Review Article

Is There Relation between PET/CT and Molecular Subtypes in Patients with Metastatic Breast Cancer

Moustafa, H [1] and Nasr, A[2].

[1] *Oncology and Nuclear Medicine Department, Cairo University and* [2] *Maadi Armed Force Hospital. Egypt*

INTRODUCTION

Breast cancer is the most prominent cancer and the second most prominent cause of mortality in women. In recent years the incidence of breast cancer has increased to 102 per 100,000 per year. Early diagnosis and accurate follow-up of these patients is important for efficient patient management [(1)]. Breast carcinoma spreads by direct invasion, by the lymphatic route, and by the blood vessel route, some of these metastases are already present at the time of diagnosis, and others become manifest clinically months, years, or decades after the initial therapy. Distant metastases are seen most commonly in the skeletal system, lung, liver, adrenal gland, and brain [(2)]. Standard imaging techniques include radiological examinations, such as X-ray mammography, Ultrasonography (US), magnetic resonance imaging (MRI).Bone scintigraphy is used for follow-up of breast cancer to detect bone metastases [(3, 4)]. (F-18-FDG-PET was introduced in clinical oncology and provides an effective and accurate imaging technique in breast cancer for restaging and detection of metastatic disease. Also, FDG-PET examination can demonstrate the proper extent of the disease within a single investigation [(5, 6)].

Corresponding Authors: Moustafa, H. **E-mail:** hosana.mostafa@kasralainy.edu.eg.

Hormonal profile of breast cancer: A crucial development in the treatment of breast carcinoma has been the realization that the presence of hormone (estrogen and progesterone) receptors in the tumor tissue correlates well with

response to hormone therapy and chemotherapy. As a matter of fact; estrogen receptor status is regarded at present as the most powerful predictive marker in breast cancer management [(7)]. Estrogen and progesterone receptors are co-dependent variables, progesterone receptor (PR) being a weaker predictor of hormone receptor response to endocrine therapy than estrogen receptor (ER).Several attempts have been made to semi-quantitate the immune-histochemical method by standardizing the technical procedure and reporting and by using the appropriate controls [(8)]. Hormone receptors can also be evaluated in paraffin-embedded breast tissue by the in situ hybridization technique and by PCR. About 80% of breast cancers are ER positive, so that an ER-negative rate of 20% or higher suggests that some problems exist with the assay [(9)]. HER2/neu is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity, which belongs to the family of epidermal growth factor receptors, its overexpression can be measured by immune-histochemistry or FISH (or its chromogenic equivalent)and a good correlation exists between these methods ([(10)]. HER2/neu overexpression is found in nearly all cases of high-grade (comedo-type) DCIS, in 20–30% of invasive ductal carcinomas, and in a smaller percentage of invasive lobular carcinomas, [(11)]. Conversely, it is typically absent in tubular carcinoma and other grade 1 carcinomas [(12)]. Breast tumors may be negative for all three markers which are diagnosed as ***triple negative***. Triple negative breast cancers represent a heterogeneous group of tumors, which exhibit the following features: morphologically usually high-grade invasive ductal carcinoma NOS, high degree of aneuploidy and higher tendency to metastasize to lungs and brain [(13)]. However, triple negative cancers are not synonymous with basal-like cancers – only 77% of cases classified by gene expression profiling as basal-like show a triple negative phenotype, while only 72% of cases of triple negative cancers exhibit a basal-like gene expression profile [(14)].

Molecular Classification of Breast Cancer: The subtypes of breast cancers recognized by their gene signature include: luminal (type A and B, and questionable type C), HER2/neu type and basal-like, among the various subtypes, the basal-like subtype is associated with the worst prognosis. Since the different subtypes of breast cancers exhibit specific characteristics, they would likely benefit from different approaches of treatment.

There are efforts to use immune-histochemistry (such as a panel including antibodies to estrogen receptor, progesterone receptor, HER2/neu, cytokeratin 5/6, EGFR, Ki-67) to assign tumors to the various molecular subtypes ***(Table 1)*** [15], but discordance is not uncommon, and there are currently no widely agreed criteria to define a positive immunostain for this purpose (such as percentage of positive cells and/or intensity of staining) [16].

Table 1: Use of immune-histochemistry as surrogate marker for the molecular subtypes of breast cancer

MOLECULAR SUBTYPE				
Immunoprofile	**Luminal A**	**Luminal B**	**HER2/ *neu***	**Basal-like**
ER, PR	ER and/or PR+	ER and/ or PR+	ER–, PR–	ER–, PR–
HER2 and others	HER2– Low Ki-67 (<14%)	HER2+ or HER2– Ki-67 ≥14%	HER2+	HER2– CK5/6 and/or EGFR+

Modified from ***Schnitt SJ.*** *(2010)*

The basal-like subtype is highly heterogeneous, and encompasses some tumors with a favorable prognosis, such as medullary carcinoma, secretory carcinoma, and adenoid cystic carcinoma, necessitating the creation of a 'low-grade' category of basal-like carcinoma [17].

It is too simplistic to try to subsume the many different types of breast carcinoma into a few molecular categories, ignoring the known distinctive types with characteristic morphology and biologic features. In fact, additional molecular subtypes have since been identified, such as molecular apocrine and claudin-low. The issues with the standardization of analytic approaches, replication, attaining adequate sample size, and the evaluation of the clinical utility in broader heterogeneous populations by prospective clinical trials still plague the many gene expression profiling studies and their applications in routine diagnosis/prognostication. Although every published microarray-based system can recognize molecular subtypes with similar survival and can also identify the basal-like subtype fairly consistently, the systems do not reliably assign the same patients to the same molecular groups for the non-basal-like tumors [18].

PET/CT in Breast Cancer: In recent years, imaging with positron emission tomography (PET) for tumor staging and therapy control has been introduced. The anatomic information it provides with

physiologic information on glucose uptake and metabolism do help in detection of early tumor recurrence [19].

Buck et al, in a series of 78 patients with a history of breast cancer underwent PET/CT exam for restaging after a rise in tumor markers or recurrent disease was suspected from clinical follow-up. Malignant lesions were detected by means of the PET/CT in 77% of patients. In 36% of the patients FDG PET/CT led to a change of the therapeutic management [20].

In ***Klagenfurt department*** a series of 41 patients with a history of breast cancer and suspected recurrence using FDG-PET/CT. A number of 22/41 lesions were detected (54%). Five patients had local recurrence with additional distant metastases; seven patients had lymph node metastases with additional distant metastases, ten patients had bone metastases including seven patients with metastases in various locations including lung, soft tissue, and adrenal gland. Patient based sensitivity and specificity of FDG-PET/CT was 96% and 89% respectively.

Diagnosis of Disease Relapse: In patients treated with surgery, loco-regional and distant metastases occur in 35% of cases within10 years of surgery [21]. The follow up of the patients is intended to make a diagnosis of cancer recurrence, with the goal to treat metastases at the earliest stage of development. Different kinds of follow-up approaches have been proposed; only clinical control in asymptomatic patients, intensive and aggressive periodic examinations with a battery of imaging and biochemical tests in asymptomatic patients, and diagnostic tests only in presence of symptoms [22].

Lonneaux et al. studied 39 breast cancer patients with FDG-PET; 34 were included because of asymptomatic tumor marker increase. PET findings were confirmed by biopsy. PET depicted 37 out of 39 sites in 31 out of 33 patients with recurrences. PET missed one patient with loco-regional recurrence and another patient developed a peritoneal metastases is 6 months after negative PET. False-positive PET corresponded to lung infections, arthrosis and a synthetic implant [23]. Overview of the diagnostic value of FDG-PET guided by a tumor marker increase, as published in different papers ***(Table 2)***.

Table 2. Results of tumor marker-guided FDG-PET in different studies on breast cancer

Author (year and ref.)	No. of patients studied	Diagnostic sensitivity	Diagnostic specificity	Remarks
Lonneaux et al. 2000	39	93%	–	PET missed only a locoregional recurrence and a peritoneal carcinosis
Pecking et al. 2001	132	93.6%	–	
Suarez et al. 2002	45	92%	75%	Clinical management was modified in patients with unsuspected primary or tumour relapse
Liu et al. 2002	30	25/28* 35/38°	90%	Demonstrated an impact in patient management
Kamel et al. 2003	35	89%	84%	PET was more sensitive than serum tumour markers in detecting relapses
Siggelkoff et al. 2003	35	80.6%	97.6%	PET had impact on staging and management in case of suspicion and in follow-up setting
Radan et al. 2007	47	90%* 99%°	71%* 72°	PET/CT led to changing clinical management in 51% of patients

*Patient-based analysis; °lesion-based analysis

Suarez et al. studied 45 women with histological diagnosis of breast cancer, who underwent a tumor-guided whole-body PET. All patients were in remission without any signs of relapses except for a progressive increase of CA 15.3 or CEA. FDG-PET results were controlled by pathology when possible or by other conventional imaging methods and clinical follow-up. PET was true positive in 24 patients and true negative in 3 patients. The diagnostic performances of tumor-marker-guided PET per patient resulted in a sensitivity, specificity and accuracy of 92%, 75% and 87% respectively [(24)]. Also, ***Liu et al.*** evaluated 30 patients with suspected recurrent breast cancer and asymptomatic tumor marker increase (CA 15.3 or CEA) with negative or equivocal other imaging modality results.

The final diagnosis of recurrent breast cancer was established by biopsy or clinical follow-up. Among the 30 patients the final diagnosis of recurrent breast cancer was established in 38 sites in 28 patients. PET accurately detected 35 out of 38 sites in 25 out of 28 patients with recurrence. The diagnostic sensitivity and accuracy of FDG-PET in patients with suspected recurrent breast cancer and asymptomatically elevated tumor marker levels were 96% and 90% respectively [(25)]. Furthermore, ***Kamel et al.*** evaluated FDG-PET in 60 patients with suspected local recurrence. In 25 patients the elevation of CA 15.3 was compared with PET results. Disease relapse was proven in 40 patients on the basis of histology and follow-up. Additionally in three patients a second cancer was diagnosed with concomitant disease relapse.

PET missed local recurrences in three patients (false negative) and was false positive in four patients. In patient-based analysis PET sensitivity, specificity and accuracy for loco-regional recurrence were 89%, 84% and 87%, while for distant metastases they were 100%, 97% and 98%, respectively. The author concluded that FDG-PET was more sensitive than serum tumor marker CA 15.3 in detecting relapsed breast cancer [(26)].

In addition, ***Siggelkoff et al.*** studied 35 patients suspected of having recurrent disease or elevated tumor markers. Depending on the region of suspicion, conventional imaging included chest X-ray, MRI, CT and US. All patients had at least a period of 12 months of follow-up. In patients examined because of elevated tumor marker CA 15.3, PET was able to detect recurrence or metastatic disease in six of the eight patients.

PET missed three tumor sites in three patients: two supraclavicular lymph node metastases and one lung metastasis. The overall sensitivity and specificity for PET on the whole series of patients were 80.6% and 97.6, respectively [(27)].

The role of PET/CT in the follow-up of 47 patients with breast cancer who presented with elevated tumor markers has been studied by ***Radan et al***. using FDG/PET studies.

PET/CT results were confirmed by pathology; further imaging and follow-up (mean 17.2 months). Thirty patients (65%) had tumor recurrence and 16 patients (35%) showed no further evidence of disease. PET/CT overall sensitivity, specificity and accuracy of 90%, 71% and 83%, respectively.

The site-based analysis gave sensitivity, specificity and accuracy of 99%, 72% and 96% respectively. PET/CT also had an impact on patient management in 24 cases (51%) [(28)].

For recurrent breast cancer and assessment of loco-regional lymph node metastases, FDG-PET was compared mainly with MRI.

Hathaway et al. compared FDG-PET and MRI in ten patients with clinical suspicion of recurrent loco-regional breast cancer. Nine patients had evidence of loco regional metastases from breast cancer. MRI was diagnostic in five and indeterminate in four patients FDG-avid tumor was identified in all nine patients [(29)].

In a similar study ***Goerres et al***. compared FDG-PET and MRI in 32 patients with suspicious loco-regional recurrence, chest wall recurrence or suspicion of secondary tumor on the contralateral side. Sensitivity, specificity and accuracy were 79%, 94% and 88% for MRI, respectively, compared

to 100%, 72% and 84% for FDG-PET respectively. In five patients (15%) PET detected metastases outside of the axial field-of-view of the MRI [30].

In a retrospective study ***Moon et al.*** investigated 57 patients using FDG-PET with clinical suspicion of recurrent or metastatic disease after a history of breast cancer.

On a patient based analysis they reported a sensitivity and specificity of 93% and 79% respectively. Furthermore, in a retrospective study of 62 patients after surgical resection of breast cancer, we have compared FDG-PET with conventional imaging, including X-ray mammography, US, CT, MRI and bone scans [31]. Patient-based sensitivity, specificity, NPV, PPV and accuracy for PET/CT were 97%, 82%, 92%, 87% and 90% respectively. For comparison, the corresponding values for conventional imaging were 84%, 60%, 75%, 73% and 74%, respectively.

Bender et al. compared the diagnostic accuracy of CT and MRI with that of whole-body FDG-PET in 75 patients with suspected recurrent or metastatic disease [32].

PET imaging correctly identified 28/29 patients with lymph node metastases (97%), 5/6 patients with lung metastases (83%) and 2 patients with liver metastases. In contrast to other author's and our experience, bone metastases were detected in all patients. FDG-PET detected eight lymph node and seven bone metastases that were not detected by CT or MRI [33]. FDG-PET was evaluated in 38/45 patients. PET was positive in 27 patients (24 true positive and 3 false positive); PET was negative in 11 patients (9 true negative, 2 false negative). Tumor marker-guided FDG-PET resulted in sensitivity, specificity, PPV and NPV of 92%, 75%, 89% and 82% respectively. In a meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases from ***Isasi et al,*** [34], including 18 studies, 16 studies reported patient-based data, two studies reported lesion-based data, and five studies reported both scenarios. Among the studies with patient-based data, the median sensitivity was 92.7% ranging from 56 to 100% and the specificity was 81.6% varying from 0 to 100%.

Diagnosis of metastatic lesions: There is evidence that FDG-PET has great potential in tumor staging ***(Fig 1)***, data from the literature indicate that in breast cancer patients, FDG-PET permits complete tumor staging with a single whole-body investigation, even allowing the diagnosis of a significant number of metastases which would have been missed or non-correctly diagnosed by CT, US, MRI, and

also bone scintigraphy, which is still widely used in breast cancer patients. In fact, clinical experience has demonstrated that FDG-PET is often superior to conventional imaging modalities in localizing tumor lesions, as significantly more lesions are detected in different sites. The role of PET in evaluating soft tissue lesions appears to be important (liver, lung, distant lymph nodes). Also, bone metastases of breast carcinoma usually accumulate FDG. The availability of hybrid PET–CT allows better performance when compared with PET alone and of course can improve the diagnostic accuracy in several situations [35, 36].

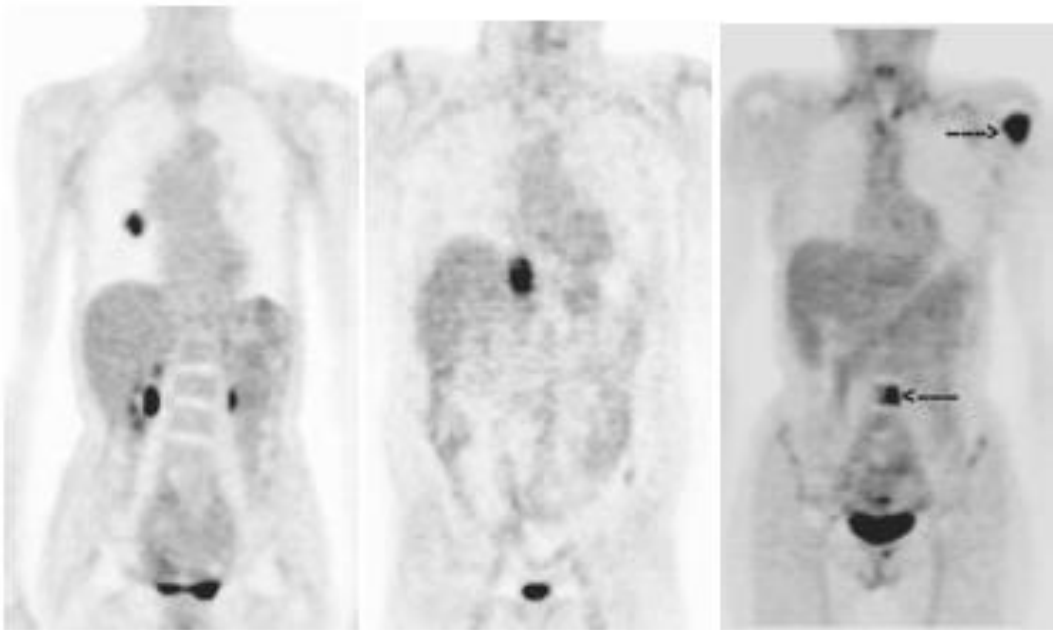

Fig. 1 FDG-PET whole-body scans coronal slices in a patient with multiple bone lesions in shoulder and lumbar-spine (arrows), liver, and lung**.**

A suggestion that PET/CT could provide more accurate diagnosis in re-staging breast cancer can be extrapolated by the work of ***Pelosi et a***l. [37]. Out of the 210 patients recruited, 40 were affected by previously treated breast cancer and examined by PET/CT (*n*=19) or PET with morphological imaging (*n*=21). In the 19 PET/CT patients, 45/47 (96%) lesions were correctly localized. The remaining two lesions with uncertain localization, both located in the mediastinum, could be referred to either lymph node or pleura. In the 21 patients studied by PET only, 58/63 (92%) lesions could be correctly localized with separate morphological imaging. Of the remaining five, four were located in the thorax and could be referred either to bone or soft tissue, and either to lymph node or lung. In the remaining one, located in the

abdomen, the focal FDG uptake could be referred either to lymph node or physiological urinary/intestinal uptake. Additional studies in breast cancer and PET/CT have yielded a higher accuracy than PET alone in re-staging breast cancer patients [(38)].

Van der Hoeven et al. demonstrated that the addition of FDG-PET to the standard work-up of this group of patients can lead to the detection of unexpected distant metastases. This may contribute to a more realistic stratification between patients with true stage III breast cancer and those who are in fact suffering from stage IV disease. The use of FDG-PET in this case prevents patients from being denied appropriate treatment [(39)].

Weir et al. demonstrated that in 165 patients with breast cancer, 5% were diagnosed with distant metastases and distant metastases were demonstrated in 30% of patients who were thought only to have loco regional recurrence [(40)].The presence of distant metastases defines stage IV; the frequency of the topographic distribution of metastases in bone is around 70–80%, 65% in lung, 60% in liver and 25% in brain. Other sites are the ovary up to 45%, thyroid 20%, kidney 15% and gastrointestinal organs 20%. It goes without saying that the diagnosis of metastases is very important because it obviously affects the prognosis and can modify the therapy.

Dose Schwarz et al confirmed the superior sensitivity of FDG-PET in visualizing distant metastases when it was compared to the association of US and bone scintigraphy [(41)].

Yang et al, found that FDG-PET for the diagnosis of bone metastases had sensitivity comparable to that of bone scintigraphy, but the specificity was so far better, with the advantage of also being able to image metastases in soft tissues [(42)].

PET/CT is response of treatment of metastatic lesions: Several studies have shown the prognostic value of FDG-PET after the first cycles of chemotherapy in different cancers [(43)]. In particular, in breast cancer, PET may differentiate responding and non-responding patients as early as after the first cycle of chemotherapy. The FDG standardized uptake value (SUV) is considered the most widely prognostic factor for assessing the response in breast cancer, even in the early phases of treatment [(44)]. As an example, a good correlation between SUV changes and clinical responses was described by ***Stafford et al.*** Although these studies involved a relatively small number of patients, there is evidence that PET may be used for early therapy evaluation of patients with breast cancer [(45)],

in particular in patients with bone-dominant metastatic disease, and in those with locally advanced breast cancer undergoing primary chemotherapy [46], *(Table 3).*

Table 3. FDG-PET in the evaluation of tumor response in metastatic disease.

Monitoring therapy of metastatic disease is difficult, since tissue sampling is not feasible; earlier response assessment could be beneficial to guide further therapy and avoid prolonged treatment with ineffective drugs; CT or MRI is still the standard method to assess treatment, but anatomic changes occur too late in order to assess early treatment response (morphological changes shown by radiological methods take 2–3 months to show evidence); metabolic changes occur much earlier and can be easily assessed with PET	Treatment of metastatic disease SUV, standardized uptake value

Van der Hiel, et al 2001 [47].

Bier sack et al. have demonstrated that a reduction of FDG uptake occurs from 8 to 60 days after the beginning of therapy, while a significant morphological reduction in tumor size requires more time. The metabolic response of the tumor always precedes the dimensionally measurable response, because the effects of the anticancer treatment primarily influence the metabolism and only at a later stage are followed by a decrease of tumor mass. The usefulness of PET in the evaluation of all different types of therapy has been studied (chemotherapy, hormone therapy, and radiotherapy); however, only the therapy response in locally advanced breast cancer patients has been investigated thoroughly [48].

Histo-pathological response could be predicted with an accuracy of around 90%. A semi quantitative evaluation (through the standardized uptake value, SUV) is of course a prerequisite when PET is used for therapy monitoring.

McDermott et al. evaluated FDG-PET for predicting tumor response to neo-adjuvant chemotherapy [49], SUV was measured after the first, second cycle, midpoint and at the end of chemotherapy. The best discrimination was measured for mean SUV at the midpoint of therapy, which correctly identified 77% of low-responding tumors, whilst identifying 100% of high-responding tumors. The predictive value of FDG-PET for the pathological response

after completion of neo-adjuvant chemotherapy was confirmed by ***Kim et al*** [(50)]. FDG-PET study at the end of treatment can be also an index of prognostic stratification for survival. ***Cachin et al.*** demonstrated that FDG-PET study performed after the last cycle of high-dose chemotherapy before autologous stem cell transplantation can powerfully stratify for survival [(51)].

CONCLUSIONS: It seems that PET/CT has diagnostic accuracy in detecting disease relapse with loco regional recurrence which is more evident in aggressive breast cancer. Also, PET/CT is very effective diagnostic whole body imaging for assessment of metastatic spread to lungs, liver, bone and adrenal metastases. Follow-up for assessment after treatment according to molecular subtypes using PET/CT is mandatory as it may be reflected on prognosis.

REFRENCES:

1. ***Brinkley D, Haybittle JL.*** The curability of breast cancer. Lancet. 2: 95–97; 1975.
2. ***Lamovec J, Zidar A.*** Association of leptomeningeal carcinomatosis in carcinoma of the breast with infiltrating lobular carcinoma. An autopsy study. Arch. Pathol. Lab. Med. 115: 507–510; 1991.
3. ***Cook G, Fogelman I***. Skeletal metastases from breast cancer: imaging with nuclear medicine. Semin Nucl. Med. 29:69–79; 1999.
4. ***Lind P, Gallowitsch H, Mikosch P, Kresnik E, Gomez I, Oman J, Dinges H, Boniface G***. Radio immunoscintigraphy with Tc99m labelled monoclonal antibody 170H.82 in suspected primary recurrent, or metastatic breast cancer. Clin. Nucl. Med. 22:30–34; 1997.
5. ***Czernin J*** FDG PET in breast cancer: A different view of its clinical use. Mol. Imag. Biol. 4:35–45; 2002.
6. ***Reske SN and Kotzerke J.*** FDG-PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, “Onko-PET III”, 21 July and 19 September 2000. Eur. J. Nucl. Med. 28:1707–1723; 2001.
7. ***Payne SJL, Bowen RL, Jones JL, Wells CA.*** Predictive markers in breast cancer – the present. Histopathology. 52: 82–90; 2008.
8. ***Yaziji H, Taylor CR, Goldstein NS, Dabbs DJ, Hammond MEH, Hewlett B, Floyd AD, Barry TS, Martin AW,***

Badve S, Baehner F, Cartun RW, Eisen RN, Swanson PE, Hewitt SM, Vyberg M, Hicks DG; Members of the Standardization Ad-Hoc Consensus Committee. Consensus recommendations on estrogen receptor testing in breast cancer by immunohistochemistry.Appl. Immunohistochem Mol. Morphol., 16: 513–520; 2008.

9. ***Carmeci C, DeConinck EC, Lawton T, Block DA, Weigel RJ.*** Analysis of estrogen receptor messenger RNA in breast carcinomas from archival specimens is predictive of tumor biology. Am. J. Pathol.150: 1563–1570; 1997.

10. ***Gupta D, Middleton LP, Whitaker MJ, Abrams J.*** Comparison of fluorescence and chromogenic in situ hybridisation for detection of HER-2/neu oncogene in breast cancer. Am. J. Clin. Pathol. 119: 381–387; 2003.

11. ***Dawkins HJ, Robbins PD, Smith KL, Sarna M, Harvey JM, Sterrett GF, Papadimitriou JM.*** What's new in breast cancer? Molecular perspectives of cancer development and the role of the oncogene c-erbB-2 in prognosis and disease. Pathol. Res. Pract.189: 1233–1252; 1993.

12. ***Oakley GJ 3rd, Tubbs RR, Crowe J, Sebek B, Budd GT, Patrick RJ, Procop GW.*** HER-2 amplification in tubular carcinoma of the breast. Am. J. Clin. Pathol. 126: 55–58; 2006.

13. ***Reis-Filho JS, Tutt ANJ.*** Triple negative tumours: a critical review. Histopathology. 52: 108–118; 2008.

14. ***Correa Geyer F, Reis-Filho JS.*** Microarray based gene expression profiling as a clinical tool for breast cancer management: are we there yet? Int. J. Surg. Pathol. 17: 285–302; 2009.

15. ***Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, Watson M, Davies S, Bernard PS, Parker JS, Perou CM, Ellis MJ, Nielsen TO.*** Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J. Natl. Cancer. Inst. 101: 736–750; 2009.

16. ***Tavassoli FA.*** Correlation between gene expression profiling-based molecular and morphologic classification of breast cancer. Int. J. Surg. Pathol. 18: 167S–169S; 2010.

17. ***Constantinidou A, Jones RL, Reis-Filho JS.*** Beyond triple-negative breast cancer: the need to define new subtypes. Expert Rev. Anticancer Ther. 10: 1197–1213; 2010.

18. ***Weigelt B, Mackay A, A'Hern R, Natrajan R, Tan DS, Dowsett M, Ashworth A, Reis-Filho JS.*** Breast cancer molecular profiling with single sample predictors: a retrospective analysis. Lancet Oncol. 11: 339–349; 2010.

19. ***Messa C, BettinardiV,Picchio M.*** PET/CT in diagnostic oncology. Q J Nucl Med Mol Imaging. 48(2):66-75; 2004.

20. ***Buck A, Wahl A, Eicher U, Blumstein N, Schirrmeister H, Helms G, Glattnig G, Neumaier B, Reske S*** Combined morphological and functional imaging with FDGPET/ CT for restaging breast cancer–impact on patient management. J. Nucl. Med. 44S:78P; 2003.

21. ***Dose J, Bleckmann S, Bachmann S et al*** Comparison of fluorodeoxy glucose positron emission tomography and conventional diagnosis procedures for the detection of distant metastases in breast cancer patients. Nucl. Med. Commun, 23:857–864; 2002.

22. ***Danforth DN Jr, Aloj L, Carrasquillo JA et al***. the role of 18F-FDG-PET in the local/regional evaluation of women with breast cancer. Breast Cancer Res Treat 75:135–146; 2002.

23. ***Lonneux M, Borbath I, Berlìere M, Kirkove C, Pauwels S.*** The place of whole body PET FDG for the diagnosis of distant recurrence of breast cancer. Clin. Positron Imaging. 3:45–49; 2000.

24. ***Suarez M, Perez-Castejon MJ, Jimenez A, Domper M, Ruiz G, Montz R, Carreras JL*** Early diagnosis of recurrent breast cancer with FDG-PET in patients with progressive elevation of serum tumor markers. Q. J. Nucl. Med. 46:113–121; 2002.

25. ***Liu CS, Shen YY, Lin CC, Yen RF, Kao CH.*** Clinical impact of 18F-FDG PET in patients with suspected recurrent breast cancer based on asymptomatically elevated tumor marker serum levels: a preliminary report. Jpn. J. Clin. Oncol. 32:244–247; 2002.

26. ***Kamel EM, Wyss MT, Fehr ML, von Schulthess GK, Goerres GW*** 18F-fl uorodeoxyglucose positron emission tomography in patients with suspected recurrence of breast cancer. J. Cancer Res. Clin. Oncol. 129:147–153; 2003.

27. ***Siggelkow W, Rath W, Buell U, Zimny M.*** FDG PET and tumour markers in the diagnosis of recurrent and metastatic breast cancer. Eur. J. Nucl. Med. Mol. Imaging. 31:S118–S124; 2004.

28. ***Radan L, Ben-Haim S, Bar-Shalom R, Guralnik L, Isreal O.*** The role of FDG-PET/CT in suspected recurrence of breast cancer. Cancer. 107:2545–2551; 2006.

29. ***Hathaway P, Mankoff D, Maravilla K, Austin-Seymour M, Gralow J, Cortese A, Hayes C, Moe R.*** Value of combined FDG PET and MRI imaging in the evaluation of suspected recurrent local-regional breast cancer: preliminary results. Radiology.210:807–814; 1999.

30. Go***erres G, Michel S, Fehr M, Kaim A, Steinert H, Seifert B, SchulthessGv, Kubik-Huch R*** Follow-up of women with breast cancer: comparison between MRI and FDG PET. Eur. Radiol.13:1635–1644; 2003.

31. ***Gallowitsch H, Kresnik E, Gasser J, Kumnig G, Igerc I, Mikosch P, Lind P*** (2003) F-18 fluorodeoxyglucose positron-emission tomography in the diagnosis of tumor recurrence and metastases in the follow up of patients with breast carcinoma: a comparison to conventional imaging. Invest Radiol. 38:250–256; 2003.

32. ***Bender H, Kirst J, Palmedo H.*** Value of 18fl uorodeoxyglucose positron emission tomography in the staging of recurrent breast cancer. Anticancer Res. 17(3B):1687– 1692; 1997.

33. ***Suarez M, Perez-Castejon M, Jimenez A, Domper M, Ruiz G, Carreras J.*** Early diagnosis of recurrent breast cancer with FDG PET in patients with progressive elevation of serum tumor markers. Q. J. Nucl. Med. 46:113 121; 2002.

34. ***Isasi CR, Moadel RM, Blaufox MD.*** A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res. Treat. 90:105–112; 2005.

35. ***Kumar R, Alavi A.*** Fluorodeoxy glucose-PET in the management of breast cancer. Radiol Clin. North Am. 42: 1113–22; 2004.

36. ***Rouesse J, Alberini JL, Wartski M et al.*** [FDG (18fluorodeoxyglucose) positron emission tomography and breast cancer. Bull Acad. Natl. Med. 189: 963–75; 2005.

37. ***Pelosi E, Messa C, Sironi S, Picchio M, Landoni C, Bettinardi V, Gianolli L, Del Maschio A, Gilardi MC, Fazio F***. Value of integrated PET/CT for lesion localization in cancer patients: a comparative study. Eur. J. Nucl. Med. Mol. Imaging 31:932–939; 2004.

38. ***Quon A, Gambhir SS.*** FDG-PET and beyond: molecular breast cancer imaging. J Clin. Oncol.10:1664–1673; 2005.

39. ***Van der Hoeven JJ, Krak NC, Hoekstra OS et al.*** 18F- 2-fluoro-2-deoxy-D-glucose positron emission tomography in staging of locally advanced breast cancer. J. Clin. Oncol. 22: 1253–9; 2004.

40. ***Weir L,Worsley D, Bernstein V.*** The value of FDG positron emission tomography in the management of patients with breast cancer. Breast J. 11: 204–9; 2005.

41. ***Dose Schwarz J, Bader M, Jenicke L, Hemminger G, Janicke F, Avril N.*** Early prediction of response to chemotherapy in metastatic breast cancer

using sequential 18FFDG PET. J. Nucl. Med, 46:1144–1150; 2005.

42. [1]***Tran A, Pio BS, Khatibi B, Czernin J, Phelps ME, Silverman DH.*** 18F-FDG PET for staging breast cancer in patients with inner-quadrant versus outer-quadrant tumors: comparison with long-term clinical outcome. J. Nucl. Med. 46:1455–1459; 2005.

43. ***Yang SN, Liang JA, Lin FJ, Kao CH, Lin CC, Lee CC.*** Comparing whole body 18F-2-deoxyglucose positron emission tomography and technetium-99m methylene diphosphonate bone scan to detect bone metastases in patients with breast cancer. J Cancer Res. Clin. Oncol, 128:325–328; 2002.

44. ***Voogd AC, Nielsen M, Peterse JL et al.*** Breast Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J. Clin. Oncol, 19:1688–1697; 2001.

45. ***Weir L, Worsley D, Bernstein V.*** The value of FDG positron emission tomography in the management of patients with breast cancer. Breast J. 11:204–209; 2005.

46. ***Van der Hiel B, Pauwels EKJ, Stokkel MP.*** Positron emission tomography with 2-(18F)-fluoro-2-deoxy-D glucose in oncology. Part IIIA: therapy response monitoring in breast cancer, lymphoma and gliomas. J. Cancer Res. Clin. Oncol.127: 269–77; 2001.

47. ***Bier sack HJ, Bender H, Palmedo H.*** FDG-PET in monitoring therapy of breast cancer. Eur. J. Nuc. Med. Mol. Imaging. 31: S112–17; 2004.

48. ***McDermott GM, Welch A, Staff RT et al.*** Monitoring primary breast cancer throughout chemotherapy using FDGPET. Breast Cancer Res Treat Aug 9; 2006 . Epub ahead of print.

49. ***Kim SJ,Kim SK, Lee ES,RoJ,Kang S.*** Predictive value of 18F FDG-PET for pathological response of breast cancer to neo adijuvant chemotherapy. Ann. Oncol. 15: 1352–7; 2004.

50. ***Cachin F, Prince HM, Hogg A, Ware RE, Hicks RJ.*** Powerful prognostic stratification by 18F fluorodeoxy glucose positron emission tomography in patients with metastatic breast cancer treated with high-dose chemotherapy. J. Clin. Oncol. 24: 3026–31. 2006.