Journal of
Cancer Science & Therapy

Evangelista et al., J Cancer Sci Ther 2012, S7
DOI: 10.4172/1948-5956.S7-003

Review Article Open Access

Nuclear Imaging and Early Breast Cancer Detection

Laura Evangelista*, Marta Burei and Anna Rita Cervino

Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology IOV–IRCCS, Padova, Italy

Abstract

The present report discuss about the most important roles of nuclear medicine related to the early detection of breast cancer. We summarily describe the established and emerging diagnostic techniques, their indications and clinical impact for planar and tomographic breast scintigraphy, positron emission tomography (PET)/computed tomography (CT) and positron emission mammography (PEM).

Keywords: Breast cancer; Positron emission tomography; Computed tomography; Nuclear imaging; Initial staging

Introduction

The concept of early detection of breast cancer (BC) is wide and can be considered as the early identification of primary cancer at different phases of disease, it means at initial staging, during and after treatment (neoadjuvant or adjuvant), and during follow-up.

Molecular breast imaging uses short-term radioactive agents that absorbed into tissues and can be imaged with a special camera. From planar to tomographic images, from technetium to fluoride, many efforts have been made for earlier individualizing the BC and for understanding the molecular pathways of tumour.

Here in, we described the usefulness of nuclear imaging modalities, considering the pros and cons of each others based on the last clinical applications, particularly for initial staging.

Conventional Nuclear Imaging

Breast scintigraphy

Since 1980s numerous pioneer studies demonstrated the usefulness of 99mTc-methoxsysiobutyl isonitrile (MIBI) scintigraphy in the evaluation of different types of neoplasm. Waxman and Khalkhali et al. [1-3] generated the clinical interest in evaluated BC with this tracer. Therefore, close to conventional imaging for the detection of primary BC in order to select patient for biopsy and spare an unnecessary surgical procedures, nuclear medicine breast imaging was added. Nowadays, breast scintigraphy or scintimammography (SM) is considered a supplemental breast exam that may be used in some patients to investigate a breast abnormality (i.e. equivocal mammograms, dense breast, breast implants, breast iatrogenic architectural distortion) [4]. Scopinaro et al. [5] showed that SM has a sensitivity of 46.5% for malignant lesions <1cm and of 96% for those superior to this size. Therefore, as suggested by Prats et al. [6], the adoption of SM in the diagnostic protocol can considerably reduce the number of biopsies performed in patients with lesions of low or indeterminate mammographic suspicion of malignancy with a diameter >1 cm (sensitivity: 94%; specificity: 75%, positive predictive value-PPV: 73% and negative predictive value-NPV: 95%). A recent meta-analysis for establishing the evidence based for the clinical use of SM, performing on 2,424 patients showed an overall sensitivity of 85% and specificity of 84% [7].

In the detection of small size BC (<1 cm), the conventional planar SM presents some limitations both physical (i.e. low intrinsic spatial resolution and poor energy resolution) and technical (i.e. high dead space at the edge of the field of view, large distance between detector and breast, poor visualization of medial and posterior breast areas, impact of scatter radiation from organ near the breast) [8,9]. As recently demonstrated by Spanu et al. [10], these limitations can be over passed by a dedicated breast camera (DBC), that is a high resolution small field of view dedicated breast camera mounted on a mammography unit. This diagnostic tool has shown a sensitivity rate of 81-90%. In particular, DBC proved an extremely highly sensitive diagnostic method in the detection of cancer in patient with ipsilateral multifocal/multicentric carcinomas, either invasive or in situ, and in those with synchronous bilateral tumours, resulting positive in 93.2% of cases. As reported in literature, conventional mammography detected multifocality/multicentricity in only the 47.5% on cases, demonstrating lower performance than DBC which identified a significantly higher number of additional invasive tumour foci (89.6% *vs.* 37.9%), most clinically occult and small in size [11,12]. The preoperative underestimation of local disease can lead to surgical under-treatment, resulting in a higher risk of local and distant recurrence. Bearing in mind that the tendency of BCs to metastasize reflects total tumour rather than the size of the largest focus, there is the risk that patients will not receive adjuvant chemotherapy or radiotherapy if additional smaller foci are missed. Therefore the early detection of multifocal/multicentric BC becomes extremely important both prognosis and therapeutic strategy.

SPET/CT

Conventional nuclear medicine imaging, such as planar or tomographic scintigraphy, is also precious in the preoperative evaluation of the effectiveness of neoadjuvant treatment in primary tumour and in lymph nodes draining the site of the tumour. The increasing development of hybrid devices, based on an X-ray tube for low-dose computed tomography (CT) added to a conventional single photon emission tomography (SPET) system had opened a new era for SPET application. The advantages of SPET/CT essentially rely

***Corresponding author:** Laura Evangelista, Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology IOV–IRCCS, Via Gattamelata, 64 Padova, Italy, Tel: +39 049 8217997; Fax: +39 049 8212205; E-mail: laura.evangelista@ioveneto.it

Received August 09, 2011; **Accepted** September 12, 2012; **Published** September 14, 2012

Citation: Evangelista L, Burei M, Cervino AR (2012) Nuclear Imaging and Early Breast Cancer Detection. J Cancer Sci Ther S7:003. doi:10.4172/1948-5956.S7-003

on the attenuation correction capabilities and on precise anatomical landmarks that permits an exact localization of a focal-uptake. SPET/CT significantly increases the diagnostic accuracy of both conventional planar and SPET imaging in several cancer field, reducing considerably the number of indeterminate findings [13-16]. In particular, 99mTc-MIBI or 99mTc-Tetrafosmin SPET/CT is able to detect residual BC, although false negative findings occurred in some patients with microscopic residues and in those with low-cellularity histotype tumours. The few data present in literature about the employment of SPET/CT in diagnosis of BC appear encouraging. They shown a sensibility values ranging from 89.2% to 90.7% in overall lesions an from 71.4% to 78.3% in the subgroup of small size (≤ 10 mm) [17,18]. Also lymph node status was evaluated in these few studies, reporting a sensitivity value of 78.3%. Spanu et al. [19] suggest a wider application of SPET/CT in the preoperative evaluation of BC patients after neoadjuvant therapy to guide the surgeon to the most appropriate breast surgical treatment and to eventually select the most suitable axillary sampling, i.e. axillary lymph node dissection (ALDN) *vs.* sentinel lymph node biopsy (SLB). Considering that SPET/CT cannot replace the pathologic examination for the assessment of lymph nodes status, given the low sensitivity for axillary lymph nodes (36.8%) and that at present ALDN is the standard procedure for nodal staging following neoadjuvant therapy, the authors hypothesize that patients with SPET/CT study positive at the axillary site should undergo ALND directly, given the high probability that there is lymph nodal involvement. On the contrary, patients with a SPEC/CT negative study, especially patients with partial or complete response of primary tumour to neoadjuvant therapy and clinically negative axilla should be selected for SLB. In these latter cases, ALND could be avoided if the sentinel node is negative, with the well known advantages in terms of reduced morbidity and cost.

Positron emission imaging devices

New nuclear diagnostic imaging tools are, nowadays, considered in the early detection or in subsequent pre-surgical planning of women with BC. Positron emission tomography (PET) with fluorodeoxyglucose (FDG) has revolutionized the diagnostic opportunities of malignancies; however, it has still a controversial role in the management of BC. In particular, PET and PET/CT provide new methods of both locally advanced BC staging and assessment of the early chemo/endocrine therapy response. The development of new radiotracers and the value in predicting treatment response represent a great area of research interest.

FDG PET/CT

In clinical practice, the application of FDG PET/CT covers different settings: from the definition of disease extension (i.e. lymph node or distant involvement) to identification of unknown foci of BC, so defined incidentalomas. Following, we described in separate paragraphs these different topics.

Primary tumour

NCCN guidelines recommend against the use of PET or PET/CT scanning in the staging of clinical stage I and II or operable III (IIIA) BC [20]. The recommendations against the use of PET are supported by several findings: the high false negative rate in the detection of breast tumours that are small (<1cm) or of low grade, the low sensitivity for detection of axillary nodal metastasis, the low prior probability that these patients have detectable metastatic disease, and the high rate of false positive scan findings [21].

Paradoxically, many are the neoplasm incidentally discovered during conventional imaging or PET/CT imaging performing for other reasons. Sometimes, these lesions result as benign findings, but in other cases they are metastatic foci by other tumour or primary tumours. Beatty et al. [22] suggested that the incident breast lesions should be better evaluated because in 55% of the cases they represent a BC. Litmanovich et al. [23] reported a percentage of 57% of unaware foci with high FDG-uptake concluding that these lesions should be considered as a second primary tumour, a lymphoma or a metastasis with higher FDG-uptake rather than benign findings. The major number of FDG-avid "incidentalomas" are positive at histological staining, but considering the low positive predictive value (PPV=25%) of the biopsy, should be necessary to perform other evaluations, such as a new mammography scan and a tissue sample by ultrasound. In incidental lesions with a low FDG-uptake, the presence of abnormal morphological pattern should be considered of a great clinical relevance.

Lymph node metastases detection

Evaluation of axillary lymph node metastases is important for BC staging and treatment planning. Monzawa et al. [24] assessed the diagnostic performance of FDG-PET/CT compared with that of ultrasonography and contrast-enhanced CT for the detection of axillary lymph node metastasis in subjects with early (clinical stage I or II) BC, taking the histopathological results of ALDN and SLB as the reference standard. Their results showed that the sensitivity of PET/CT was disappointingly low and only 20%, and was inferior to that of ultrasonography and contrast enhanced CT, which were also hardly sufficient for staging. Recently a study by Cooper et al. [25] evaluated the diagnostic accuracy, cost-effectiveness and effect on patient outcomes of PET, with or without CT, and MRI in the evaluation of axillary lymph node metastases in patients with newly diagnosed early-stage BC. PET/CT resulted less sensitive than PET only (56 *vs.* 66%) but with a similar specificity (96 *vs.* 93%). PET performed less well for small metastases; the mean sensitivity was 11% for micrometastases (≤ 2 mm). Conversely, PET/CT detected extra-axillary lymph node involvement in almost one-third of the patients with stage II-III BC, including regions not evaluable with ultrasound. PET/CT may be useful as an additional imaging tool to assess extra-axillary lymph node metastasis, with an impact on the adjuvant radiotherapy management [26]. As suggested by Wahl et al. [27] and Eubank et al. [28] PET/CT may be useful in assessing patients with medially or superiorly situated BCs that may drain preferentially or exclusively to internal mammary or supraclavicular lymph nodes.

Early distant metastases detection

The evidence of occult metastasis, missed by staging examination can be detected by PET/CT scan according to Koolen et al. [29]. The authors demonstrated that in 80% studied patients, additional lesions were exclusively seen with PET/CT, leading to a change in treatment in 8% of them. Furthermore, they showed that in 84% of patients with a negative staging PET/CT, no metastases developed during the follow-up.

The report by Groheux et al. [30] included 39 patients with stage II or III BC after conventional work-up. PET/CT revealed occult metastases in four patients. These were bone metastases in three patients and pleural involvement in one patient. Fuster et al. [31] studied 60 consecutive patients with BC stage IIb or higher. PET/CT sensitivity and specificity in detecting distant metastasis were 100 and 98%,

respectively, versus 60 and 83% for conventional work-up (contrast-enhanced chest CT, liver ultrasonography, 99mTc-HDP bone scan). Metastases missed by conventional work-up were visualized in eight patients. The sites of involvement were bone (six cases), and/or lung (two cases) and/or liver (two cases). PET/CT is also highly sensitive in detecting pleural, mediastinal, abdominal and pelvic metastases. In this study PET/CT diagnosed both patients with liver metastases, whereas liver ultrasound detected only one of the two cases. PET performs well to assess lung nodules larger than 8 mm [32], but it lacks sensitivity in smaller lesions, due to partial volume effect and respiratory motion.

Bone is the main site of metastatic spread in BC history and bone scintigraphy and/or MRI are the gold standard for its diagnosis. Bone marrow metastases represent metabolic bone changes that appear before morphologic ones [33,34]. PET/CT imaging is more efficient than contrast enhanced CT in this latter case and its ability to detect osteoblastic lesions is significantly better than that of bone scintigraphy [35]. Osteolytic lesions are more common than sclerotic type (80 *vs.* 15–20%). FDG may miss sclerotic lesions, but a better specificity for PET/CT than for bone scintigraphy in their detection has been recently reported [36,37].

CT is the imaging modality of choice for evaluating suspected liver metastases. Unenhanced CT is useful in a few cases, especially for detecting calcifying or hemorrhagic metastases from colon or BC. If the clinical suspicion of a lesion is high and the CT scan is negative, MRI or PET can be considered as alternative tests for further assessment. In a meta-analysis comparing ultrasound, CT, MRI, and PET in the detection of hepatic metastases from gastrointestinal tract cancers, Kinkel et al. [38] reported the highest sensitivity for FDG-PET. The main limitation of PET is its low sensitivity for brain metastases.

In literature, only some studies report with detail about the diagnostic accuracies of PET/CT at early diagnosis of BC [24,25,29,31,39-42], as depicted the (Table 1).

PEM

Due to the limited resolution of PET equipment and the space limitations of the current protocols for CT acquisition, small-size breast tumours are not visible using this technique, until they reach a certain size, and they can be visualized with other techniques like MRI. This is what has led to the development of a PET device dedicated to the breast, such as positron emission mammography (PEM). There are several commercial firms which have developed the PEM and, although they are still in early clinical development, initial results show sensitivity levels of 93% [43], similar to MRI and also high specificity levels 93% [44] higher than MRI. With dedicated configurations, the recent PEM system has high spatial resolution, up to 2.4 mm. In the prospective study from Eo et al. [45], the imaging sensitivity of PEM was compared with that of PET/CT in relation to tumor size. The results showed that PEM had significantly higher sensitivity in small-sized tumours <2 cm than PET/CT. However, in literature the data is controversy about the diagnostic power of PEM being reported different rates of accuracies [46-50] (Table 2).

An issue to resolve is which will be the interrelation between MRI and PEM and if a coexistence of both techniques is possible or if one of them will prevail over the other. PEM proved to be complementary to MR imaging for defining preoperative disease extent in the isplateral breast of women with newly diagnosed BC.

PEM was more specific than MR imaging and less likely prompt unnecessary biopsies. The advantage of PEM-guided biopsy is that the lesion can be easily re-imaged to determine whether the region of FDG uptake has been removed or reduced sufficiently to ensure adequate sampling without injecting additional contrast as in MRI or additional radiation dose as is required during stereotactic biopsies. In addition, the specimen scan allows the physician to evaluate the radiotracer distribution in the biopsy cores, without the interference of normal background breast tissue radiotracer uptake, thus providing confirmation of adequate sampling and to help direct the pathologist's attention to the areas of interest [51].

Conclusion

Until now, many efforts have been made for the detection of primary tumour and metastasis but the future challenge is to apply specific tracers as histological, molecular and biochemical markers of several cellular processes including apoptosis, proliferation, P-glycoprotein expression and neoangiogenesis. Furthermore, an integration of the

Authors (ref)	N. of pts	Primary tumour			Lymph node metastasis*			Distant metastasis		
		Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Monzawa et al. [24]	50				20 (axillar nodes)	97	-	-	-	-
Cooper et al. [25]					56%	96%	-	-	-	-
Koolen et al. [29]	154	-	-	-	-	-	-	100	96	97
Fuster et al. [31]	60	-	-	-	70 (axillar nodes)	100	-	100	98	-
Heusner et al. [39]	61	-	-	-	58 (axillar nodes)	92	79			
Segaert et al. [40]	70	97	-	-	62.5	100		96	-	-
Heusner et al. [41]	40	95	-	-	80 (axillar nodes)	-		100		
Niikura et al. [42]	225	-	-	-	-	-	-	97.4	91.2	-

*axilla and loco-regional lymph nodes

Table 1: Diagnostic accuracies of FDG PET/CT in detection of primary and metastatic foci of breast cancer.

Authors (ref)	Journal	Scanner	N of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Murthy et al. [46]	J Nuc Med	Laboratory PEM System	16	80	100	100	67	86
Berg et al. [44]	Breast J	PEM flex	77	93	83	87	91	88
Berg et al. [47]	Radiology	Naviscan	388	41	79.9	66	-	64.9
Tafra et al. [48]	Am J Surg	-	44	89	-	-	-	-
Rosen et al. [49]	Radiology	Laboratory PEM System	23	86	67	90	25	83
Levine et al. [50]	Ann Surg Oncol	Laboratory PEM System	17*	86	91	86	91	89
Eo et al. [45]	The Breast	PEM flex Solo II; Naviscan	113	95	-	-	-	-

*18 lesions

Table 2: Diagnostic accuracies for detection of primary breast cancer according to PEM.

new emerging techniques with the established ones in order to take advantage of the combination of both should be evaluated. The work in a multimodality environment could represent the way for reaching these purposes.

References

1. Waxman AD (1997) The role of (99m)Tc methoxyisobutylisonitrile in imaging breast cancer. Semin Nucl Med 27: 40-54.
2. Khalkhali I, Mena I, Jouanne E, Diggles L, Venegas R, et al. (1994) Prone scintimammography in patients with suspicion of carcinoma of the breast. J Am Coll Surg 178: 491-497.
3. Khalkhali I, Baum JK, Villanueva-Meyer J, Edell SL, Hanelin LG, et al. (2002) (99m)Tc sestamibi breast imaging for the examination of patients with dense and fatty breasts: multicenter study. Radiology 222: 149-155.
4. Schillaci O, Buscombe JR (2004) Breast scintigraphy today: indications and limitations. Eur J Nucl Med Mol Imaging 31: S35-S45.
5. Scopinaro F, Schillaci O, Ussof W, Nordling K, Capoferro R, et al. (1997) A three center study on the diagnostic accuracy of 99mTc-MIBI scintimammography. Anticancer Res 17: 1631-1634.
6. Prats E, Aisa F, Abós MD, Villavieja L, García-López F, et al. (1999) Mammography and 99mTc-MIBI scintimammography in suspected breast cancer. J Nucl Med 40: 296-301.
7. Hussain R, Buscombe JR (2006) A meta-analysis of scintimammography: an evidence-based approach to its clinical utility. Nucl Med Commun 27: 589-594.
8. Rhodes DJ, O'Connor MK, Phillips SW, Smith RL, Collins DA (2005) Molecular breast imaging: a new technique using technetium Tc 99m scintimammography to detect small tumors of the breast. Mayo Clin Proc 80: 24-30.
9. Spanu A, Cottu P, Manca A, Chessa F, Sanna D, et al. (2007) Scintimammography with dedicated breast camera in unifocal and multifocal/multicentric primary breast cancer detection: a comparative study with SPECT. Int J Oncol 31: 369-377.
10. Spanu A, Chessa F, Battista MG, Sanna D, Cottu P, et al. (2009) Scintimammography with high resolution dedicated breast camera and mammography in multifocal, multicentric and bilateral breast cancer detection: a comparative study. Q J Nucl Med Mol Imaging 53: 133-143.
11. Kolb TM, Lichy J, Newhouse JH (2002) Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology 225: 165-175.
12. Van Goethem M, Schelfout K, Dijckmans L, Van Der Auwera JC, Weyler J, et al. (2004) MR mammography in the pre-operative staging of breast cancer in patients with dense breast tissue: comparison with mammography and ultrasound. Eur Radiol 14: 809-816.
13. Chowdhury FU, Scarsbrook AF (2008) The role of hybrid SPECT-CT in oncology: current and emerging clinical applications. Clin Radiol 63: 241-251.
14. Spanu A, Solinas ME, Chessa F, Sanna D, Nuvoli S, et al. (2009) 131I SPECT/CT in the follow-up of differentiated thyroid carcinoma: incremental value versus planar imaging. J Nucl Med 50: 184-190.
15. Wong KK, Cahill JM, Frey KA, Avram AM (2010) Incremental value of 111-in pentetreotide SPECT/CT fusion imaging of neuroendocrine tumors. Acad Radiol 17: 291-297.
16. Ndlovu X, George R, Ellmann A, Warwick J (2010) Should SPECT-CT replace SPECT for the evaluation of equivocal bone scan lesions in patients with underlying malignancies? Nucl Med Commun 31: 659-665.
17. Schillaci O, Danieli R, Filippi L, Romano P, Cossu E, et al. (2007) Scintimammography with a hybrid SPECT/CT imaging system. Anticancer Res 27: 557-562.
18. Spanu A, Chessa F, Sanna D, Cottu P, Manca A, et al. (2009) Scintimammography with a high resolution dedicated breast camera in comparison with SPECT/CT in primary breast cancer detection. Q J Nucl Med Mol Imaging 53: 271-280.
19. Spanu A, Sanna D, Chessa F, Farris A, Nuvoli S, et al. (2011) The usefulness of Tc-99m-tetrofosmin SPECT/CT in the detection of residual tumors and axillary lymph node metastases in breast cancer patients following neoadjuvant therapy. Clin Nucl Med 36: 997-1002.
20. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
21. Groheux D, Giacchetti S, Espié M, Vercellino L, Hamy AS, et al. (2011) The yield of 18F-FDG PET/CT in patients with clinical stage IIA, IIB, or IIIA breast cancer: a prospective study. J Nucl Med 52: 1526-1534.
22. Beatty JS, Williams HT, Gucwa AL, Hughes MP, Vasudeva VS, et al. (2009) The predictive value of incidental PET/CT findings suspicious for breast cancer in women with non-breast malignancies. Am J Surg 198: 495-499.
23. Litmanovich D, Gourevich K, Israel O, Gallimidi Z (2009) Unexpected foci of 18F-FDG uptake in the breast detected by PET/CT: incidence and clinical significance. Eur J Nucl Med Mol Imaging 36: 1558-1564.
24. Monzawa S, Adachi S, Suzuki K, Hirokaga K, Takao S, et al. (2009) Diagnostic performance of fluorodeoxyglucose-positron emission tomography/computed tomography of breast cancer in detecting axillary lymph node metastasis: comparison with ultrasonography and contrast-enhanced CT. Ann Nucl Med 23: 855-861.
25. Cooper KL, Meng Y, Harnan S, Ward SE, Fitzgerald P, et al. (2011) Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. Health Technol Assess 15: 1-134.
26. Aukema TS, Straver ME, Peeters MJ, Russell NS, Gilhuijs KG, et al. (2010) Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. Eur J Cancer 46: 3205-3210.
27. Wahl RL, Siegel BA, Coleman RE, Gatsonis CG; PET Study Group (2004) Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. J Clin Oncol 22: 277-285.
28. Eubank WB, Mankoff DA, Takasugi J, Vesselle H, Eary JF, et al. (2001) 18fluorodeoxyglucose positron emission tomography to detect mediastinal or internal mammary metastases in breast cancer. J Clin Oncol 19: 3516-3523.
29. Koolen BB, Vrancken Peeters MJ, Aukema TS, Vogel WV, Oldenburg HS, et al. (2012) 18F-FDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques. Breast Cancer Res Treat 131: 117-126.
30. Groheux D, Moretti JL, Baillet G, Espie M, Giacchetti S, et al. (2008) Effect

of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. Int J Radiat Oncol Biol Phys 71: 695-704.

31. Fuster D, Duch J, Paredes P, Velasco M, Muñoz M, et al. (2008) Preoperative staging of large primary breast cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. J Clin Oncol 26: 4746-4751.

32. Evangelista L, Panunzio A, Cervino AR, Vinante L, Al-Nahhas A, et al. (2012) Indeterminate pulmonary nodules on CT images in breast cancer patient: The additional value of 18F-FDG PET/CT. J Med Imaging Radiat Oncol 56: 417-424.

33. Lonneux M, Borbath I I, Berlière M, Kirkove C, Pauwels S (2000) The Place of Whole-Body PET FDG for the Diagnosis of Distant Recurrence of Breast Cancer. Clin Positron Imaging 3: 45-49.

34. Evangelista L, Panunzio A, Polverosi R, Ferretti A, Chondrogiannis S, et al. (2012) Early bone marrow metastasis detection: The additional value of FDG-PET/CT *vs.* CT imaging. Biomed Pharmacother .

35. Cook GJ, Houston S, Rubens R, Maisey MN, Fogelman I (1998) Detection of bone metastases in breast cancer by 18FDG PET: differing metabolic activity in osteoblastic and osteolytic lesions. J Clin Oncol 16: 3375-3379.

36. Du Y, Cullum I, Illidge TM, Ell PJ (2007) Fusion of metabolic function and morphology: sequential [18F] fluorodeoxyglucose positron-emission tomography/computed tomography studies yield new insights into the natural history of bone metastases in breast cancer. J Clin Oncol 25: 3440-3447.

37. Shie P, Cardarelli R, Brandon D, Erdman W, Abdulrahim N (2008) Meta-analysis: comparison of F-18 Fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. Clin Nucl Med 33: 97-101.

38. Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF (2002) Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. Radiology 224: 748-756.

39. Heusner TA, Kuemmel S, Hahn S, Koeninger A, Otterbach F, et al. (2009) Diagnostic value of full-dose FDG PET/CT for axillary lymph node staging in breast cancer patients. Eur J Nucl Med Mol Imaging 36: 1543-1550.

40. Segaert I, Mottaghy F, Ceyssens S, De Wever W, Stroobants S, et al. (2010) Additional value of PET-CT in staging of clinical stage IIB and III breast cancer. Breast J 16: 617-624.

41. Heusner TA, Kuemmel S, Umutlu L, Koeninger A, Freudenberg LS, et al. (2008) Breast cancer staging in a single session: whole-body PET/CT mammography. J Nucl Med 49: 1215-1222.

42. Niikura N, Costelloe CM, Madewell JE, Hayashi N, Yu TK, et al. (2011) FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. Oncologist 16: 1111-1119.

43. Schilling K, Narayanan MS, Kalinyak JE (2008) Multimodality effect of breast density, menopausal status and hormone use in high resolution positron emission mammography. Proceedings of the 94th Annual Meeting of the Radiological Society of North America (RSNA '08).

44. Berg WA, Weinberg IN, Narayanan D, Lobrano ME, Ross E, et al. (2006) High-resolution fluorodeoxyglucose positron emission tomography with compression ("positron emission mammography") is highly accurate in depicting primary breast cancer. Breast J 12: 309-323.

45. Eo JS, Chun IK, Paeng JC, Kang KW, Lee SM, et al. (2012) Imaging sensitivity of dedicated positron emission mammography in relation to tumor size. Breast 21: 66-71.

46. Murthy K, Aznar M, Thompson CJ, Loutfi A, Lisbona R, et al. (2000) Results of preliminary clinical trials of the positron emission mammography system PEM-I: a dedicated breast imaging system producing glucose metabolic images using FDG. J Nucl Med 41: 1851-1858.

47. Berg WA, Madsen KS, Schilling K, Tartar M, Pisano ED, et al. (2011) Breast cancer: comparative effectiveness of positron emission mammography and MR imaging in presurgical planning for the ipsilateral breast. Radiology 258: 59-72.

48. Tafra L, Cheng Z, Uddo J, Lobrano MB, Stein W, et al. (2005) Pilot clinical trial of 18F-fluorodeoxyglucose positron-emission mammography in the surgical management of breast cancer. Am J Surg 190: 628-632.

49. Rosen EL, Turkington TG, Soo MS, Baker JA, Coleman RE (2005) Detection of primary breast carcinoma with a dedicated, large-field-of-view FDG PET mammography device: initial experience. Radiology 234: 527-534.

50. Levine EA, Freimanis RI, Perrier ND, Morton K, Lesko NM, et al. (2003) Positron emission mammography: initial clinical results. Ann Surg Oncol 10: 86-91.

51. Kalinyak JE, Schilling K, Berg WA, Narayanan D, Mayberry JP, et al. (2011) PET-guided breast biopsy. Breast J 17: 143-151.

This article was originally published in a special issue, **Cancer Screening & Early Detection** handled by Editor(s). Dr. Arutselvan Natarajan, Stanford University, United States