SPECT/CT. The fact that no patient was upstaged from benign to malignant suggests a high negative predictive value for SPECT/CT. This would however need to be corroborated by a study involving a larger patient population. SPECT/CT resulted in significantly fewer equivocal diagnoses compared to SPECT in the whole patient sample studied ($p=0.0015$) as well as in subgroups with and without bone pain ($p=0.0455$ and $p<0.0001$ respectively) and in those with breast ($p=0.01333$) and prostate cancer ($p<0.0001$). These data support the use of SPECT/CT for improving diagnostic confidence when investigating cancer patients for skeletal metastases as found by other groups.[21,65,66,67] Because bone pain is the most common neurologic symptom, and sometimes the only presenting symptom in malignancy, we also sought to investigate the implication, if any, of the presence or absence of bone pain on the diagnoses of bone metastases using SPECT/CT in cancer patients.[90,91,92] It is interesting to note is that regardless of whether or not patients complain of bone pain, there is a significant reduction in the number of equivocal diagnoses and a significant increase in accuracy from SPECT to SPECT/CT. This implies that if an equivocal lesion is detected in a patient with or without bone pain, SPECT/CT must be performed in all cases. With breast and prostate cancer the benefit of SPECT/CT was also present when looking at these groups separately, suggesting that its additional value may also be independent of the underlying primary tumour.

The diagnosis was altered in 17 out of 42 patients (40.5%) which is consistent with the

results of Roach and co-workers who recorded an alteration in 56% of patients in their study.[66] Of the seventeen patients in whom the diagnosis was altered by SPECT/CT, fourteen had correct diagnoses (true positive and true negative) while two were incorrect (false negative and false positive) and a single patient remaining with an equivocal diagnosis after SPECT/CT. This further strengthens the grounds for the use of SPECT/CT because the diagnoses were correctly altered in the vast majority (82%) of patients in whom there was a change. In terms of accuracy, a similar trend was observed as that seen in the reduction of equivocal lesions. SPECT/CT showed significantly greater accuracy compared to SPECT alone in the total patient sample ($p=0.0026$) and in the subgroups of patients with and without bone pain ($p=0.0233$ and $p<0.0001$ respectively) as well as for patients with breast ($p=0.0233$) and prostate cancer ($p<0.0001$). These statistics also support the use of SPECT/CT in the investigation of cancer patients for metastatic bone disease as it increases the proportion of correct diagnoses compared to SPECT.

In the lesion-wise analysis we observed how SPECT/CT influenced the interpretation of each skeletal lesion. There were 189 lesions seen on SPECT alone with 58 (31%) of these being equivocal. Of the 86 benign SPECT lesions, four were false-negative while eight of the 45 malignant SPECT lesions were false-positive. This implies that SPECT was correct 90% of the time in the 69% of cases in which a diagnosis could be reached. SPECT/CT resulted in fewer equivocal lesions than SPECT, with a diagnosis being reached in 91% of lesions. Furthermore, SPECT/CT was correct 98% of the time that a diagnosis could be reached. Consequently SPECT/CT resulted not only in fewer

equivocal lesions, but also in increased accuracy in the interpretation of these lesions, further supporting its use. Overall, SPECT/CT significantly reduced the number of equivocal skeletal lesions compared to SPECT from fifty-eight (31%) to seventeen (9%) ($p<0.0001$).

Although SPECT/CT resulted in a statistically significant reduction in the proportion of equivocal lesions detected in the vertebral column as a whole ($p<0.0001$), as well as in the cervical, thoracic and sacral vertebrae, this reduction was not significant when the lumbar spine was considered separately ($p=0.22067$). This may be due to the larger size of lumbar vertebrae which facilitates more accurate localisation of lesions, enabling them to be classified as benign or malignant with SPECT alone more easily. Consequently the addition of the CT component in SPECT/CT may not improve the diagnostic confidence in equivocal lumbar lesions significantly. Other skeletal regions such as the skull, pelvis, chest wall and extremities also showed a significant reduction in the number of equivocal lesions on SPECT/CT compared to SPECT. Although usually reserved for investigating complex structures such as vertebrae, these results suggest that SPECT/CT is of benefit when investigating other skeletal regions including the chest wall. This skeletal region is of particular concern because computed tomographic images undergo degradation due to motion artefact as well as higher incidence of SPECT and CT misregistration.[67] The accuracy of SPECT/CT was shown to be significantly superior to that of SPECT in most skeletal regions except the skull where the accuracy of the two modalities was the same. This statistic should, however be considered with caution due to the small number of lesions detected in the skull.

On a patient-wise basis, even in patients with a decisive diagnosis on SPECT, there was a change in the number of patients diagnosed as both malignant and benign. This change affected similar proportions of patients who had malignant bone disease on SPECT (3/15), compared to those with benign disease (1/6). This suggests that in addition to equivocal diagnoses, patients who have unequivocal diagnoses on SPECT (i.e. lesions with a decisive diagnosis) may still require further investigation with SPECT/CT as there is still a significant possibility of a false-positive and false negative diagnosis.

The diagnosis of a lesion as malignant or benign on bone scan or other modality may have a significant influence on the management of a patient. The presence of skeletal metastases may indicate short patient survival time and a need for additional or intensified treatment.[93] In lung cancer, for example, it may determine whether a patient undergoes surgical lobectomy or pneumonectomy, or palliative chemotherapy and/or radiotherapy. In a symptomatic patient with bone metastases, therapy may be tailored to include radiotherapy of the symptomatic metastatic lesion(s) in order to control the pain, or to prevent pathological fractures if weight-bearing bones are involved. If, however the pain is attributed to a benign lesion, appropriate less aggressive therapy may be indicated.

Bone scintigraphy is the most frequently performed study in most nuclear medicine departments, commonly being used in the evaluation of cancer patients for both staging and follow-up. It is a very sensitive modality that can be used for whole-body screening for the presence of skeletal metastases in many cancer patients. The specificity of bone scintigraphy in the diagnosis of skeletal metastases is not as high however, because most patients may also have benign skeletal disorders which may be difficult to differentiate from malignancy on scintigraphy alone.[94,95,4] This is particularly true for vertebral lesions where the superimposition of structures on planar scintigraphy results in difficulty in locating lesions to particular vertebral sites. The addition of SPECT has led to a significant improvement in our ability to locate lesions on bone scintigraphy. The problem of superimposition of overlying activity with planar scintigraphy is minimised by using SPECT, which also enables more accurate anatomical localisation of lesions and easier differentiation between benign and malignant lesions. SPECT has become broadly available in most centres and several single photon emitting radiopharmaceuticals have been demonstrated to be of clinical value in a wide variety of neoplasms, including bone.[96] Due to its superior contrast, SPECT also leads to the visualisation of lesions that may not have been seen on planar scintigraphy. This enables the detection of lesions that will initially have been invisible or equivocal on planar scintigraphy. However, the status of some lesions remains unclear after SPECT.

The integration of Computed Tomography (CT) in the same gantry with a dual-head

camera system (SPECT/CT) has led to improved diagnostic accuracy compared to SPECT alone.[67] SPECT/CT serves as a method of correlating anatomical information from CT with functional information from SPECT, hence enabling more accurate localisation and characterisation of SPECT lesions using the CT component. This is of great benefit in complex structures such as vertebrae where the location of a lesion determines whether it is classified as malignant or benign (e.g. pedicle or facet joint respectively).[58]In addition, a small number of purely lytic lesions that are not normally visible on bone scintigraphy may be seen on the CT images, despite the relatively poor CT quality of many commonly available SPECT/CT systems.

Despite its advantages over SPECT alone, SPECT/CT still results in some lesions remaining equivocal. A disadvantage of SPECT/CT performed using a system similar to that used for this study, is that it results in additional imaging time of about fifteen minutes per volume imaged, thereby reducing patient throughput. It is notable that this study was performed using a low dose localising CT, which may be relevant if SPECT/CT is to be used more routinely in these patients in future. Though minimal, the CT component of SPECT/CT results in additional radiation dose burden to the patient in the order of about 0.5mSv.[97] This is relatively low when compared to conventional CT which subjects a patient to an effective dose of 5-15mSv depending on the region of the body being scanned.[68] These drawbacks are however acceptable when considering the significant reduction in equivocal findings and enhanced accuracy of performing these studies.

The six to nine month period that was chosen for follow-up in this study was used because it allowed enough time for updating of patient records and because repeat bone scans are often performed at least three months after the initial scan. During this period, benign lesions commonly remain unchanged whereas the appearance of malignant lesions may change, depending on the aggressiveness of the tumour, whether or not therapy has been administered, the amount of time elapsed after therapy, and the response to therapy. When chemotherapy has been administered to a patient with malignant bone disease, a flare response may occur in which uptake of ^{99m}Tc-MDP will be increased in intensity and/or extent due to reparatory processes taking place.[60,77,61,98,99,100] The increase in extent may be a result of the artefactual effect of increased intensity. Sometimes lesions that would not have been visible initially may become apparent on follow-up scan. This phenomenon may be evident up to six months post-therapy and may erroneously be interpreted as indicating progression of malignant bone disease. Interpretation of studies was done with this possibility in mind, and taking into consideration clinical information regarding recent therapy in order to minimise incorrect interpretation. A positive response to chemotherapy may also be seen as a reduction in the intensity of ^{99m}Tc-MDP uptake and/or a reduction in the number of lesions seen on bone scan. If radiotherapy has been administered to skeletal lesions, the region of the skeleton subjected to radiation will initially be seen as a photopenic area which later shows increased tracer uptake during repair. If therapy has not been given, malignant lesions may show increased intensity and/or extent of tracer uptake compared to the baseline study due to progression of malignant skeletal

disease, sometimes with evidence of new lesions. There may be difficulties in differentiating between a flare response and progression of malignant skeletal disease as both are characterised by similar scintigraphic features. This problem may be alleviated by repeating the bone scan at a later date, usually set at three months. Some tumours have predominantly lytic skeletal metastases which may not be visualised on bone scan. A repeat bone scan after therapy may however show evidence of these lesions as a flare response. Depending on their size, lytic lesions may be seen on the CT component of SPECT/CT, hence reducing the number of false negative studies.

LIMITATIONS

The selection of lesions used in this study is complex due to the nature of the techniques involved. Initially planar images were used to identify equivocal lesions, the location of which determined the location of SPECT/CT volumes. As a result some of these lesions remained equivocal, and some were considered benign or malignant on SPECT. In addition the volumes may have included other lesions already considered benign or malignant on planar imaging. A third group of lesions that were seen on the SPECT study were those that were not seen on the planar study, but also happened to be located in the SPECT/CT volumes. This study did not analyse these different subgroups of lesions to determine whether the additional value of SPECT/CT varied between them.

The gold standard used in this study had some weaknesses which included the fact that none of the patients imaged had biopsy done to establish the diagnoses of equivocal SPECT lesions. The study done by Horger and co-workers, which had similarities to ours, had biopsies done in five patients while in some, radiologic follow-up was used (37 patients).[21] Radiological studies used in this case included conventional radiography, CT and MRI. In our study as well as in Horger's study, most patients underwent radiological studies as follow-up probably due to the ready availability and relative low cost of radiography and CT when compared to MRI. A major limitation was the lack of common gold standard criteria for the establishment of the correct diagnosis. It would have been ideal to use the same gold standard in all patients, but this became impractical because the decision of which investigational modality to use in determining the correct diagnosis was left to the referring physician(s). Our study also lacked any histopathologic analysis to confirm the diagnoses. We relied on radiologic follow-up and assessment of clinical information.

Additionally, since the study was carried out over a one year period, the interpretation of patient studies may not have been done uniformly by the same readers when comparing the initial studies with those done towards the end of the study. Studies done towards the end may have lower incidence of equivocal lesions as the readers will have acquired more experience as the study progressed and would have been more decisive in making their interpretations.

Another limitation was the relatively small number of patients in our sample leading to low statistical power of most of our statistical analyses. Most of the literature reviewed to date shows a similar weakness of relatively low patient numbers.[21,65,66,67] Because only a single SPECT/CT system is available in our department, the number of patients recruited for the study had to be limited in order to allow for use of the system for other clinical work. This issue is also a major challenge in most nuclear medicine centres in the developing world where SPECT/CT is not yet widely available. However, this was not considered as a major issue since, except for the lumbar spine, most of our results were significant. There may be some benefit in performing a larger series specifically looking at the impact of SPECT/CT when assessing lumbar spinal lesions.

CONCLUSION

SPECT/CT performs significantly better than SPECT alone for the interpretation of lesions in all regions of the skeleton. However, it may contribute less in the lumbar spine, therefore if facilities are limited, it may be reasonable to use SPECT only for equivocal lumbar lesions in most of which the use of SPECT gives a correct diagnosis after consideration of the pattern and intensity of tracer uptake. There is no evidence that this finding is dependent on the primary tumour, or the presence of bone pain. These findings were made both in terms of patients and individual lesions.

RECOMMENDATIONS

1. The results of this study support the use of SPECT/CT in all cases of malignant disease that are being investigated for metastatic malignant bone disease where equivocal lesions exist on planar scintigraphy.

2. Due to the limited availability of SPECT/CT technology, selection criteria for patients undergoing SPECT/CT must be refined so as to optimise its utilisation in nuclear medicine departments. Therefore its use in patients with equivocal planar lesions should be restricted to those patients in whom,

   a. the correct classification of the lesion(s) in question is expected to alter the management of the patient (e.g. in a patient with multiple unequivocal metastatic skeletal lesions, the correct classification of additional lesions may not affect management of the patient), and

   b. where equivocal lesions exist outside of the lumbar spine on planar scintigraphy, SPECT/CT is suggested for lumbar lesions only if SPECT facilities are available.

3. Because there is equal benefit in the use of SPECT/CT in patients with and without bone pain, there is no basis for the use of this criterion in deciding whether or not to use SPECT/CT on a particular patient.

4. SPECT/CT images should be interpreted with the aid of a diagnostic radiologist, with careful inspection of CT images in order to get the best possible result from a patient

study. Alternatively, Nuclear Medicine physicians need to acquire sufficient experience with this aspect of CT interpretation. A wide variety a SPECT/CT systems are commercially available, ranging from those with low dose CT systems intended only for attenuation correction and localisation to full dose multislice diagnostic CT. This work was performed using a low dose CT system intended only for attenuation correction and localisation. Despite this limitation, the CT study had a marked impact on the interpretation of bony lesions. It can be expected that the impact of a technically superior CT will be greater. In this situation radiological expertise is likely to be more necessary however.

5. At this stage there is no evidence to suggest that these recommendations should be applied differently for different malignancies.

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