

REVIEW ARTICLE

The role of general nuclear medicine in breast cancer

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Abstract

The rising incidence of breast cancer worldwide has prompted many improvements to current care. Routine nuclear medicine is a major contributor to a full gamut of clinical studies such as early lesion detection and stratification; guiding, monitoring, and predicting response to therapy; and monitoring progression, recurrence or metastases. Developments in instrumentation such as the high-resolution dedicated breast device coupled with the diagnostic versatility of conventional cameras have reinserted nuclear medicine as a valuable tool in the broader clinical setting. This review outlines the role of general nuclear medicine, concluding that targeted radiopharmaceuticals and versatile instrumentation position nuclear medicine as a powerful modality for patients with breast cancer.

Introduction

Worldwide, breast cancer is the most common cancer in women with ~1.68 million newly diagnosed cases in 2012.¹ Estimated incidence is increasing worldwide and reported highest in developed countries such as the United Kingdom (UK) and the United States of America (USA), with a notable increase in both Australia and New Zealand.¹ Many factors such as genetic predisposition; prior personal or familial history of breast or other cancers; endogenous (lifetime cycle of oestrogen levels) and exogenous (hormone replacement therapy) hormone levels; and age (age of greatest risk is between 40 and 59 years old in the USA) predispose women to a higher lifetime risk.² Modifiable environmental and lifestyle factors such as excessive alcohol consumption, obesity and physical inactivity have also contributed to increased risk of and death from breast cancer.^{1,2} Mortality attributed to breast cancer is currently the second leading cause of death for women in developed regions.¹

Globally, a 20% increase in frequency and 14% rise in mortality since 2008 support clinical approaches that both mitigate risk and increase early detection and treatment.¹ In the latter, tailored management using a multimodality approach is readily achievable when incorporating nuclear medicine technology in the diagnostic plan. Developments in instrumentation such as the high-resolution dedicated breast device coupled with the diagnostic versatility of conventional cameras have reinserted nuclear medicine as a valuable tool in the broader clinical setting. This review outlines the critical role of general nuclear medicine in the care of women with breast cancer including detection and stratification (malignant vs. benign), guiding treatment using sentinel node imaging, monitoring cardiotoxicity from therapeutic regimens and evaluating local and global progression or recurrence. In addition, a brief overview describing the role of positron emission tomography/computed tomography (PET/CT) is discussed.

Scintimammography

Scintimammography provides non-invasive *in vivo* characterisation of malignant from benign processes and is best used in clinical scenarios where the mainstay anatomic modalities mammography and ultrasound are limited.^{3,4} Targeted uptake improves diagnostic integrity and decreases the rate of false-positives commonly seen in anatomical imaging which, in turn, reduces unnecessary invasive procedures and biopsies.^{5–7} Technetium-99m (Tc-99m) sestamibi is the radiopharmaceutical of choice for single-photon studies in breast imaging due in part to an overall tumour to background ratio of 6:1.^{3,8,9} The recommended administered dose range is 740–1100 MBq (20–30 mCi), resulting in an absorbed dose between 40.0 and 55.5 mGy to the large intestine (critical organ), 20 mGy to the kidney, bladder wall, and gallbladder wall each, and 2 mGy to the breast (lowest dose).¹⁰ An effective dose (a summed entire body exposure estimate that is weighted based on tissue radiosensitivity) was estimated to be 5.9–9.4 mSv compared to 0.44 mSv for digital mammography.¹⁰ As much as 90% of Tc-99m sestamibi dose is localised to the dense mitochondria characteristic of malignant cells, with uptake dependent on regional blood flow, tumour angiogenesis, increased metabolism and driven by plasma membrane potentials and mitochondrial membrane potentials.^{9,11–14} Tumour efflux of Tc-99m sestamibi has been correlated with cellular expression of P-glycoprotein, a protective transmembrane protein pump found in cells that over-express the multi-drug resistant gene.¹¹ These findings are clinically relevant as Tc-99m sestamibi can provide an *in vivo* prediction of anticancer drug efficacy.^{11,13} Moreover, faster rates of Tc-99m sestamibi efflux have been associated with higher levels of P-glycoprotein expression.¹¹

Uptake of Tc-99m sestamibi may be non-specific, for example, in sites of prior surgical intervention or inflammation, and as such increased perfusion to these sites may result in false-positives.^{9,12,15–17} False-positive uptake has also been associated with benign diseases such as hyper-proliferative breast disease and atypical hyperplasia.¹⁸ A higher predilection towards malignant transformation has been demonstrated with both pathologies, speculating that a false-positive finding in these patients may reflect premalignant potential.^{18,19}

Nuclear medicine scintimammography employs a wide range of instrumentation applications. In recent years, conventional planar scintimammography has been enhanced by single-photon emission computed tomography (SPECT) and hybrid SPECT/CT.²⁰ Hybrid SPECT/CT adds clinical value by co-registering physiologic with anatomical data to assist non-palpable

lesion biopsies, radiotherapy planning and treatment follow-up.^{20,21} Dedicated small field of view (FOV) breast-specific gamma imaging (BSGI) devices have also emerged internationally.^{17,22–24}

For both scintimammography and BSGI, planar (anterior, lateral, oblique) orientations are obtained 5–15 min post-injection.^{3,5,10} Lateral and oblique images are acquired as the patient lies prone with pendent breasts while supine positioning is employed for anterior, oblique and SPECT tomographic acquisitions.¹⁰ Image acquisition in both positions is preferred.¹⁰ Prone positioning better separates breast tissue from high radiopharmaceutical uptake in the myocardium and liver improving visualisation of breast activity by reducing photon scatter and improving image contrast.¹⁰ Additionally, enhanced evaluation of the chest wall, better outline of the breast contour and improved spatial resolution (decreasing breast to camera distance) are advantages of the prone position. Supine positioning improves visualisation of primary lesion and internal mammary or axillae involvement.^{10,17} Analogous to mammography, BSGI obtains two 10-min images in the craniocaudal and mediolateral oblique orientations per breast.⁹

Of great importance to patient diagnosis and prognosis is breast lesion size and palpability as small non-palpable lesions often indicate early disease. Characterising mammographically non-palpable and *probably benign* lesions as metabolically benign could obviate the need for a difficult biopsy procedure and instead support clinical observation.⁶ Conversely, given the high specificity of scintimammography, a positive scintigraphic finding would support recommending an invasive evaluation.⁶ While multiple studies confirmed the dedicated camera design combined with breast positioning during BSGI provided better detection of sub-centimetre and non-palpable lesions compared to scintimammography,^{21,25–28} overall sensitivity and specificity was 82% and 85%, respectively, showing no improvement over SPECT, which was 86% and 87% respectively.²⁹

Indeed, the dedicated camera design of BSGI is highly sensitive for detecting local disease, but is limited in the broader clinical setting compared to planar, SPECT, and SPECT/CT cameras that can investigate regional, axial and global disease. For example, SPECT scintimammography allows simultaneous tomographic evaluation of axial lymph node involvement.^{7,25} A study assessing 80 confirmed breast cancer participants for nodal involvement highlighted an overall specificity of 97.5% and sensitivity of 85% using SPECT.⁷ At present BSGI does not allow accurate detection of axial lymph node involvement.²⁵ Moreover, when available, a dual acquisition protocol (planar and SPECT) further enhances the diagnostic value of scintimammography as illustrated

in a study investigating the value of scintimammography in inconclusive triple diagnosis (mammography, ultrasound and fine-needle aspiration). Mathieu *et al.*³⁰ showed planar had higher specificity compared to SPECT (79.5% vs. 67%), but the addition of a SPECT acquisition detected 20% more lesions than planar alone. Additionally in this cohort, SPECT-altered patient management in 49% of cases, 51% of whom received a cancer diagnosis suggesting SPECT may also have an impact on mortality rates.³⁰

Sentinel Lymph Node Scintigraphy

The most important prognostic factor for newly diagnosed patients with invasive breast cancer is axillary nodal bed status, a characterisation that is also critical for determining appropriate treatment.^{31–33} Imaging modalities are generally neither sensitive nor specific for axillary staging and so nodal involvement must be explored surgically.^{31,32} Introduced as a less invasive alternative to traditional staging methods that often increase morbidity like axillary lymph node dissection (ALND), determining sentinel lymph node status via biopsy (SLNB) can predict nodal involvement with high accuracy.^{31,33–35} Because the sentinel node is the initial relay receiving lymphatic drainage directly from the tumour, a histopathologically negative sentinel node implies that the ipsilateral nodal bed is free from metastatic disease.³³ Sparing the healthy nodal bed reduces both cost³⁶ and common comorbidities associated with ALND.^{31,37} An axillary recurrence rate of 0–2% is associated with negative sentinel node status.³³

Nuclear medicine planar (dynamic or static) and/or SPECT/CT sentinel node imaging using radiolabelled colloids provide surgeons with a visual map to guide accurate localisation of sentinel nodes and atypical drainage patterns.^{31,38,39} Identification of the sentinel node is crucial to the success of SLNB and with a detection rate between 94% and 100% preoperative sentinel node imaging is ideally suited for this purpose.^{34,37,38,40–42} For patients with multicentric and multifocal disease whose lymphatic drainage patterns may vary, sentinel node imaging and SPECT/CT of all tumours may provide a more accurate approach to map and biopsy sentinel nodes for staging.⁴³

Radiocolloid injection techniques vary and include periareolar (Fig. 1), peritumoural, subdermal, subareolar, intradermal, intratumoural and subtumoural.^{34,44,45} The two most common injection sites are periareolar (superficial) by means of the richly lymphatic subareolar plexus, which generate quick visualisation of the drainage channels with high target count rates; or peritumoural (deep), which can trace accessory drainage patterns,

specifically the intra-mammary chain seen in ~20–30% of patients.^{31,34,45–48} Evidence suggests the injection site is considered somewhat versatile because time-to-visualisation rates are apparently influenced rather than false-negative rates.^{34,44} Literature also suggests variable lymphatic drainage patterns affect the ability to predict which lymphatic vessels would drain the tumour and thus should be considered when choosing an injection technique.⁴⁶ As a precaution, it can be debated that an injection in proximity to the primary tumour would best represent true lymphatic physiology.^{45,46} Identifying all possible lymphatic drainage patterns is critical to patient care and justifies the current trend towards peritumoural versus periareolar injections.^{34,45,47}

Lymphatic transport of radiocolloid particles after injection can be influenced by particle size and dose concentration. Adequate lymphatic migration of large colloid particles is hindered by their size often resulting in either delayed visualisation or non-visualisation of axillary sentinel nodes.^{44,49} Conversely, particles that are very small rapidly migrate and may not remain trapped in the sentinel node.^{44,49} Solvent volumes should be adjusted to injection technique so that lymphatic physiology is accurately represented. For example, smaller volumes are more suitable for peritumoural injections as increased pressure may cause leakage into the extravascular space that may then travel to adjacent lymphatic channels.^{44,46}

Planar acquisitions (Fig. 1) consistently provide preoperative sentinel node mapping⁵⁰ and the addition of multimodality SPECT/CT further enhances this role. Oriented SPECT/CT slices offer surgeons precise anatomic localisation of nodal uptake, reducing the duration of the surgical procedure and improving biopsy accuracy (Fig. 2).^{41,46,49} Evidence also showed SPECT/CT can identify difficult to interpret drainage patterns and sentinel nodes not visualised on planar (such as parasternal nodes), which limits blind exploratory surgery.^{50,51} Patient positioning and acquisition parameters are crucial for accurate visualisation of lymphatic drainage patterns and marking sentinel nodes. Patient images, patient markings, and an audible gamma probe collectively aid surgeons in intraoperative identification of the radioactive sentinel node or nodes for excision.⁴⁶

Tc-99m Multigated Radionuclide Angiography

It is well documented across cancer research that the use of multidrug chemotherapy induces cardiac abnormalities and requires routine monitoring of left ventricular ejection fraction.^{52–54} Among the rapidly increasing

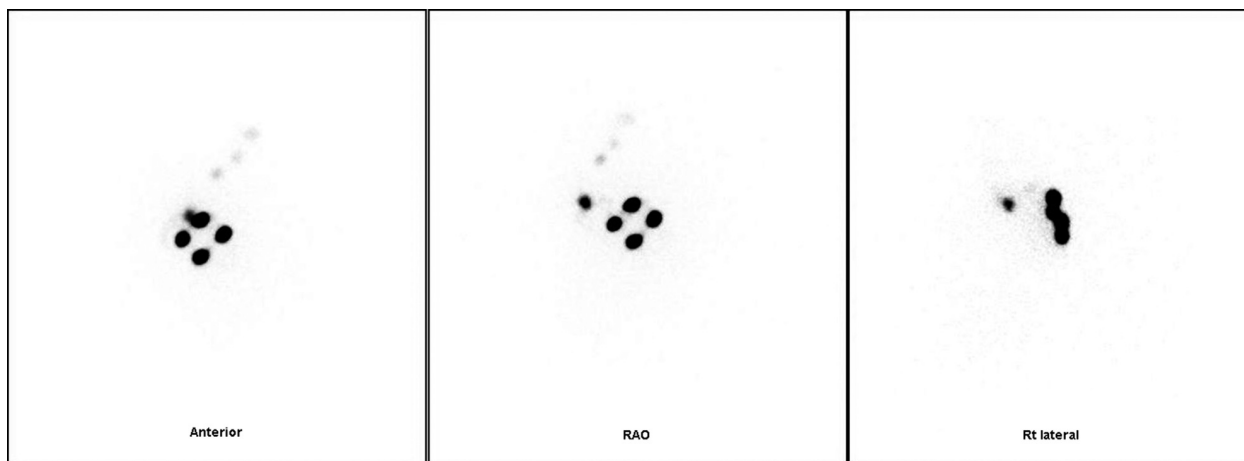


Figure 1. Sentinel node localisation study of the right breast showing four periareolar radiopharmaceutical injections oriented on anterior, right anterior oblique (RAO) and right lateral planar images. An intense focal uptake lateral to the injection sites is identified as well as faint uptake in three axillary lymphatic chain nodes. Image courtesy of Regional Imaging, a member of I-MED Network Radiology, Wagga Wagga, NSW.

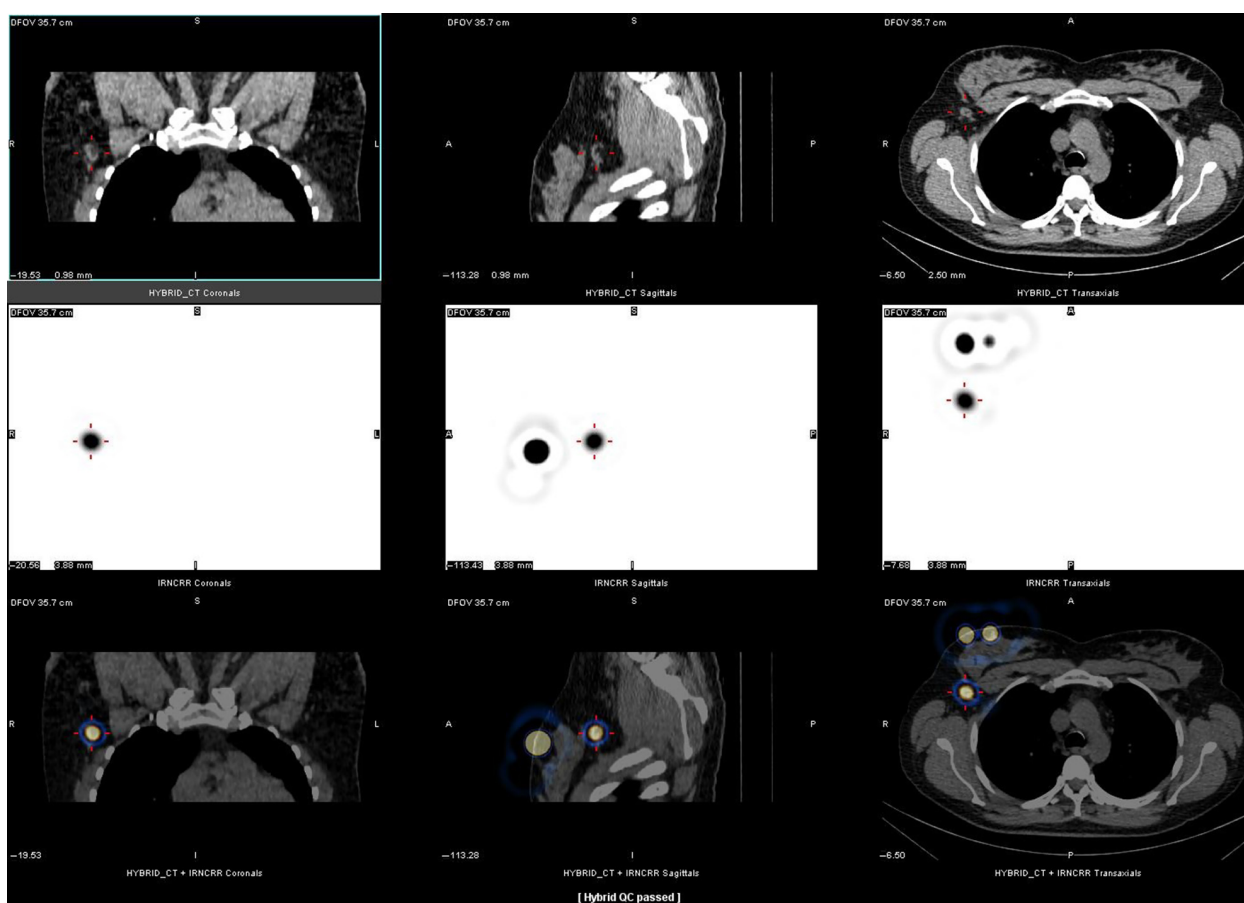


Figure 2. Fused SPECT/CT images provide surgeons with a more accurate anatomical visualisation of the sentinel node with regard to the breast and axilla by depicting the precise location in the axillary area adjacent to the first and second rib saving valuable intraoperative time and increasing surgical confidence. SPECT, single-photon emission computed tomography. Image courtesy of Regional Imaging, a member of I-MED Network Radiology, Wagga Wagga, NSW.

variety of anti-cancer drugs used in breast cancer treatment, the anthracyclines and the monoclonal antibody trastuzumab, are the agents with well-known cardiotoxicity.^{53,55} Anthracycline chemotherapy causes cumulative dose-dependent cardiotoxicity with direct and irreversible cellular damage to myocytes, which can result in congestive heart failure and even cardiac death.⁵² Trastuzumab can induce high cardiotoxicity rates particularly when combined with anthracyclines.^{52,54,56,57} Additionally, radiation therapy and chemotherapy drugs are pericardial irritants and as such increase the risk of pericardial effusion complications, making early diagnosis critical to decrease primary or contributory associated deaths seen in ~86% of symptomatic cancer patients.^{52,54} Radiation-induced heart disease such as coronary artery disease, valvular disease, constructive pericarditis and myocardial dysfunction including congestive heart failure can significantly limit a patient's quality of life.^{52,53,58} Thus, it is imperative to effectively ascertain the extent of a patient's risk for a cardiac event. The standard method to detect cardiotoxicity and pericardial effusions is acquiring ejection fraction measurements performed prior to and post-chemotherapy treatment in breast cancer patients.⁵⁹ Serial evaluation allows clinicians to monitor the patient's cardiac response to treatment reducing the risk of chemotherapy-induced comorbidities.

Multigated radionuclide angiography (RNA) or equilibrium radionuclide angiocardigraphy (ERNA) is regarded as the gold standard to measure cardiac function with high reproducibility and low inter-observer variability in patients undergoing chemotherapy.^{59,60} RNA is a non-invasive technique that uses Tc-99m pertechnetate-erythrocyte labeling to assess regional and global wall motion, ventricular systolic and diastolic function (both right and left ventricular ejection fractions), and ventricular volumes. Red blood cell labeling with Tc-99m pertechnetate is performed using *in vivo*, *in vitro*, or modified *in vivo* methods as described in the literature.^{56,59} For any given clinical situation, the selection of a blood pool agent will depend on the acceptable level of image quality, requirements for patient throughput, and the level of expertise of the technical staff. Patient acceptance may also influence product selection. For example, some patients may refuse *in vitro* labelled red blood cells based on religious beliefs regarding transfusions.⁶¹

Following radiopharmaceutical administration, planar, SPECT or combination acquisitions are obtained.⁶² To visualise all left ventricular wall segments, positioning for planar acquisition includes anterior, lateral, and left anterior oblique (LAO) views with a caudal tilt to best isolate the left ventricle from the left atrium and facilitate accurate processing.^{53,56} Using electrocardiogram leads, images are simultaneously registered with the patient's

gated heartbeat to evaluate regional left ventricular wall motion and contractility.⁵⁹ The final result is a series of cine images of the heart that provide a map of sequential contractions or phase imaging to precisely quantify left ventricular volume and visually assess dyssynchrony.⁵⁹ The addition of a SPECT-gated technique acquires serial three-dimensional images that better differentiate the left and right ventricles without any overlap to inclusively calculate left and right ventricular ejection fractions and assess regional wall motion.⁵⁹

Early detection of cardiotoxic findings on serial imaging allows timely intervention to prevent associated patient morbidities or mortalities from trastuzumab- and anthracycline treatment.⁵² Evaluation of global LV systolic function and diastolic performance indexes using RNA has proven effective for early assessment of functional changes after chemotherapy compared to baseline, emphasising that serial imaging is critical at all treatment stages to assess patient prognosis.^{53,59} A reduction in the peak fill rate as measured by multigated RNA indicates worsening diastolic function, a parameter that is often impaired before declining systolic function in anthracycline-induced cardiotoxicity and more importantly, is an early indication of compromised cardiac function.^{56,63} Small or moderate cases of pericardial effusions do not compromise LVEF but may induce comorbidities such as compromised breathing, induced chest pain and abdominal fullness, and difficulty swallowing.⁵² Visualisation of a photopenic U-halo on the anterior and LAO projections of an ERNA scan may indicate the initial stages of pericardial effusion and allow early intervention and treatment adjustments to potentially mitigate progression.⁶⁰

Whole Body Bone Scan in Metastatic Disease

Bone metastases are present in ~80% of women with metastatic disease highlighting the predilection of breast cancer cells to metastasise to bone.⁶⁴ Once bone metastases are diagnosed, median survival is between 2.1 and 6 years. Additionally, patients may experience a deterioration in their quality of life from associated complications of metastatic disease.⁶⁵ Consequently, initial staging and regular follow-up evaluations for restaging are critical to improving quality of life and survival.^{64,66,67} Whole body (WB) bone scanning is a relatively inexpensive and non-invasive examination that is recommended for accurate staging of disease burden and follow-up evaluation in symptomatic or high-risk patients.^{65,68}

WB bone scanning by means of planar, SPECT, and/or SPECT/CT is a powerful first-line staging and treatment

response tool.^{68–71} WB bone scintigraphy uses bone-seeking radiopharmaceuticals that localise to sites of increased perfusion and bony turnover characteristic of bone metastases thus making it a highly sensitive tool for detecting osteoblastic and lytic/sclerotic mixed lesions (Fig. 3).⁶⁸ Adding cross-sectional data from SPECT has been shown to detect more lesions than planar and improve specificity particularly in the axial skeleton where lesion uptake is difficult to discriminate from trauma or degenerative uptake (Fig. 4).^{66–68} Moreover, incorporating hybrid SPECT/CT data can better evaluate abnormal tracer uptake in benign skeletal pathology such as degenerative changes or cysts (Fig. 5). Co-registered data can also ascertain lytic lesions, which if the reparative process is not induced will appear cold on planar images and thus difficult to detect.^{66,69,72} A study by Iqbal *et al.*⁷³

found an incremental improvement from 6.1% to 78.8% in the diagnostic accuracy of characterising vertebral metastases when adding SPECT/CT data to planar. The prognostic value of co-registered SPECT/CT can be noted in the results of a recent trial that down-staged 33.8% and up-staged 2.1% of breast cancer patients when compared to planar and SPECT bone scan.⁶⁹

Assessing systemic (chemotherapy or hormone therapy) or local (radiotherapy) treatment response is an area where nuclear medicine can excel. WB bone scanning provides earlier and more representative information as it depicts the body's physiologic response to therapeutic interventions and often offers better prognostic value than an anatomical response.^{70,74} In some instances, bone scintigraphy may highlight an osteoblastic bone reaction commonly referred to as the bone 'flare phenomenon,'

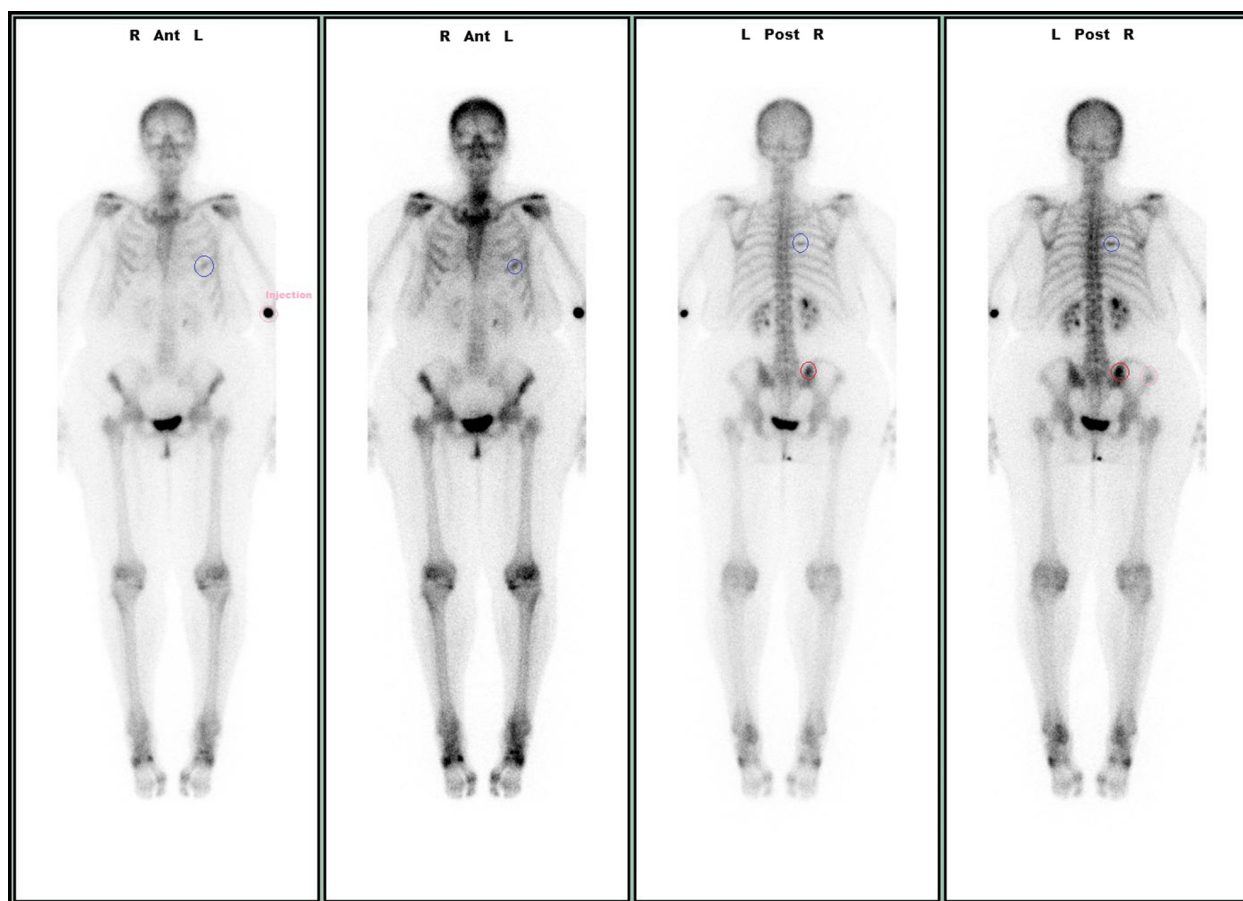


Figure 3. Breast cancer patient referred for a whole body bone scan (WBBS) to evaluate metastatic disease. Dual intensity anterior and posterior WB images show a focal increased radiopharmaceutical uptake in the fifth and seventh ribs (blue circles) likely consistent with metastatic disease. There is focal uptake in the left anterior and posterior superior iliac spine near the sacroiliac joint suspicious for metastatic disease (red circles). Bilateral radiopharmaceutical uptake is also noted in the acromioclavicular joints, hip joints, knee joints and tarsometatarsal joints consistent with degenerative changes. SPECT/CT was performed on the lumbar/pelvic region for further evaluation. SPECT, single-photon emission computed tomography. Image courtesy of Regional Imaging, a member of I-MED Network Radiology, Wagga Wagga, NSW.

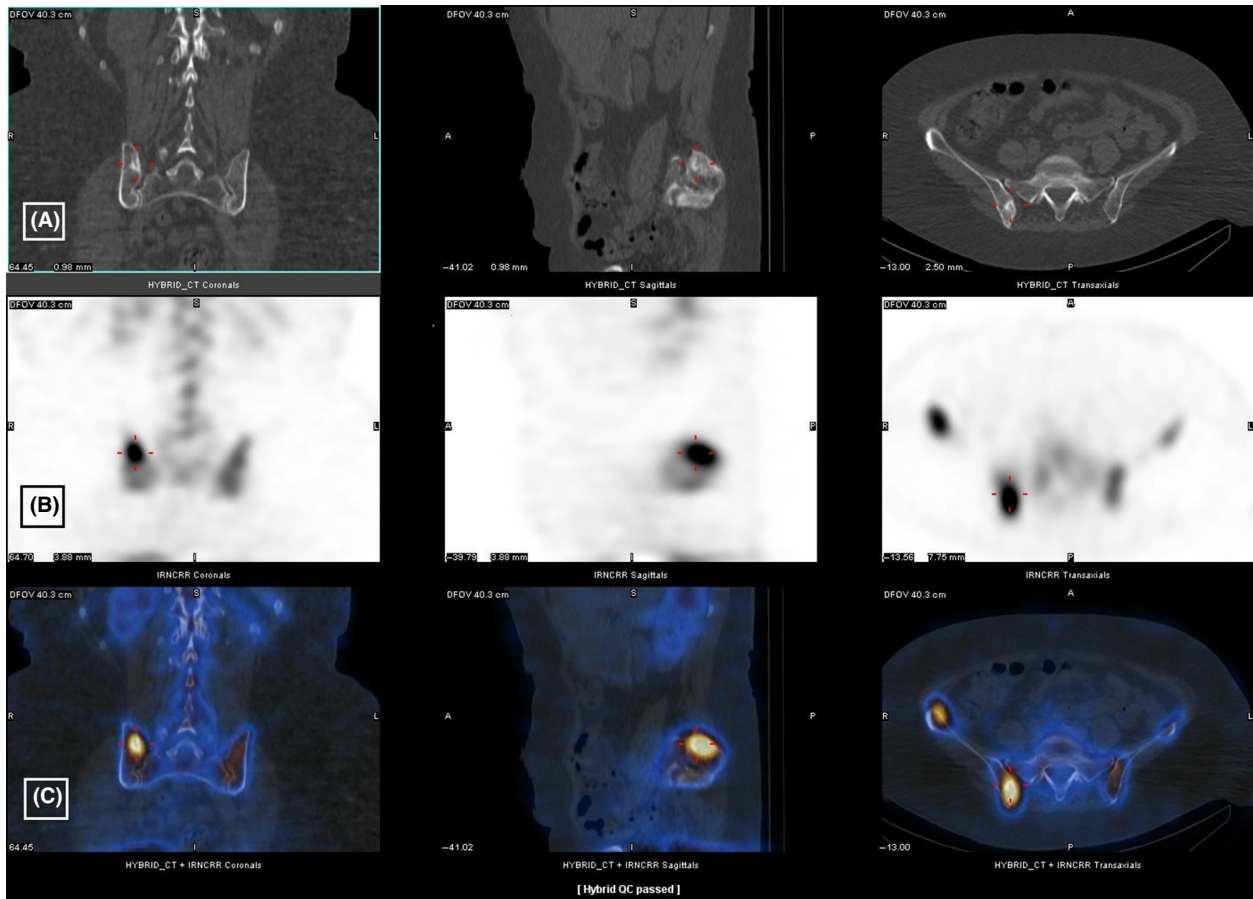


Figure 4. (B) SPECT images show intense focal uptake in the iliac crest of the left pelvic bone in the area near the anterior superior iliac spine and the posterior superior iliac spine near the left sacroiliac joint as visualised on the WBBS. (A) CT images demonstrate underlying sclerosis and distorted bony outline in the corresponding areas. (C) Fused SPECT/CT images clearly identify these areas as consistent with metastatic disease. SPECT, single-photon emission computed tomography; WBBS, whole body bone scan. Image courtesy of Regional Imaging, a member of I-MED Network Radiology, Wagga Wagga, NSW.

characterised by increased radiotracer uptake as a result of a therapeutic increased osteoblastic activity denoting healing bone.⁷⁴ Flare is visualised on the WB bone scan as an exaggerated appearance of disease that is either representative of healing bone or previously invisible lesions.⁷⁴ In either instance, visualisation of the flare response on bone scintigraphy may provide valuable prognostic information indicative of healing or progression of disease.

Positron Emission Tomography/Computed Tomography

In the United States, oncologic studies accounted for ~94% of the estimated 1.5 million PET/CT procedures performed in 2011.⁷⁵ The tumour-avid glucose analog F-18 fluoro-2-deoxyglucose (F-18 FDG) has gained

widespread acceptance as a marker of cellular metabolism providing insight into cancer physiology at the molecular level.⁷⁶ The ability of PET/CT to accurately stage WB metastatic disease as well as quantify and evaluate therapeutic response has significantly impacted and tailored the care breast cancer patients receive.^{76,77}

High sensitivity and specificity best appropriate PET/CT for detecting distant metastases as the system may not adequately resolve small primary breast lesions or axillary nodal regions.^{78,79} Currently under investigation to address this limitation, dedicated positron emission mammography (PEM) devices were designed to improve detection of small primary lesions by maximising system spatial resolution.⁸⁰ PET/CT is comparable to and in some instances may outperform whole body bone scan (WBBS) in the detection of breast cancer metastases to

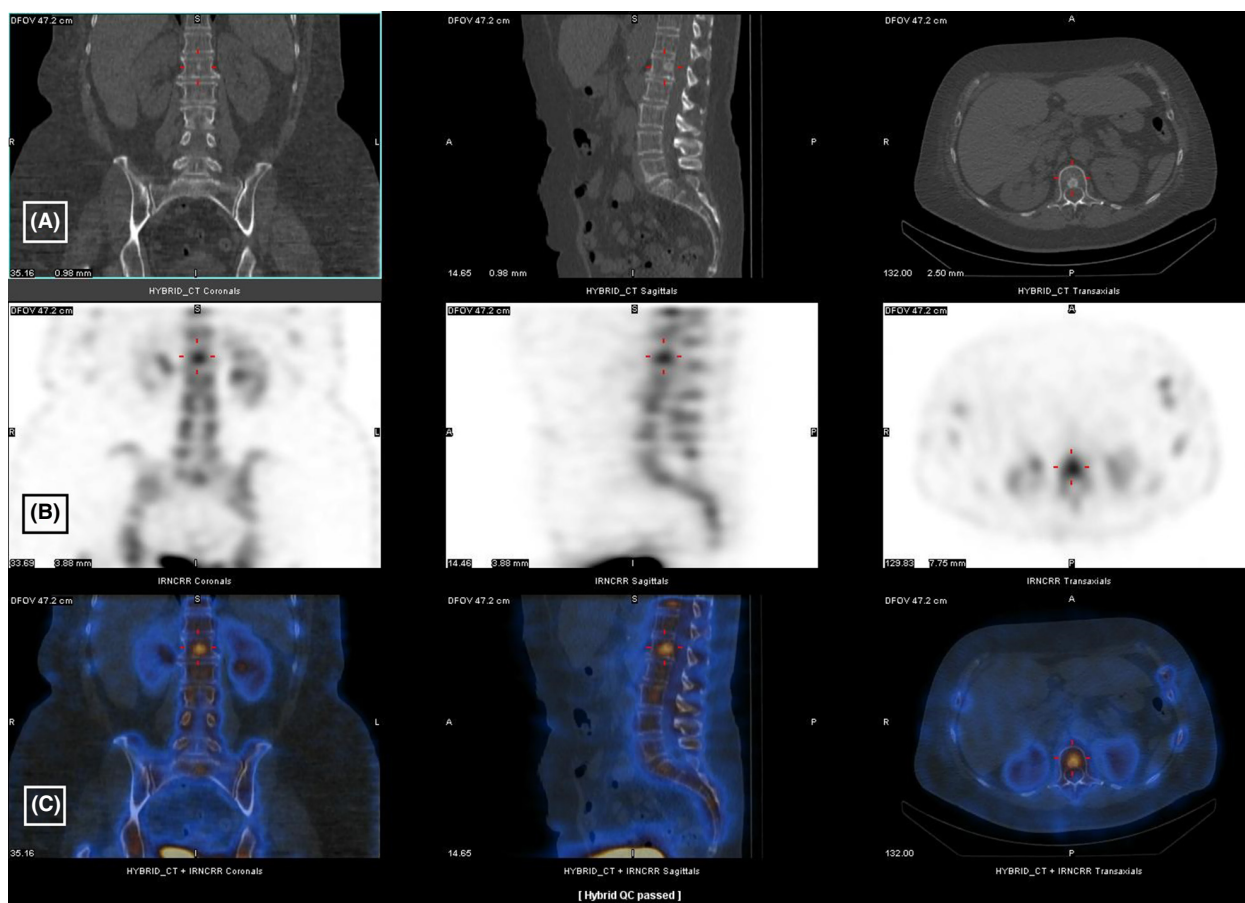


Figure 5. SPECT/CT images of the same patient revealing sclerosis in the vertebral body of L1 on CT images (A) which correspond to an area of increased focal uptake on SPECT (B) and fused SPECT/CT (C) most consistent with metastatic disease. This lesion was not apparent on WBBS. Additionally, degenerative changes (which affect intervertebral discs or facet joints) and metastatic disease (which primarily affect the vertebral body) are both common pathologies occurring in the lumbar region and thus require anatomic information for an accurate diagnosis. These images clearly highlight the significance of hybrid imaging in evaluating vertebral metastatic involvement and increasing diagnostic confidence. SPECT, single-photon emission computed tomography; WBBS, whole body bone scan. Image courtesy of Regional Imaging, a member of I-MED Network Radiology, Wagga Wagga, NSW.

bone, showing similar sensitivity but greater specificity as a result of improved metabolic and morphologic characterisation of osseous lesions.^{76,77,81}

F-18 FDG can also provide an earlier and more objective prediction and assessment of response in many therapeutic settings.^{77,79} Using a standardised protocol, serial standard uptake value (SUV) measurements are derived directly from tumour metabolic avidity and thus provide a semi-quantitative representation of cancer physiology over time.⁷⁹ There is also a positive correlation between prognostically poor aggressive disease and a higher lesion SUV_{max} , including values obtained from osseous lesions.^{76,77} Novel positron-emitting radiopharmaceuticals designed to boost specificity by targeting oestrogen, progesterone, oestrogen growth factor and somatostatin receptors identified on breast tumours

have also been explored by PET/CT.^{82,83} Tumour characterisation, tailored therapy investigations, disease burden extent and disease monitoring with serial imaging are facilitated by receptor-mediated molecular imaging.⁸⁴

Conclusion

Nuclear medicine fills a physiologic niche in medical imaging for cancer patients, providing information representative of function and is a fundamental component of disease diagnosis, treatment and prognosis. Specifically for breast cancer care, general nuclear medicine supplies diagnostic value at each stage of the disease and is considered first-line modality in multiple clinical scenarios. The versatility of gamma cameras equipped with SPECT and/or SPECT/CT are indeed a

suitable tool for patients in the broader clinical setting offering a very detailed look into the current physiologic state of the body structures and their functions. PET/CT has emerged as a powerful oncologic tool and with the advent of targeted radiopharmaceuticals is predicted to undergo a highly anticipated expansion in the management of breast cancer. In the full scope of physiologic breast cancer imaging, future studies should investigate multi-acquisition (planar and SPECT) and multi-modality (SPECT/CT) imaging to further recognise the added value of instrument hybridisation protocols and processes in nuclear medicine imaging.

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Conflict of Interest

The authors declare no conflict of interest.

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