ASSESSMENT OF THE IMPACT OF THE APPLICATION OF SINGLE PHOTON EMISSION COMPUTERIZED TOMOGRAPHY AND SPECT-CT ON LESION CATEGORIZATION

By

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TABLE OF CONTENTS

DECLARATION

I, Garba Haruna Yunusa, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Objectives: To assess initial experience with the use of a new SPECT-CT in the evaluation of lesions.

Methods: The folder number, radiopharmaceutical used and type of scan of patients examined with a new Siemens T6 SPECT-CT between 2 April and 31 December 2013 were retrieved. The number of ^{99m}Tc-MDP bone scans was sufficient for a detailed analysis. The scans were re-processed and reported by the observer before he was given any clinical information. Whole body planar, whole body planar plus SPECT and whole body planar plus SPECT-CT images were assessed successively in three separate sessions at least two weeks apart. At each session, the certainties of detection, localisation, and categorisation of each lesion were recorded.

Results: A total of 539 lesions were seen on the whole body, SPECT and CT images in 133 patients. The whole body images showed no lesions in three patients and 378 lesions in 130 patients, 117(31%) lesions in areas not covered by the SPECT. SPECT detected 122 additional lesions in 79 patients. Thirty-nine (12.2%) lesions were seen only on CT in 32 (24.1%) patients.

For the 261 lesions seen on the planar images in the SPECT FOV, lesion detection was definite in 233 (89.3%), localisation definite in 151(57.9%) and categorisation definite in 123 (47.1%) lesions. On the SPECT, definite lesion detection, localisation and categorisation were recorded respectively for 259 (99.2%), 228 (87.4%) and 176 (67.4%) of the 261 lesions. Lesion detection, localisation and categorisation certainties were definite for 100%, 99.1% and 94.7% of the SPECT-CT lesions respectively.

Conclusion: Whole body planar scintigraphy is essential in lesion detection. SPECT markedly improves lesion detection and localisation and CT enhances lesion categorisation.

1.0 RESEARCH PROTOCOL

This research protocol was submitted to the Faculty of Health Sciences, University of Cape Town before commencement of the study.

1.1 Background

The use of hybrid imaging consisting of Single Photon Emission Computerized Tomography (SPECT) and X-ray transmission Computerized Tomography (CT) scan is increasing globally. This mode of hybrid imaging has the advantage of providing functional and morphologic information for a given lesion or pathology in a single session. The aim of this study is to see to what extent the addition of SPECT and SPECT-guided multi-slice CT affects categorization of lesions demonstrated on conventional static planar imaging in the department of nuclear medicine at Groote Schuur Hospital.

1.2 Literature review

Radionuclide imaging by the use of SPECT is currently an important component of evaluation of various diseases with a high degree of sensitivity due to its ability to provide functional information early in the disease even before morphological changes become visible on other imaging modalities.[1,2] However, the limited spatial resolution of SPECT necessitated the introduction of X-ray based computerized tomography which has superior spatial resolution and provides morphologic information that helps in better localization of lesions seen on functional and metabolic imaging. This form of hybrid imaging has improved the staging of disease

as well as the prognostic and treatment monitoring potentials of the functional and metabolic information provided by conventional nuclear medicine examinations.[3,4] There is dearth of literature reporting the utility, sensitivity, specificity and accuracy of this imaging technique as it applies to non-skeletal nuclear medicine examinations.

In a report of initial two-year clinical experience with SPECT-CT by Jacene et al, 54% of the cases studied had additional information for image interpretation derived from the fusion of the SPECT with the CT images mostly as a result of improved localization of abnormal and physiologic SPECT findings by the CT data.[3] This study also reported improved diagnostic certainty in 24% of the cases and beneficial alteration of image interpretation in 13% of the cases. However, some of the limitations reported in this study included the low-resolution single-slice CT used which did not reveal the exact anatomical sites of abnormal radiotracer accumulation especially in the interpretation of abdominal findings on ^{111}In-Pentetreotide scans, as well as the prolonged CT acquisition time of 10-15 minutes by the single-slice scanners that resulted in increased patient motion and degradation of image quality. Prolonged acquisition time has been addressed by the recent introduction of multi-slice CTs in newer versions of the SPECT-CT systems.[4]

The new SPECT-CT in the department of Nuclear Medicine at Groote Schuur Hospital is equipped with a six-slice multi-detector CT which is likely to overcome

some of the limitations reported in the use of single slice CT, hence the need for this research.

Over the years, the main advantages of hybrid SPECT-CT imaging included accurate localization and characterization of endocrine and neuroendocrine tumors, solitary pulmonary nodules, lung cancers, brain tumors, lymphoma, prostate cancer, malignant and benign bone lesions, sentinel lymph node localization as well as precise definition of the diagnostic and prognostic profile of cardiovascular patients.[4] Adaptation of the CT field of view to foci of increased bone metabolism in a technique referred to as SPECT-guided CT has been shown to accurately classify previously indeterminate lesions on planar and SPECT imaging in the axial skeleton with certainties of 92% to 100%.[5–7] These studies limited their observations to the evaluation of foci of increased bone metabolism classified as indeterminate on SPECT in cancer patients, therefore inclusion of other systems in the evaluation of the clinical value of SPECT-CT is likely to reveal some of its potentials.

In a review by Mohan *et al* on the assessment of the additional value of SPECT-CT amongst patients referred from the orthopaedic clinics, it was observed that when compared with planar imaging, SPECT-CT provided additional information in 81% of the patients.[8] SPECT-CT provided specific diagnosis in 46% of the patients in this series, and more accurate localization of degenerative or post-surgical changes in the remaining 54% of the patients. This is similar to findings by Langroudi *et al* and Mohan *et al,* in studies comparing SPECT-CT with planar imaging in the evaluation

of foot and ankle pathology.[9,10] Images acquired with a 16-slice CT were used in these studies.

Ndlovu *et al* reported a SPECT-CT accuracy of 52% in a study of cancer patients with equivocal lesions on planar bone imaging for skeletal metastases.[11] This study recommended the utilization of SPECT-CT in the evaluation of equivocal lesions in instances where correct classification of lesions is expected to alter the patient's management regardless of the tumor primary or presence of bone pain. The type of CT scanner used in this study was not mentioned.

Report of comparison of planar imaging with SPECT/16-multislice CT (MSCT) among paediatric patients by Andersen *et al*, showed that additional structural information was gained in 93% of the cases and additional nuclear medicine information was gained in 80% of the cases, while specific information for biopsy guidance was gained in 40% of the cases studied.[12]

1.3 Objectives

1. To assess the initial experience with the use of SPECT-guided CT in the evaluation of lesions since the installation of SPECT-CT in the Nuclear Medicine department at Groote Schuur Hospital in 2012.
2. To assess the impact of the addition of 6 slice CT in SPECT-CT on lesion categorization.

3. To assess whether or not, there is significant difference between the use of SPECT alone and fused SPECT-CT in lesion categorization.

1.4 Methods

1.4.1 Study design

The study will involve retrospective evaluation of SPECT-CT examinations performed in the department of nuclear medicine of the Groote Schuur Hospital from April 2012 to December 2013. Currently, there are 139 SPECT-CT scans conducted for diagnostic purposes that are eligible for inclusion into the study. This number is expected to increase to about 200 by December 2013. Therefore, about 200 cases will be included in the study.

1.4.2 Materials

All patients were examined on a stand-alone Symbia T6 SPECT-CT system (Siemens Medical Solutions). Some of the patients were initially scanned on the Siemen's eCam Signature series dual head gamma camera and later transferred to the stand-alone Symbia hybrid SPECT-CT for a SPECT-guided CT acquisition based on lesions found on the initial planar and SPECT images. Examinations will be processed and analyzed on the Siemens physicians' workstations.

1.4.3 Subjects

Patients were referred to the nuclear medicine department for ^{99m}Tc-MDP bone scintigraphy, ^{123}Iodine/^{131}Iodine diagnostic scan, ^{131}Iodine post-therapy scan,

^{123}Iodine metaiodobenzyl guanidine (^{123}I-MIBG) scan, parathyroid scintigraphy, ^{99m}Tc-Octreotide scan for suspected neuroendocrine tumors, infection imaging and sentinel lymph node localization. The original raw SPECT-CT data of patients will be retrieved from the archives and re-processed for analysis.

1.4.4 Inclusion criteria

SPECT examinations conducted between April 2012 and December 2013 that had CT scans performed as result of lesions observed in the initial part of the study as well as studies with clear cut indications for the need to use CT data in order to aid localization.

1.4.5 Exclusion criteria

1. Examinations with poor technical quality
2. Examinations with poor co-registration of the SPECT and CT data
3. All SPECT myocardial perfusion studies
4. All SPECT cerebral perfusion studies

1.4.6 Ethical issues

The study is retrospective in nature and shall involve analysis of routine examinations conducted following protocols derived from already established standard international guidelines on the use of radiopharmaceuticals and SPECT-CT imaging according to the Society of Nuclear Medicine (SNM) and European Association of Nuclear Medicine (EANM).[13–15] The radiation dose to the patient was

not increased at all because no additional imaging was done in the course of the study. Patients' confidentiality will be observed throughout the study by the use of a coding system and in compliance with Helsinki declaration.[16] Patients' names will not be used in the study or the final report at the end of the study.

The patients' data to be used in the study is from the Nuclear Medicine database already registered by the Human Research Ethics Committee of the Faculty of Health Sciences with reference number: R006/2012 (see copy of approval attached, appendix I).

1.4.7 Data collection

The observer is blinded to the history, clinical examinations, laboratory and histology results as well as the previous reports issued. Patients' age and sex will be recorded. The type of nuclear medicine study, images acquired (static planar, SPECT and SPECT-CT) will be retrieved from the archives, re-processed and reviewed. The location and number of lesions observed from the studies as well as level of diagnostic certainty will be recorded. In patients referred for bone scan for malignant disease, the lesions will be categorized successively in separate reading sessions on planar, SPECT and SPECT-CT images using a 3-point scoring system: 1=benign; 2=indeterminate and 3= malignant. An appropriate classification will be used for the remaining types of scans. Lesions will simultaneously be further sub-categorized based on the level of diagnostic certainty, which will be graded on a three-point scale: 1= certain, 2= equivocal and 3= uncertain. (Appendix II).

A time difference of at least 2 weeks in-between the independent interpretations of the planar alone, planar plus SPECT and fused SPECT-CT images will be allowed. A single observer who will be blinded to the previously issued report of the examinations will carry out the interpretations. Comparison will then be made between the final results and the report issued to the referring clinicians, which was interpreted by qualified nuclear medicine physicians and radiologists.

Data will be analyzed for sensitivity, specificity, positive predictive value, negative predictive value and accuracy for planar, planar plus SPECT and SPECT-CT sub-groupings where possible. Comparison will be made between the groups. Assessment will be made of improvements or lack of, on lesion localization, categorization and diagnostic certainty.

1.5 Limitations

The study being retrospective in nature is a limitation.

A single observer will be involved in the study due to time constraints.

Histological validation will not be included in this study.

1.6 Funding

All imaging results to be reviewed were part and parcel of routine patient examinations for treatment. Therefore, no funding is required in this regard. The researcher will personally fund the purchase of the stationaries as well as photocopies and printing of relevant documents required during the study.

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2.0 LITERATURE REVIEW

2.1 Objectives Of Literature Review

The objectives of this study were to assess the initial experience with the use of a new SPECT- CT in the evaluation of lesions; the impact of the addition of 6-slice CT on lesion categorization, and the difference between the use of SPECT alone and fused SPECT-CT in lesion localization and categorization.

The main objective of this literature review is to identify studies on the use of SPECT-CT on lesion categorization as well as its impact on observer's confidence and management outcome.

2.2 Literature search strategy

Internet search of PubMed and Google scholar databases was undertaken. Key phrases searched were single photon emission computerized tomography/computerized tomography AND lesion categorization OR characterization. Studies considered for review include: comparison of SPECT-CT versus SPECT scintigraphy alone, SPECT-CT versus SPECT versus planar scintigraphy, and SPECT-CT in patients with indeterminate lesions on conventional scintigraphy either for benign or malignant conditions.

2.3 Literature

The use of hybrid imaging consisting of Single Photon Emission Computerized Tomography (SPECT) and X-ray transmission Computerized Tomography (CT) scan is increasing globally. This mode of hybrid imaging has the advantage of providing functional and morphologic information for a given lesion or pathology in a single session. SPECT image acquisition improves lesion detection when compared to two-dimensional planar imaging by removing out-of-plane information thereby increasing image contrast.[1] The aim of this literature review is to appraise the available reports on the use of SPECT-CT on lesion categorization as well as review the impact of SPECT-CT on lesion categorization when compared to conventional planar scintigraphy and SPECT imaging.

Radionuclide imaging by the use of SPECT is currently an important component of evaluation of various diseases with a high degree of sensitivity due to its ability to provide functional information early in the disease even before morphological changes become visible on other imaging modalities.[2,3] However, the limited spatial resolution of SPECT necessitated the introduction of X-ray based computerized tomography which has superior spatial resolution and provides morphologic information that helps in better localization of lesions seen on functional and metabolic imaging. This form of hybrid imaging has improved the staging of disease as well as the prognostic and treatment monitoring potentials of the functional and metabolic information provided by conventional nuclear medicine examinations.[4,5]

There is dearth of literature reporting the utility, sensitivity, specificity and accuracy of this imaging technique as it applies to non-skeletal nuclear medicine examinations. This was attributed to slower growth of SPECT-CT when compared to PET-CT.[4]

In a report of initial two-year clinical experience with SPECT-CT by Jacene et al, 54% of the cases studied had additional information for image interpretation derived from the fusion of the SPECT with the CT images mostly as a result of improved localization of abnormal and physiologic SPECT findings by the CT data.[4] This study also reported improved diagnostic certainty in 24% of the cases and beneficial alteration of image interpretation in 13% of the cases. However, some of the limitations reported in this study included the low-resolution single-slice CT used which did not reveal the exact anatomical sites of abnormal radiotracer accumulation especially in the interpretation of abdominal findings on ^{111}In-Pentetreotide scans, as well as the prolonged CT acquisition time of 10-15 minutes by the single-slice scanners that resulted in increased patient motion and degradation of image quality. Prolonged acquisition time has been addressed by the recent introduction of multi-slice CTs in newer versions of the SPECT-CT systems.[5] Therefore, the increasing availability of new hybrid SPECT-CT imaging equipment with advanced technology offers the opportunity to shorten image acquisition time and to provide accurate attenuation correction and image co-registration.

Over the years, the main advantages of hybrid SPECT-CT imaging included accurate localization and characterization of endocrine and neuroendocrine tumors, solitary pulmonary nodules, lung cancers, brain tumors, lymphoma, prostate cancer, malignant and benign bone lesions, sentinel lymph node localization as well as precise definition of the diagnostic and prognostic profile of cardiovascular patients.[5] Hybrid imaging using SPECT-CT can improve the staging, prognostic and treatment-monitoring potential of the functional and metabolic information provided by nuclear medicine tests. Adaptation of the CT field of view to foci of increased bone metabolism in a technique referred to as SPECT-guided CT has been shown to accurately classify previously indeterminate lesions on planar and SPECT imaging in the axial skeleton with certainties of 92% to 100%.[6–8] These studies limited their observations to the evaluation of foci of increased bone metabolism classified as indeterminate on SPECT in cancer patients, therefore inclusion of other systems in the evaluation of the clinical value of SPECT-CT is likely to reveal some of its potentials.

In a retrospective study of 57 SPECT-guided CTs done by Römer *et al.*[7] among cancer patients referred for bone scintigraphy who showed foci of increased metabolism, 52 foci (91%) were classified as indeterminate lesions on SPECT alone. Of these indeterminate SPECT findings, 63% were correlated with benign findings following the application of CT. Majority of these benign findings included osteochondrosis, spondylosis and spondylarthosis of the spine. With the application of CT in this study, 29% of the lesions were categorized as osteolysis or sclerotic

metastasis.[7] Nevertheless, 8% of the lesions still remained indeterminate despite application of CT. These lesions were mainly in the ribs and the scapula. This study was able to clarify more than 90% of the SPECT findings otherwise classified as indeterminate in an analysis that was masked to pretest clinical probability and the planar scan findings.

Strobe *et al.*[8] in a prospective study assessed the performance of planar bone scintigraphy compared with SPECT and SPECT fused with CT in the characterization of focal bone lesions in the axial skeleton. This study evaluated the visibility of lesions, diagnostic performance, certainty in diagnosis and performance for specific diagnoses using histologic, MRI and clinical follow-up findings as reference standards. This study revealed sensitivity and specificity for differentiation of benign and malignant bone lesions were respectively 82% and 94% for planar scintigraphy, 91% and 94% for SPECT, and 100% and 100% for SPECT fused with CT. This study also showed that SPECT fused with CT significantly ($p= 0.004$) increased certainty in diagnosis when compared with planar scintigraphy or SPECT and as such was considered as the best tool for making a specific diagnosis.[8]

In a review by Mohan *et al* on the assessment of the additional value of SPECT-CT amongst patients referred from the orthopaedic clinics, it was observed that when compared with planar imaging, SPECT-CT provided additional information in 81% of the patients.[9] SPECT-CT provided specific diagnosis in 46% of the patients in this series, and more accurate localization of degenerative or post-surgical changes in

the remaining 54% of the patients. This is similar to findings by Langroudi *et al* and Mohan *et al,* in studies comparing SPECT-CT with planar imaging in the evaluation of foot and ankle pathology.[10,11] Images acquired with a 16-slice CT were used in these studies.

Ndlovu *et al* reported a SPECT-CT accuracy of 52% in a study of cancer patients with equivocal lesions on planar bone imaging for skeletal metastases.[12] This study showed significant reduction in proportion of lesions (p= 0.0001) and patients (p=0.0015) with equivocal findings on planar scintigraphy following the utilization of SPECT-CT and therefore, recommended the utilization of SPECT-CT in the evaluation of equivocal lesions in instances where correct classification of lesions is expected to alter the patient's management regardless of the tumor primary or presence of bone pain. The type of CT scanner used in this study was not mentioned.

Recently in a study by Palmedo *et al*.[13] designed to prospectively assess the additional value of SPECT-CT of the trunk used in conjunction with conventional nuclear imaging and its effects on patient management in a large patient series, it was observed that the sensitivities, specificities, and negative and positive predictive values on a per-patient basis were 93%, 78%, 95% and 59% for planar, 94%, 71%, 97% and 53% for SPECT, and 97%, 94%, 97% and 88% for SPECT-CT, respectively. The specificity and positive predictive value were significantly ($p < 0.01$) better with SPECT-CT in all subgroups. SPECT-CT improved diagnostic accuracy for defining the extent of multifocal metastatic disease in 34.6 % of the

patients in this study. Therefore, it was concluded that SPECT-CT had a significant effect on clinical management because of correct down staging and upstaging, better definition of the extent of metastases, and a reduction in further diagnostic procedures.

In a review of the synergistic value of SPECT-CT fusion to radioimmunoscintigraphic imaging (RIS) of prostate cancer, Sodee *et al*.[14] opined that 111In-Capromab Pentetide (ProstaScint) SPECT-CT imaging can be used not only to identify primary, metastatic and prostate cancer recurrence but also to guide external beam radiation therapy (EBRT), intensity modulated radiation therapy (IMRT), and brachytherapy as well as to monitor treatment of the disease. This corroborated the earlier observations by Jana and Blaufox[15] that, there is a possibility of ProstaScint scan in conjunction with CT in a SPECT-CT scanner in increasing the accuracy of this tracer. Kizu *et al.*[16] reported an accuracy of 87.1% after using SPECT and fused multidetector CT images for the localization of pelvic sentinel nodes in 11 patients with prostatic carcinoma. Similarly, Zhang et al reported SPECT-CT to be superior to planar imaging in the detection of SNs in 27 patients with early stage cervical cancer scheduled for radical hysterectomy and total pelvic lymphadenectomy.[17] This was attributed to the exact anatomical localization of the sentinel node.

Report of comparison of planar imaging with SPECT/16-multislice CT (MSCT) among paediatric patients by Andersen *et al*, showed that additional structural information was gained in 93% of the cases and additional nuclear medicine

information was gained in 80% of the cases, while specific information for biopsy guidance was gained in 40% of the cases studied.[18]

In a study by Filippi and Schillaci[19] carried out to assess the usefulness of hybrid SPECT-CT in Tc99m-HMPAO labeled leukocytes scintigraphy for bone and joint infections, SPECT-CT provided accurate anatomic localization of all positive foci and also provided significant additional contribution with regards to the final diagnosis in 10 of the 28 patients (35.7%) studied. SPECT-CT differentiated soft tissue from bone involvement both in patients with osteomyelitis and in patients with orthopaedic implants. It allowed correct diagnosis of osteomyelitis in patients with structural alterations after trauma and identified synovial infection without prosthesis involvement in patients with knee implant. In a similar study using Tc99m-labeled antigranulocyte antibodies Horger *et al.*[20] reported that SPECT-CT improves the accuracy of immunoscintigraphy for the diagnosis of chronic osteomyelitis, especially in discriminating soft tissue from bone involvement.

In the assessment of the incremental value of SPECT-CT versus planar imaging using ^{131}I SPECT-CT in the follow-up of differentiated thyroid carcinoma Spanu *et al.*[21] observed that SPECT-CT correctly characterized 48 foci unclear on planar imaging and also defined the location and extent of these foci. SPECT-CT was a determinant in classifying as neoplastic those foci for which planar imaging seemed to exclude malignancy, discriminating between residue and lymph node metastases in the neck, some of which were adjacent to the salivary glands and had been missed on

planar scintigraphy. This study showed that SPECT-CT had an incremental value over planar imaging in 67.8% of patients, modified therapeutic management in 35.6% of positive cases, and avoided unnecessary treatment in 20.3% of patients with only single benign lesions or physiologic uptake.

Tharp *et al*.[22] also demonstrated that SPECT-CT had an incremental diagnostic value for 58% of the patients studied. SPECT/CT improved the characterization of indeterminate findings as definitely benign in 13% of patients and the precise localization of metastases to the skeleton in 17% of patients, and to the lungs versus the mediastinum in 7% of patients. SPECT-CT further optimized the localization of radioiodine uptake to nodal metastases versus remnant thyroid tissue. Overall, additional findings at SPECT-CT had an effect on management for 41% of patients by influencing referral for ^{131}I treatment, tailoring of the administered radioiodine dose, and/or the addition of surgery or external radiation therapy when indicated. The findings are similar to those by Ruf *et al*.[23] who reported that SPECT-CT correctly classified most radioiodine-avid foci as benign or malignant, provided a superior anatomical localization for 44% of lesions, and modified the therapeutic procedure in 25% of patients.

Krausz and co-workers reported that Tc99m-MIBI SPECT-CT of the parathyroid glands contributed to the localization of parathyroid adenomas in patients with primary hyper-parathyroidism, and to planning the surgical exploration in 39% of patients, predominantly those with ectopic para-thyroid adenomas or who had

distorted neck anatomy.[24] This is in agreement with the findings by Serra *et al*.[25] who examined the role of SPECT-CT in the preoperative assessment of hyperparathyroid patients and reported that SPECT-CT provided additional data in 39% of lesions and modified the surgical approach in 19% of patients with retro-tracheal glands.

Hillel *et al* in a study of 29 patients most of whom had a diagnosis of carcinoid and were referred for ^{111}In-pentetreotide somatostatin receptor imaging (SRI) with SPECT-CT, 64% of the abnormal foci were established to be previously unknown location while SPECT-CT changed the location of at least one lesion in 36% of the cases.[26] This study concluded that the application of SPECT-CT in what was referred as functional anatomic mapping (FAM) can improve the reporting accuracy for SPECT SRI with significant impact on patient management. In a similar study by Castaldi *et al*.[27] involving 54 patients with known or suspected neuroendocrine tumour (NET), SPECT-CT improved image interpretation in 23 cases, provided precise anatomical localization of increased tracer uptake in 20 cases and disease exclusion in sites of physiological uptake in 5 cases. SPECT-CT also allowed definition of the functional significance of lesions detected by diagnostic CT in 10 patients in addition to the modification of clinical management in 14 cases by changing the diagnostic approach in 8 and the therapeutic modality in six. Krausz *et al*, reported that SPECT-CT affected the diagnostic interpretation in 32% of patients with known or suspected NETs and resulted in changes in management in 14% by altering the surgical approach, sparing unnecessary surgery, and/or modifying the

therapeutic modality.[28] Pfannenberg *et al*.[29] reported that, therapy was modified in 28% of patients owing to the results of image fusion: in 5 patients tumor could be excluded, in 3 patients the individuals were spared unnecessary surgery due to detection of additional lesions indicating systemic tumor spread, in 4 patients the surgical approach was modified owing to precise tumor localization and minimization of the surgical field, and in 2 patients medical and radio-peptide therapy was modified.

In the evaluation of the added value of SPECT-CT for the correlation of MIBG scan and diagnostic CT in neuroblastoma and pheochromocytoma, Rozovsky *et al*.[30] reported that SPECT-CT provided additional clinical information in 53% of the cases. SPECT-CT differentiated between bilateral symmetric upper thoracic activity, probably related to physiological muscular or brown fat uptake, and malignant lesions, such as skeletal metastases in the scapula, ribs, or malignant supraclavicular lymphadenopathy.

Lerman *et al*.[31] assessed whether SPECT-CT improves sentinel node identification in overweight patients. In this study, SPECT-CT accurately identified sentinel nodes (SN) in 75% of patients for whom the identification of SNs by the intraoperative blue dye technique failed. Even-Sapir *et al*.[32] and Lerman *et al.*[33] have reported that, SPECT-CT data allowed the detection of ‘‘hot’’ nodes missed by planar imaging, excluded sites of false-positive non-nodal uptake, and accurately localized axillary and extra-axillary hot nodes. These studies also agree with the findings by Husarik

and Steinert[34] who evaluated the clinical use of integrated SPECT-CT in the identification of the sentinel lymph nodes in patients with operable breast cancer. This study showed that localization and identification of sentinel lymph nodes was more accurate by integrated SPECT-CT imaging in comparison with planar images and SPECT images, respectively. SPECT-CT showed more accurate information in 82% of the patients by demonstrating the exact anatomical information needed to assign the SN levels according to the American Joint Committee on Cancer (AJCC). SNs close to the injection sites that were not visible on planar images due to scatter radiation were detected with SPECT/CT in 14% of the patients. This is in agreement with the findings by Even-Sapir et al and Lerman *et al*.[32,33]

Kretschmer *et al* found SPECT-CT to be an excellent tool to anatomically localize the SN in malignant melanoma draining to the pelvic region.[35] Garcia-Burillo *et al*.[36] prospectively assessed the impact of SPECT-CT sentinel lymph node identification in papillary thyroid cancer with respect to lymphatic staging and surgical management improvement. This study showed that, lymphoscintigraphy revealed at least one sentinel lymph node (SLN) in 19 of 24 patients (79 %) on planar and SPECT-CT images, as well as in 23 of 24 patients (96 %) during surgery using a hand-held gamma probe. SPECT-CT detected latero-cervical drainage in a significant percentage of patients, thereby allowing the detection of occult lymph node metastases and improving the surgical management in patients with papillary thyroid carcinoma (PTC). In a similar study Wagner and co-workers evaluated SPECT-CT topographic mapping of SNs before gamma-probe guided biopsy in 30

patients with head and neck squamous cell carcinoma and found that SPECT-CT enhances anatomical orientation and diagnostic sensitivity with more detected SNs than by planar lymphoscintigraphy.[37]

Schillaci O *et al* evaluated the usefulness of RBC SPECT and transmission computed tomography (RBC SPECT-CT) performed simultaneously with a hybrid imaging system for correct characterization of hepatic lesions in patients with suspected haemangioma, and assessed the additional value of fused images compared with SPECT alone. SPECT-CT had a significant impact on results in 33.3% of the patients with four lesions defined as indeterminate on SPECT images, accurately characterizing the hot spot foci located near vascular structures.[38]

The applicability of single photon emission computed tomography-computed tomography (SPECT-CT) in patients with acute lower gastrointestinal bleeding undergoing scintigraphy with ^{99m}Tc-labelled red blood cells (RBC), and assessment of the additional clinical value of fused images when compared to the standard radionuclide scan were evaluated by Schillaci and co-workers.[39] In this study, SPECT-CT had significant impact on the scintigraphic results in 7/19 patients (36.8%), it precisely localized the bleeding foci whose location could not be identified in standard scans in 6 patients, and in one it excluded the presence of an active gastrointestinal hemorrhage.

2.4 Summary

This literature review has shown that fusion of functional information obtained from radionuclide imaging with morphologic information obtained from x-ray computerized tomography has improved lesion localization, characterization and diagnostic accuracy.

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3.0 JOURNAL ARTICLE

(See appendix III for SA Journal of Radiology Author guidelines)

Title: Assessment of the impact of application of single photon emission computerised tomography and SPECT-CT on lesion categorisation in bone scintigraphy.

3.1 Abstract

Objectives: To assess initial experience with the use of a new SPECT-CT in the evaluation of lesions.

Methods: The folder number, radiopharmaceutical used and type of scan of patients examined with a new Siemens T6 SPECT-CT between 2 April and 31 December 2013 were retrieved. The number of ^{99m}Tc-MDP bone scans was sufficient for a detailed analysis. The scans were re-processed and reported by the observer before he was given any clinical information. Whole body planar, whole body planar plus SPECT and whole body planar plus SPECT-CT images were assessed successively in three separate sessions at least two weeks apart. At each session, the certainties of detection, localisation, and categorisation of each lesion were recorded.

Results: A total of 539 lesions were seen on the whole body, SPECT and CT images in 133 patients. The whole body images showed no lesions in three patients and 378 lesions in 130 patients, 117(31%) lesions in areas not covered by the SPECT. SPECT detected 122 additional lesions in 79 patients. Thirty-nine (12.2%) lesions were seen only on CT in 32 (24.1%) patients.

For the 261 lesions seen on the planar images in the SPECT FOV, lesion detection was definite in 233 (89.3%), localisation definite in 151(57.9%) and categorisation definite in 123 (47.1%) lesions. On the SPECT, definite lesion detection, localisation and categorisation were recorded respectively for 259 (99.2%), 228 (87.4%) and 176 (67.4%) of the 261 lesions. Lesion detection, localisation and categorisation certainties were definite for 100%, 99.1% and 94.7% of the SPECT-CT lesions respectively.

Conclusion: Whole body planar scintigraphy is essential in lesion detection. SPECT markedly improves lesion detection and localisation and CT enhances lesion categorisation.

3.2 Introduction

The use of hybrid imaging consisting of Single Photon Emission Computerised Tomography (SPECT) and X-ray transmission Computerised Tomography (CT) scan is increasing globally. It has the advantage of providing functional and morphologic information for a given lesion. Radionuclide imaging has high sensitivity early in the disease before morphological changes become visible on other imaging modalities.[1] The addition of CT provides morphological information with high spatial resolution. The combination of SPECT and CT has improved staging of disease as well as the prognostic and treatment monitoring potentials of the functional and metabolic information provided by conventional nuclear medicine examinations.[2,3]

Over the years, the use of SPECT-CT has been shown to accurately re-classify lesions previously classified as indeterminate on planar and SPECT imaging in both skeletal and non-skeletal nuclear medicine examinations with certainties of 88% to 100%.[4–7] However, the limitations in previous studies included the low-resolution of the CT used which did not reveal the exact anatomical sites of abnormal radiotracer accumulation, and the prolonged CT acquisition time of 10-15 minutes by the dual slice CT scanners that resulted in increased patient motion and degradation of image quality.[8] Prolonged acquisition time and poor spatial resolution have been addressed by the recent introduction of multi-slice CT scanners in newer versions of the SPECT-CT systems.[7,8]

A new SPECT machine integrated with a helical 6-slice CT was installed in the Department of nuclear medicine at Groote Schuur Hospital in March 2012. The objectives of this study were to assess the initial experience with the use of SPECT-guided CT in the evaluation of lesions; the impact of the addition of 6-slice CT in SPECT-CT on lesion categorisation, and the difference between the use of SPECT alone and fused SPECT-CT in lesion localisation and categorisation.

3.3 Methods

Approval for the study was obtained from the Research Ethics Committee of the Faculty of Health Sciences University of Cape Town and Groote Schuur Hospital (Ref 613/2013, see approval in appendix IV). All of the scans were done for diagnostic purposes and the initial reports issued used for patient management.

The folder number, radiopharmaceutical used and type of scan of all patients examined on the new stand-alone Siemens T6 SPECT-CT (Siemens Medical Solutions SW, Erlangen) machine between 2 April 2012 and 31 December 2013 were retrieved from the electronic archives of the Nuclear Medicine Department. SPECT-CTs done for myocardial perfusion and cerebral perfusion were excluded from the analysis. In patients who had multiple studies, only the first study was included. The number of bone scans was deemed sufficient for a detailed analysis.

Each patient had planar whole-body and selected static images. SPECT and subsequently CT images of the region of clinical interest were recorded depending on the abnormalities seen on the initial images or the indication for the study as deemed fit by the supervising Nuclear Medicine registrar or consultant at the time of image acquisition.

Whole body images were acquired using a low energy high-resolution collimator with a matrix size of 256 x 256 and a scan speed of 14cm per second. SPECT images were obtained using a 128 x 128 matrix with 25 seconds per step acquiring 64

projections with 180^0 rotation for each gamma camera head. CT images were acquired using a low dose protocol without intravenous contrast administration. The low dose CT parameters used were: 2.5-30mAs, 120 kV, slice thickness of 1.25-5mm and pitch of 1.2-1.5.

SPECT images were reconstructed using the Flash 3D ordered subset expectation maximization (OSEM) iterative reconstruction algorithm in four subsets and eight iterations, and smoothed with a spatial Gaussian filter 6.0 (FWHM). The CT images were reconstructed using high-resolution reconstruction algorithms (B08s kernel) while the images were viewed using the Siemens B80s kernel, for bone and B31s kernel for soft tissues.

For the purposes of this study, all examinations were re-processed and reported on the Siemens (Syngo VE32B, 2008, Siemens Medical Solutions, SW, Erlangen) and HERMES (version V1.0, 2005, Hermes Medical Systems, Sweden) physicians' workstations. During the reconstruction and review of the images for this study, the observer was blinded to the history, clinical examination findings, laboratory and histology results as well as the previous reports issued. The location and level of diagnostic certainty were recorded for each lesion. A four-point score was assigned for each lesion for the certainty of lesion detection, localisation and categorisation (Table 1). The lesions were assessed successively in separate reading sessions on planar, planar plus SPECT and planar plus SPECT-CT images with at least two weeks

in between the sessions. The information on patient demographics and indications for the study were made available for the observer.

Table 1: Scores for certainty of lesion detection, localisation and categorisation.

Score	Certainty	Description
0	Unknown	Don't know
1	Possible	Might know
2	Probable	Have a good idea
3	Definite	Sure

Data analysis was performed on per lesion and per patient basis. Assessments were made on per lesion and per patient bases for lesion detection, localisation, and categorisation. Analysis of levels of certainty for lesion detection, localisation and categorisation was made for planar, planar plus SPECT and planar plus SPECT-CT.

3.4 RESULTS

Within the period under review, 2 April 2012 to 31 December 2013, 241 SPECT-CT scans were done. The type of scan and radiopharmaceutical used in the 185 studies left after exclusion of 50 follow-up scans, 4 technically poor quality studies and 2 with an incomplete dataset are summarized in Table 2.

Table 2: Distribution of cases according to radiopharmaceuticals.

Radiopharmaceutical	Indication	Number
^{99m}Tc-MDP	Metastatic survey	57
	Musculoskeletal pain	39
	Infection/inflammation	22
	CRPS*	4
	Other	11
	Sub-total Bone scans	133
^{123}I-Sodium iodide	Thyroid carcinoma metastatic survey	21
^{123}I-Sodium iodide	Ectopic thyroid tissue	1
^{131}I-Sodium iodide	Thyroid carcinoma metastatic survey	5
^{131}I-Sodium iodide	Post-therapy metastatic survey	1
^{123}I-mIBG	Evaluation for paheochromocytoma/paraganglioma	3
^{67}Ga-Gallium citrate	Infection/inflammation	7
^{99m}Tc-MIBI	Parathyroid adenoma	4
^{99m}Tc-HMPAO leukocytes	Infection/inflammation	2
^{99m}Tc-Octreotide	Evaluation for neuroendocrine tumours	2
^{99m}Tc-RBC	Evaluation for liver haemangioma/splenic remnant	6
Total		185

*CRPS: complex regional pain syndrome.

The 133 patients referred for ^{99m}Tc-MDP bone scintigraphy comprised 92 (69.2%) females and 41 (30.8%) males with a mean age of 53.3 ± 15.7 years. Majority of the patients were referred for metastatic survey (42.9%), or because of musculoskeletal pain (29.3%) or suspected infection/inflammation (16.5%). A total of 539 lesions were seen on the whole body, SPECT and CT images (Table 3).

Table 3: Lesions detected on ^{99m}Tc-MDP bone scan.

	Lesions	Patients	
	(n=539)	(n=133)	%
Whole body images	**378**	**130[§]**	**97.7**
Outside SPECT FOV	117	64	48.1
In SPECT FOV	261	128	96.2
In CT FOV	197	115	86.5
SPECT images	**383**	**133**	**100**
In CT FOV	279	124	93.2
SPECT-CT images	**318**	**133**	**100**
Both SPECT & CT	171	73	54.9
SPECT only	108	60	45.1
CT only	39	32	24.1

FOV: field of view.
[§]No lesions were seen on the whole body images in three patients.

There were three patients in whom no lesions were seen on the whole body images. SPECT and SPECT-CT were done because of clinical information: one patient was a 49 year old female with breast carcinoma who complains of back pain; the second patient was a 28 year old female with three month history of wrist pain, while the

third patient was a 39 year old female with history of injury to the right knee four weeks prior to presentation. In the remaining 130 patients 378 lesions were detected on the whole body images, 261(69.0%) lesions within the field of view (FOV) of the SPECT images and 117(31%) in areas not covered by the SPECT. SPECT detected a total of 383 lesions in 133 patients, 122 (31.9%) of the lesions were not seen on the whole body images. These additional lesions were detected in 79 patients. SPECT-CT detected 318 lesions in 133 patients, 171 (53.8%) lesions were seen on SPECT and CT, 108 (34.0%) lesions on SPECT only, and 39 (12.2%) lesions on CT only. The 39 additional lesions were detected in 32 (24.1%) patients.

On planar images, lesion detection certainty was definite for 346 (91.5%), probable for 30 (7.9%) and possible for 2 (0.6%) lesions (Table 4). Lesion localisation and categorisation certainties were respectively 63.5% and 53.9% definite, for the lesions detected on the whole body images (Tables 5 and 6).

Table 4: Lesion detection certainty.

Certainty, n (%)	Possible	Probable	Definite	Total
WB images	2(0.6)	30(7.9)	346(91.5)	378 (100)
Planar SPECTFOV	0 (0)	28(10.7)	233(89.3)	261 (100)
SPECT images	0 (0)	2 (0.5)	381(99.5)	383 (100)
SPECT in CTFOV	0 (0)	0 (0)	279(100)	279 (100)
SPECT-CT images	0 (0)	0 (0)	301(94.7)	318 (100)

WB: whole body

Table 5: Lesion localisation certainty.

Certainty, n (%)	Possible	Probable	Definite	Total
WB images	0(0)	138(36.5)	240(63.5)	378 (100)
Planar SPECTFOV	0(0)	110(42.1)	151(57.9)	261 (100)
SPECT images	0(0)	55 (14.4)	328(85.6)	383 (100)
SPECT in CTFOV	0(0)	3 (1.1)	276(98.9)	279(100)
SPECT-CT images	0(0)	3(0.9)	315(99.1)	318(100)

WB: whole body

Table 6: Lesion categorisation certainty.

Certainty, n (%)	Possible	Probable	Definite	Total
WB images	2(0.6)	172(45.5)	204(53.9)	378 (100)
Planar SPECTFOV	2 (0.8)	136 (52.1)	123 (47.1)	261 (100)
SPECT images	0(0)	116 (30.3)	267 (69.7)	383 (100)
SPECT in CTFOV	0(0)	17(6.1)	262(93.9)	279(100)
SPECT-CT images	0(0)	17(5.3)	301(94.7)	318(100)

WB: whole body

For the 261 lesions seen on the planar images in the SPECT FOV, lesion detection was definite in 233 (89.3%), localisation was definite in 151(57.9%) and categorisation was definite in 123 (47.1%) lesions. On the SPECT, definite lesion detection, localisation and categorisation were recorded for 259 (99.2%), 228 (87.4%) and 176 (67.4%) of the 261 lesions respectively (Table 7).

Table 7: Certainty scores for planar lesions seen on SPECT.

Certainty, n (%)	Possible	Probable	Definite	Total
Detection	0(0)	2 (0.8)	259 (99.2)	261 (100)
Localisation	0(0)	33 (12.6)	228 (87.4)	261 (100)
Categorisation	0(0)	85 (32.6)	176 (67.4)	261 (100)

On SPECT, out of the 383 lesions detected the certainty of lesion detection, localisation and categorisation were definite for 381 (99.5%), 328 (85.6%) and 267 (69.7%) lesions respectively. For the 279 SPECT lesions seen in the CT FOV in 124 patients the lesion detection, localisation and categorisation was definite in 279 (100%), 276 (98.9%) and 262 (93.9%) lesions respectively.

Lesion detection certainty was definite for all the 318 (100%) SPECT-CT lesions, while lesion localisation and categorisation certainties were definite in 99.1% and 94.7% of the lesions respectively.

Of the 42 lesions categorised as indeterminate on planar, 20/42 (47.6%) and 35/42 (83.3%) were re-categorized following the addition of SPECT and SPECT-CT respectively (Table 8). There were 78 (39.6%), 88 (44.7%) and 93 (47.2%) lesions categorised as degenerative on planar, planar plus SPECT and planar plus SPECT-CT respectively.

Table 8: ^{99m}Tc-MDP scintigraphy categorisation of lesions in CT FOV.

Lesion category	Planar alone n (%)	Planar + SPECT n (%)	Planar + SPECT-CT n (%)
Indeterminate	42 (21.3)	22 (11.2)	7 (3.6)
Metastasis	16 (8.1)	19 (9.6)	17 (8.6)
Degenerative	78 (39.6)	88 (44.7)	93 (47.2)
Infection/Inflammation (Bone/Joints)*	47 (23.9)	49 (24.9)	51 (25.9)
Infection/Inflammation (Soft tissues)**	1 (0.5)	2 (1.0)	2 (1.0)
Others***	13 (6.6)	17 (8.6)	27 (13.7)
Total	197 (100)	197 (100)	197(100)

* Arthritis, Charcot's, osteomyelitis, discitis, arthropathy, spondylosis, enthesopathy, pseudoarthrosis.
** Cellulitis, adenopathy.
*** Fracture, non-union, malunion, haemangioma, avascular necrosis, enchondroma, CRPS, prosthetic loosening, Heterotropic calcifications, dislocation/subluxation

3.5 Discussion

This study reports the initial experience with new multi-slice SPECT-CT scanner and the impact of the addition of SPECT with low dose CT in the evaluation of lesions in patients referred for ^{99m}Tc-MDP bone scintigraphy.

The need to perform planar whole-body imaging prior to SPECT image acquisition is demonstrated in this study by the finding of 31% of lesions in areas not covered by the SPECT. This is in addition to the fact that, on planar images, the detection of more than 91% of the 378 lesions seen was certain. These findings underscore the role of whole-body planar scintigraphy as the mainstay for the detection of skeletal metastases for more than 40 years.[9,10] Therefore, these findings emphasize the value of performing planar whole body images before proceeding with SPECT and subsequently SPECT-CT image acquisition.

This study shows that SPECT not only improved the ability of radionuclide imaging to detect lesions by revealing 31% more lesions, it also increased observer's confidence regarding lesion localisation. This is in agreement with earlier reports that showed SPECT is more sensitive than planar in detecting and localising lesions, particularly vertebral lesions with a 20%-50% increase in lesion detection.[1,11,12] The addition of SPECT has been shown to increase the accuracy of lesion categorisation by improving localisation, especially in complex skeletal structures such as spine, skull and pelvis.[1,13] In this study, the addition of SPECT has markedly improved the observer's confidence with regards to lesion detection, localisation and

categorisation by increasing certainty from 89.3% to 99.2%, 57.9% to 87.4% and 47.1% to 67.4% respectively when compared with planar imaging.

The addition of CT detected 39 more lesions in 24% of the patients while SPECT-CT markedly increased the interpreter's confidence with respect to lesion localisation and categorisation from 85.6% to 99.1% and 69.7% to 94.7% respectively in comparison to SPECT and planar images. This agrees with the reports from other studies.[2,4–7,14,15] In addition, some of these studies reported marked reduction of indeterminate lesions from a rate of between 48% and 72% using whole-body planar scintigraphy with or without SPECT, to a rate between 0% and 15%.[4–6] The current study showed a reduction in the indeterminate lesion rate among patients referred for ^{99m}Tc-MDP bone scintigraphy from 21.3% on planar alone to 11.2% and 3.6% following the addition of SPECT and SPECT-CT respectively. While the proportion of SPECT-CT indeterminate lesions is similar to that found in the study reported by Palmedo et al[15], the lower rate found on the planar images in the current study may be due to the criteria used when referring patients for scintigraphy.

The CT component of the hybrid imaging SPECT-CT systems can assist in the diagnosis of benign skeletal findings, such as osteophytes or degenerative changes, or haemangiomas causing abnormal tracer uptake in patients referred for metastatic survey. However, it is important to note that foci of increased tracer uptake on bone scintigraphy due to metastatic bone lesions may not show any

morphologic abnormality on CT. Likewise lytic bone lesions with increased tracer uptake on bone scintigraphy may only be visualised on CT after they have destroyed 50-75% of the trabecular bone.[1,3,4,11] Therefore under these circumstances the lack of anatomical abnormalities despite abnormal tracer uptake suggests medullary disease, hence the need to have the SPECT-CT images. Improved lesion categorisation on SPECT-CT makes a difference with regards to patient management decisions especially in patients referred for skeletal survey for metastases or musculoskeletal pain in patients with known malignancy.[4–7,11,15]

Some of the limitations of this study include the retrospective nature of the study as well as the lack of an independent standard such as histological correlation, or, clinical or imaging follow-up.

In conclusion, this study has shown that whole body planar scintigraphy is essential in lesion detection while SPECT improves lesion detection and observer's confidence regarding lesion localisation. The use of SPECT-CT showed marked impact on lesion categorisation as well as improved observer's confidence.

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CT for bone scintigraphy: diagnostic value and effect on patient management in oncological patients. Eur J Nucl Med Mol Imaging. 2014; 41(1):59-67.

APPENDIX I

DATABASE APPROVAL

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

20 November 2012

REF NO: R006/2012

Dr T Kotze
Nuclear Medicine
C3
NGSH

Dear Dr Kotze

PROJECT TITLE: *NUCLEAR MEDICINE DATABASE*

Thank you for registering your database with the Health Sciences Human Research Ethics Committee.

The HREC has approved the registration of your database.

Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

The registration of this database is valid until **30 November 2015.**

Please provide the HREC with an update if the database continues beyond this period.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

S Thomas

APPENDIX II

DATA SHEET

FOLDER NUMBER…… DATE……..

STUDY SERIAL NUMBER……..

PLANAR ☐
PLANAR + SPECT ☐
SPECT+CT ☐

Technical quality:
Good ☐
Sub-optimal/Inadequate ☐
Poor ☐

Total number of lesions……..

No.	Certainty	Position	Certainty	Characteristics	Categorization	Certainty

Lesion certainty: 0=unknown, 1=possible, 2=probable, 3=definite

APPENDIX III

SA JOURNAL OF RADIOLOGY AUTHOR GUIDELINES

Structure and style of your original research article

The page provides an overview of the structure and style of your original research article to be submitted to the *SA Journal of Radiology*. The original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal presented according to a clear and well-structured format (3000 words or less with up to 10 illustrations and a maximum of 15 references).

Please use British English, that is, according to the Oxford English Dictionary. Avoid Americanisms (e.g. use 's' and not 'z'). Consult the Oxford English Dictionary when in doubt and remember to set your version of Microsoft Word to UK English.

- **Language:** Manuscripts must be written in British English.
- **Line numbers:** Insert continuous line numbers.
- **Font:**
  - **Font type:** Palatino
  - **Symbols font type:** Times New Roman
  - **General font size:** 12pt
- **Line spacing:** 1.5
- **Headings:** Ensure that formatting for headings is consistent in the manuscript.
  - First headings: normal case, bold and 14pt
  - Second headings: normal case, underlined and 14pt
  - Third headings: normal case, bold and 12pt
  - Fourth headings: normal case, bold, running-in text and separated by a colon.

Our publication system supports a limited range of formats for text and graphics. Text files can be submitted in the following formats only:

- Microsoft Word (.doc): We cannot accept Word 2007 DOCX files. If you have created your manuscript using Word 2007, you must save the document as a Word 2003 file before submission.
- Rich Text Format (RTF) documents uploaded during Step 2 of the submission process. Users of other word processing packages should save or convert their files to RTF before uploading. Many free tools are available that will make this process easier.

For full details on how to ensure your manuscript adheres to the house style, **click here**.

The structure and style of your original article

Page 1

The format of the **compulsory cover letter** forms part of your submission and is on the first page of your manuscript and should always be presented in English. You should provide all of the following elements:

- **Article title:** Provide a short title of 50 characters or less.
- **Significance of work:** Briefly state the significance of the work being reported on.
- **Full author details:** Provide title(s), full name(s), position(s), affiliation(s) and contact details (postal address, email, telephone and cellular number) of each author.
- **Corresponding author:** Identify to whom all correspondence should be addressed to.
- **Authors' contributions:** Briefly summarise the nature of the contribution made by each of the authors listed.
- **Summary:** Lastly, a list containing the number of words, pages, tables, figures and/or other supplementary material should accompany the submission.

Page 2 and onwards

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- **Background:** *Why is the problem important to us?* State the context and purpose of the study (that is, mention what practical, scientific or theoretical gap your research is filling).
- **Objectives:** *What problem are you trying to solve*? What is the scope of your work (is it a generalised approach or for specific situation)? Be careful not to use too much jargon.
- **Method:** *How did you go about solving or making progress on the problem*? How was the study performed and which statistical tests were used (what did you actually do to get the results)? Clearly express the basic design of the study, name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- **Results:** *What is the answer*? State the main findings. (As a result of completing the above procedure or study, what did you learn, invent or create?) Identify trends, relative change or differences on answers to questions.
- **Conclusion:** *What are the implications of your answer*? Briefly summarise any potential implications (e.g. the larger implications of your findings, especially for the problem or gap identified in your motivation).

Do not cite references in the abstract and do not use abbreviations excessively in the abstract.

The following headings serve as a guide for presenting your research in a well-structure format. As an author you should include all first level headings but subsequent headings (second and third level headings) can be changed.

Introduction (first-level heading): The introduction contains two subsections, namely the background section and the literature review.

- **Problem statement (second-level heading):** The problem statement, also referred to as the setting section, should be written from the viewpoint of readers, that is, without specialist knowledge in that area. This statement must clearly state and illustrate the introduction to the research and its aims in the context of previous work bearing directly on the subject. The setting section to the article normally contains the following five elements:

- **Key focus (third-level heading):** A thought-provoking introductory statement on the broad theme or topic of the research.
- **Background (third-level heading):** Background or the context to the study (explaining the role of other relevant key variables in this study).
- **Trends (third-level heading):** The most important published studies previously conducted on this topic or that has any relevance to this study (provide a high-level synopsis of the research literature on this topic).
- **Objectives (third-level heading):** Indicate the most important controversies, gaps and inconsistencies in the literature that will be addressed by this study. In view of the above trends, state the core research problem and specific research objectives that will be addressed in this study and provide the reader with an outline of what to expect in the rest of the article.
- **Contribution to field (third-level heading):** Explanation of the study's academic (theoretical and methodological) or practical merit and/or importance (provide the value-add and/or rationale for the study).

Literature review (second-level heading): The literature review is the second subsection under the Introduction and provides a brief and concise overview of the literature under a separate second-level heading, e.g. literature review. A synthesis and critical evaluation of the literature (not a compilation of citations and references) should at least include or address the following elements (ensure these are in the literature review):

- definitions of all conceptual (theoretical) key concepts
- a critical review and summary of previous research findings (theories, models, frameworks, etc.) on the topic
- a clear indication of the gap in the literature and for the necessity to address this void
- a clearly established link that exists between formulated research objectives and theoretical support from the relevant literature.

Research method and design (first-level heading): The methods should include:

- **Materials (second-level heading):** Describe the type of organism(s) or material(s) involved in the study.
- **Setting (second-level heading):** Describe the site and setting where your field study was conducted.
- **Design (second-level heading):** Describe your experimental design clearly, including a power calculation, if appropriate. Note: additional details can be placed as an online supplementary addendum.
- **Procedure (second-level heading):** Describe the protocol for your study in sufficient detail (with a clear description of all interventions and comparisons) so that other scientists could repeat your work to verify your findings.
- **Analyses (second-level heading):** Describe how the data were summarised and analysed, with additional details placed in the online supplementary information.

Results (first-level heading): This section provides a synthesis of the obtained literature grouped or categorised according to an organising or analysis principle.

Tables may be used or models may be drafted to indicate key components of the results of the study.

- Organise the results based on the sequence of tables and figures that you will include in the manuscript.
- The body of the Results section is a text presentation of the key findings, which includes references to each of the tables and figures.
- Statistical test summaries (test name, p-value) are usually reported parenthetically (that is, inserted as a parenthesis in brackets) together with the biological results they support; use SI unit.
- Present the results of your experiment(s)/research data in a sequence that will logically support (or provide evidence against) the hypothesis or answer the question that was stated in the Introduction.

All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Ethical considerations (first-level heading): Articles based on the involvement of humans have been conducted in accordance with relevant national and international guidelines. Approval must have been obtained for all protocols from the author's institutional or other relevant ethics committee and the institution's name and permit numbers should be provided at submission.

- **Potential benefits and hazards (second-level heading:** What risks to the subject are entailed in involvement in the research? Are there any potential physical, psychological or disclosure dangers that can be anticipated? What is the possible benefit or harm to the subject or society as a result of their participation or from the project as a whole? What procedures have been established for the care and protection of subjects (e.g. insurance, medical cover) and the control of any information gained from them or about them?
- **Recruitment procedures (second-level heading):** Was there any sense in subjects being obliged to participate – as in the case of students, prisoners, learners or patients – or were volunteers being recruited? If participation was compulsory, the potential consequences of non-compliance must be indicated to subjects; if voluntary, entitlement to withdraw consent must be indicated as well as when that entitlement lapses.
- **Informed consent (second-level heading):** Authors must include how informed consent was handled in the study.
- **Data protection (second-level heading:** Authors must include in detail the way in which data protection was handled.

Trustworthiness (first-level heading): This refers to the findings of the study being based on the discovery of human experience as it was experienced and observed by the participants.

- **Reliability (second-level heading):** Reliability is the extent to which an experiment, test, or any measuring procedure yields the same result on repeated trials. Without the agreement of independent observers able to replicate research procedures, or the ability to use research tools and procedures that yield consistent measurements, researchers would be unable to satisfactorily draw conclusions, formulate theories, or make claims about their research' ability to be generalised.
- **Validity (second-level heading):** Validity refers to the degree to which a study accurately reflects or assesses the specific concept that the researcher is attempting to measure. While reliability is concerned with the accuracy of the actual measuring instrument or procedure, validity is concerned with the study's success at measuring what the researchers set out to measure. Researchers should be concerned with both external and internal validity. External validity refers to the extent to which the results of a study are generalisable or transferable. Internal validity refers to:
  - the rigor with which the study was conducted (e.g. the study's design, the care taken to conduct measurements, and decisions concerning what was and wasn't measured).
  - the extent to which the designers of a study have taken into account alternative explanations for any causal relationships they explore.

In studies that do not explore causal relationships, only the first of these definitions should be considered when assessing internal validity.

Discussion (first-level heading): This section normally contains the following four elements. It is suggested that subheadings are used in this section:

- **Outline of the results (second-level heading):** Restate the main objective of the study and reaffirm the importance of the study by restating its main contributions; summarise the results in relation to each stated research objective or research hypothesis; link the findings back to the literature and to the results reported by other researchers; provide explanations for unexpected results.
- **Practical implications (second-level heading):** Reaffirm the importance of the study by restating its main contributions and provide the implications for the practical implementation your research.

Limitations of the study (first-level heading): Point out the possible limitations of the study and

APPENDIX IV

RESEARCH ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 552-24 Old Main Building
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04 October 2013

HREC REF: 613/2013

Dr G H Yunusa
c/o Dr A Brink
Radiation Medicine
CB, Nuclear Medicine
NGSH

Dear Dr Yunusa

PROJECT TITLE: ASSESSMENT OF THE IMPACT OF THE APPLICATION OF SINGLE PHOTON EMISSION COMPUTERIZED TOMOGRAPHY (SPECT) AND SPECT-CT ON LESION CATERGORIZATION

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th October 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB0001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Conference on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312