Utility of ^{18}FDG-PET/CT in breast cancer diagnostics – a systematic review

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ABSTRACT

^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) is a non-invasive method for visualization of focally increased metabolism in the presence of discrete morphological changes. Based on a systematic review of current literature, PET/CT cannot be recommended as a primary diagnostic procedure in breast cancer; but it has the potential to be useful for the detection of distant metastases and for monitoring response to chemotherapy in breast cancer patients. PET/CT should still be regarded as a supplement to conventional diagnostic procedures such as CT and MRI.

Breast cancer (BC) is the most frequent malignant disease among women in Denmark with more than 4,100 new cases and nearly 1,300 deaths annually [1, 2]. The prognosis depends on a number of tumour characteristics, e.g. tumour size, spread to regional lymph nodes and distant metastases. Early diagnosis improves survival [3]. Positron emission tomography (PET) is a visualisation technique based on increased uptake of the radioactively marked glucose analogue ^{18}F-fluorodeoxyglucose (^{18}FDG) in cells with augmented glucose metabolism (**Figure 1**). Used in combination with computed tomography (CT), the technique facilitates a more precise localization of areas with an increased fluorodeoxyglucose (FDG) uptake [4]. This systematic review gives an overview of the utility of ^{18}FDG-PET/CT for primary diagnosis, staging and response to chemotherapy in BC.

MATERIAL AND METHODS

A literature search was performed in the Medline database using the following search terms: "positron emission tomography", "breast neoplasms", "neoplasm staging", "primary tumour", "diagnosis", "axillary staging", "axillary metastases", "distant metastases", "recurrence", "bone metastases", "bone scintigraphy", "chemotherapy", "response to therapy" and "metastases". Further references were found by chain searching. Reviews and original papers were selected from 1992 to 2010. The sections "primary tumour" and "the axilla" comprise only studies assessing primary, operable BC, while the section on "distant metastases" focuses on ^{18}FDG-PET for detection of distant metastases at baseline, in connection with recurrence and bone metastases.

RESULTS

Primary tumour

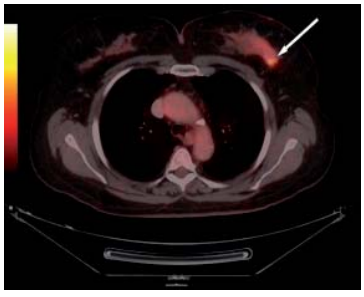
Table 1 shows a total of 19 studies on ^{18}FDG-PET for the detection of primary breast tumours compared with histopathologic examination of tumour tissue after biopsy or surgery. Sensitivity ranged from 48% to 96% and specificity from 73% to 100%. Cermic et al [5] examined 162 patients with biopsy-verified BC and showed that sensitivity increased with tumour size. In Danforth et al's material [6], sensitivity increased with grade of malignancy from 83% for grades I and II to 96% for grades III and IV.

Avril et al [7] examined 144 patients in whom suspected malignancy had been detected by mammography or clinical examination and achieved 80% sensitivity and 76% specificity. For carcinoma in situ, the sensitivity was 42% which rose to 68% for tumours < 20 mm and to 100% for tumours > 50 mm. The poor detection rate for smaller tumours is probably the main limitation for the use of ^{18}FDG PET in the diagnosis of primary BC [8-10]. Kumar et al [11] reported an eight fold higher risk of false negative results in the detection of primary tumours measuring less than 10 mm than in tumours measuring more than 10 mm.

The axilla

The primary sites for lymph node metastases from BC

FIGURE 1



Example of a positron emission tomography/computed tomography of a patient with left-sided breast cancer. The arrow points towards increased fluorodeoxyglucose uptake laterally in the left breast.

SYSTEMATIC REVIEW

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Dan Med Bul 2011;58(7):A4289

ABBREVIATIONS

^{18}FDG = ^{18}F-fluorodeoxyglucose
^{99m}Tc-HMDP = ^{99m}technetium-hydroxymethylene diphosphonate
ALND = axillary lymph node dissection
BC = breast cancer
CT = computed tomography
MRI = magnetic resonance imaging
PET = positron emission tomography
SLN = sentinel lymph node biopsy
SUV = standardised uptake value
US = ultrasound

are the axillary, periclavicular and parasternal lymph nodes. Surgery includes lumpectomy or mastectomy and sentinel lymph node biopsy (SLN) or axillary lymph node dissection (ALND). If ^{18}FDG-PET can be used as a non-invasive identification of lymph node metastases, SLN can be avoided when no metastases are found, and if positive, ALND can be performed directly.

Table 2 shows that the sensitivity for diagnosis of axillary metastases was 79-100% in studies performed before 2000. More recent studies have reported a lower sensitivity, some studies down to 20% (Table 2). Danforth er al [6] found a sensitivity of 43% for stage I and II disease, and 83% for stage III and IV. Avril et al [12] reported a sensitivity and a specificity of 79% and 96%, respectively. These figures increased to 94% and 100%, respectively, when the analysis included only patients with primary tumours > 20 mm. In a subset of the Gil-Reno study [13], the sensitivity was 100% among 50 females with grade III invasive ductal carcinomas.

Table 2 is divided into two parts, the lower showing ^{18}FDG-PET only studies, while the top part shows nine more recent studies with PET combined with CT ([14-18] and more). Eight of these studies compared PET/CT with other diagnostic modalities, and seven studies reached the conclusion that PET/CT was not significantly different from traditional methods such as SLN, ultrasound (US) or CT scan for the detection of axillary metastases. The sensitivity ranged from 20% to 98% and the specificity from 84% to 100%. Piperkova et al [15] compared PET/CT with CT and found a sensitivity and specificity of 98% versus 88% and 94% versus 42%, respectively. Based on the PET/CT results, staging and, consequently, therapy was changed in 65% of the patients. The authors concluded that PET/CT played a more important role than diagnostic CT alone in the detection of lymph node metastases.

TABLE 1

Overview of studies on ^{18}F-fluorodeoxyglucose-positron emission tomography for the detection of primary breast tumours.

Reference, year	Patients, n	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Heusner et al, 2008[a] [17]	40	95	–	–	–
Cermik et al, 2008 [5]	162	72	–	–	–
Kumar et al, 2006 [11]	111	48	97	98	40
Heinisch et al, 2003 [8]	36	76	73	80	69
Danforth et al, 2002 [6]	46	90	–	–	–
Rieber et al, 2002 [32]	43	93	–	–	–
Schirrmeister et al, 2001 [29]	117	93	75	92	78
Avril et al, 2000 [7]	144	80	76	89	61
Yutani et al, 2000 [33]	40	79	–	–	–
Hubner et al, 2000 [34]	35	96	91	–	–
Rostom et al, 1999 [10]	93	91	83	–	–
Noh et al, 1998 [26]	26	96	100	–	–
Palmedo et al, 1997 [9]	20	92	86	–	–
Scheidhauer et al, 1996 [19]	30	91	86	95	75
Avril et al, 1996 [35]	51	68	84	87	70
Bruce et al, 1995 [36]	15	93	–	–	–
Adler et al, 1993 [37]	28	96	100	–	–
Nieweg et al, 1993 [38]	13	91	89	–	–
Tse et al, 1992 [39]	14	80	100	–	–

NPV = negative predictive value; PPV = positive predictive value.
a) ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography.

Distant metastases

BC spreads locally to the skin, to the soft tissue surrounding the scar and to lymph nodes, while distant metastases are located primarily to bones, lungs, the liver and to the central nervous system.

Baseline: Six studies (marked in **Table 3**) have focused on the utility of ^{18}FDG-PET for the detection of distant metastases at baseline staging ([16, 17, 19, 20] and more). These studies showed a sensitivity of 80-100% and a specificity of 75-100%. Four of the studies ([16, 20] and more) included patients with primary tumours exceeding 30 mm and/or a high malignancy grade. The two remaining studies [17, 19] included 70 patients with suspected BC based on mammography or X-ray and both had a sensitivity and a specificity of 100%.

Recurrence: Table 3 shows 22 studies including a total of 1,105 patients with prior BC and clinical suspicion of recurrence. The sensitivity for detection of distant metastases ranged from 83% to 100% and the specificity from 20% to 100%. In five studies of combined PET/CT (marked in Table 3), the sensitivity was 90-97% and the specificity was 71-92%, which indicates a marginally increased diagnostic precision.

Comparison with conventional methods: In six studies comparing PET with multi-modal detection methods (chest X-ray, US of the abdomen and bone scintigraphy) and CT, PET had a clearly better sensitivity ([16, 17] and more). Three studies compared PET with magnetic resonance imaging (MRI) and found a high sensitivity and precision compared with MRI. Lymph node metastases were detected significantly more frequently with PET than with MRI.

Bone metastases: The bones are frequent sites of BC metastases: almost 71% of patients with metastatic BC develop bone metastases.

Table 4 shows eight studies comparing FDG-PET with ^{99m}Technetium bone scintigraphy for the detection of bone metastases and one study which compared PET with CT/MRI. PET sensitivity ranged from 17% to 100% (46-93% using conventional methods) and PET specificity from 88% to 100% (81-100% using conventional methods). It has been reported that PET was superior for the detection of osteolytic metastases with a visualisation rate of 100% versus 70% for scintigraphy. However, scintigraphy outperformed PET in osteosclerotic lesions with a 100% visualization rate versus 56% for PET.

Response to chemotherapy

An effective method for monitoring of the response to chemotherapy is needed to ensure early identification of non-responders. Conventional methods include physical examination, X-ray, US and mammography, but the clinical response does not necessarily reflect the patho-anatomical response. Several studies have demonstrated that changes in tumour metabolism may occur early and precede tumour size reduction. ^{18}FDG-PET is therefore relevant for assessment of the therapeutic response based on early changes in the tumour-glucose metabolism.

^{18}FDG-PET for prediction of the therapeutic response during systemic chemotherapy was assessed in 104 patients with primary BC or locally advanced BC. The histopathologic response after surgery was used as "gold standard". Patients underwent a PET scan at baseline and after the first and second series of chemotherapy with calculation of a standardised uptake value (SUV = a quantitative measure of FDG uptake). In responding patients, the SUV decreased after the initial series by 51% ± 18% compared with the baseline value. Among non-responders, the reduction was 37% ± 21%. After the second series, the SUV decreased by 63% ± 19% among responders compared with 48% ± 19% among non-responders. Already at baseline, a difference in FDG was observed as responder SUV was 7.4 ± 3.6 compared with 5.5 ± 3.7 in non-responders. The study confirms experiences from previous studies.

Six studies evaluated the therapeutic response in patients with metastatic breast cancer. Three studies found a significant SUV reduction after one or two series of chemotherapy. In one study, the SUV fell to 72% of the baseline value after the initial series and to 54% after the second series among responders, compared with reductions to 94% and 79, respectively, among non-responders. However, in another study there was no statistically significant difference between responders and non-responders until after the third series when responders' SUV was reduced by 52% compared with 16% among non-responders.

TABLE 2

Overview of studies on ^{18}F-fluorodeoxyglucose-positron emission tomography for the detection of axillary metastases.

Reference, year	Patients, n	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Chae et al, 2009[a] [18]	108	49	84	–	–
Taira et al, 2009[a] [22]	90	48	92	72	81
Heusner, 2009[a, b]	61	58	92	82	77
Monzawa, 2009[a, b]	50	20	97	75	74
Ueda et al, 2008[a] [14]	183	58	95	85	83
Fuster et al, 2008[a] [16]	52	70	100	–	–
Heusner et al, 2008[a] [17]	30	80	–	–	–
Piperkova et al, 2007[a] [15]	49	98	94	99	85
Veronesi et al, 2007[a] [21]	236	37	96	88	66
Mahner et al, 2008 [20]	119	86	97	–	–
Kumar et al, 2006 [11]	80	44	95	89	–
Chung, 2006[b]	51	60	100	100	51
Gil-Rendo et al, 2006 [13]	275	85	99	98	86
Fehr, 2004[b]	24	20	93	67	62
Lovrics, 2004[b]	98	40	97	82	80
Zornoza et al, 2004 [30]	200	84	98	98	–
Wahl et al, 2004 [31]	360	61	80	62	79
Barranger et al, 2003 [28]	32	20	100	100	59
Rieber et al, 2002 [32]	40	80	95	94	95
Van der Hoeven, 2002[b]	70	25	97	89	61
Danforth et al, 2002 [6]	46	68	67	81	50
Greco et al, 2001 [23]	167	94	86	84	95
Schirrmeister et al, 2001 [29]	117	79	92	82	91
Yang, 2001[b]	18	50	100	100	80
Ohta, 2000[b]	32	70	100	–	–
Yutani et al, 2000 [33]	40	50	100	100	73
Rostom et al, 1999 [10]	74	86	100	–	–
Crippa et al, 1998 [24]	72	85	91	–	–
Smith et al, 1998 [25]	50	90	97	95	96
Noh et al, 1998 [26]	26	100	92	–	–
Adler et al, 1997 [27]	52	95	66	63	95
Avril et al, 1996 [35]	51	79	96	95	84
Scheidhauer et al, 1996 [19]	18	100	89	90	100
Utech, 1996[b]	124	100	75		100

NPV = negative predictive value; PPV = positive predictive value.
a) ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography; b) For a full list of references, please contact the authors.

DISCUSSION

Primary tumour

All studies were affected by selection bias as all included patients were selected with a verified or suspected BC. Almost all studies concluded that ^{18}FDG-PET is not suitable for the detection of primary tumours due to its low sensitivity in 0-10 mm tumours. This may be due to the technique's limited spatial resolution and few metabolically active cells in 0-10 mm tumours. Thus, ^{18}FDG-PET is suitable neither for detection of primary tumours, nor

TABLE 3

Overview of studies on ^{18}F-fluorodeoxyglucose-positron emission tomography for the detection of distant metastases from breast cancer.

Reference, year	Metastases	Patients, n	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Aukema, 2010[a,c]	Distant	56	97	92	94	96
Schmidt, 2008[a,c]	Distant	33	91	90	–	–
Haug, 2007[a,c]	Distant	34	96	89	96	89
Radan, 2006[a,c]	Distant	46	90	71	84	80
Fueger, 2005[a,c]	Distant	58	94	84	89	91
Fuster et al, 2008[a, b] [16]	Distant	60	100	98	–	–
Heusner et al, 2008[a, b] [17]	Distant	40	100	100	100	100
Mahner et al, 2008[b] [20]	Distant	69	93	85	–	–
Port, 2006[b,c]	Distant	80	80	94	–	–
Landheer, 2005[b,c]	Distant	17	100	75	20	100
Scheidhauer et al, 1996[b] [19]	Distant	30	100	100	100	100
Landheer, 2005[c]	Distant	25	95	20	83	50
Weir, 2005[c]	Distant	27	89	88	–	–
Eubank, 2004[c]	Distant	125	94	91	98	77
Grahek, 2004[c]	Distant	75	84	78	92	61
Goerres, 2003[c]	Distant	32	100	72	74	100
Kamel, 2003[c]	Distant	27	100	97	96	100
	Local		89	84	89	84
Gallowitsch, 2003[c]	Distant	62	97	82	87	96
Lin, 2003[c]	Distant	36	83	85	79	89
	Local		100	97	80	100
Liu, 2002[c]	Distant	30	96	–	–	93
Dose, 2002[c]	Distant	50	86	90	93	83
Suárez, 2002[c]	Distant	38	92	75	89	82
Pecking, 2001[c]	Distant	119	93	30	87	46
Eubank, 2001[c]	Distant	33	85	90	–	–
Kim, 2001[c]	Distant	27	94	80	89	89
	Local		88	100	100	80
Hathaway, 1999[c]	Local	10	100	100	100	100
Moon, 1998[c]	Distant	57	93	79	82	92
Bender, 1997[c]	Local	75	80	96	89	93
	Bones		100	98	94	100
	Lungs		83	97	71	99
	Liver		100	97	50	100
	Lymph nodes		97	91	88	98

Local = in the axillary and supraclavicular region.
NPV = negative predictive value; PPV = positive predictive value.
a) ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography; b) Baseline;
c) For a full list of references, please contact the authors.

for screening. However, dedicated breast PET/CT scanners are in the pipeline. In the future, they are expected to change the diagnostic capacity of PET/CT scanners for detecting malignant breast tumours.

The axilla

Early positive results were not confirmed. On the contrary, it seems that ^{18}FDG-PET cannot be used for detection of axillary metastases as its sensitivity is too low. The SLN method has improved over time to detect more micro metastases, thus improving the gold standard and making the sensitivity appearing lower in more recent studies. In eight studies ([14-17, 21-22] among others) PET/CT was compared with other diagnostic modalities and the studies concluded that PET/CT was not – either alone or in combination with US and mammography – sufficiently reliable for detection of axillary metastases. However, according to Piperkova et al [15], PET/CT did prove superior to CT alone for the detection of axillary metastases.

The gold standard of all studies was SLN with subsequent immunohistochemistry. Generally, a high specificity was observed, implying that a positive finding in the axilla may be seen as reliable indicator of lymph node involvement. Veronesi et al [21] showed that in 38 of 43 cases with a positive scan, metastases were found in the lymph nodes. When an axillary FDG uptake is observed, there is a high probability of metastases and in these cases, SLN may be omitted and axillary dissection may be performed directly. On the other hand, the reliability of a negative PET scan is very low, and thus PET cannot replace SLN.

The results from the reviewed studies vary which may be due to differences in the implementation of the gold standard and differences in scanning procedures and assessment criteria. The major source of error is the considerable variation from one study population to the other with respect to the prevalence of lymph node involvement.

Distant metastases

Generally, the studies showed that a positive PET scan predicted metastatic activity, while a negative scan with considerable probability indicated absence of disease. PET may thus be considered a sensitive diagnostic test which may play an important part in the detection of metastases either at baseline or in recurrent BC.

A general source of error is the lack of a common reference for verification of distant metastases. Biopsies have rarely been taken for histological examination of the metastases, possibly due to inaccessible locations. Diagnostic methods such as CT and MRI have therefore been employed as uncertain gold standards. In comparison to conventional methods, PET has superior sensitivity ([16, 17] among others). A meta-analysis from January 2010 concluded that ^{18}FDG-PET and MRI were equal for the detection of metastases.

The results on bone metastases are contradictory but there is an overall agreement that PET and bone scintigraphy are mutually complementing methods. PET is superior for the detection of osteolytic metastases, while bone scintigraphy should be preferred for osteosclerotic lesions. A possible explanation for this may be that osteoblast proliferation in osteosclerotic lesions increases the bone matrix whereby the cell density and therefore the FDG uptake is decreased. A meta-analysis

from April 2010 compared ^{18}FDG-PET, bone scintigraphy and MRI and concluded that MRI is superior to PET for the diagnosis of bone metastases.

The use of the Na-^{18}F-fluoride PET tracer has yielded a higher sensitivity for the detection of bone metastases than conventional bone scintigraphy and PET/CT with ^{18}FDG. Therefore there is a potential for development of new methods using the Na-^{18}F-fluoride PET tracer in future detection of bone metastases.

Response to chemotherapy

^{18}FDG-PET has the potential to assess the effect of chemotherapy in patients with locally advanced or metastatic BC. Five studies found that a change in FDG uptake after the first series predicted a therapeutic response, while others found no statistically significant difference in the SUV of responders and non-responders until after the second or third series. A persisting, high FDG uptake during chemotherapy predicts resistance with a high probability, while a clear decrease in uptake provides some indication of therapeutic response. However, absence of FDG uptake is not a reliable indicator of absence of tumour tissue, as chemotherapy may reduce the metabolic activity and therefore FDG uptake to below detectable limits.

Histopathologic response criteria and SUV threshold values are not identical across studies. These practical procedures should be standardised to improve the basis of comparison. Results are promising and point to ^{18}FDG-PET as an important clinical method for the assessment of therapy response in patients with BC.

CONCLUSION

^{18}FDG-PET alone or in combination with CT is not a reliable method for the diagnosis and screening of primary tumours of the breast due to a too low sensitivity for 0-10 mm tumours. The sensitivity for detection of lymph node metastases is also low. However, the generally high specificity seems to indicate that a positive PET of the axilla is a reliable indicator of lymph node involvement.

A positive PET can predict metastatic or recurrent disease, while a negative scan with a high probability indicates absence of disease in patients with suspected metastatic or recurrent disease. PET has a high sensitivity for detection of osteolytic bone metastases, and it seems useful to employ this method as a complement to bone scintigraphy. However, the method has a low sensitivity for detection of osteosclerotic lesions and it should therefore not replace scintigraphy.

FACTS

^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) is a non-invasive method for the visualisation of focally increased metabolism that may be used even in connection with modest morphological tissue changes.

^{18}FDG-PET/CT is not suitable for primary diagnosis of breast tumours due to the too low sensitivity in tumours ranging from 0-10 mm.

^{18}FDG-PET/CT is not suitable for primary detection of lymph node metastases in the axilla due to the too low sensitivity in micro metastases.

^{18}FDG-PET/CT is a suitable method for the detection of distant metastases, but cannot replace conventional methods such as computed tomography, magnetic resonance imaging and bone scintigraphy.

^{18}FDG-PET/CT is a promising method for monitoring of response to chemotherapy.

TABLE 4

Overview of studies on ^{18}F-fluorodeoxyglucose-positron emission tomography for the detection of bone metastases from breast cancer.

		^{18}FDG-PET, %		^{99m}Tc-scintigraphy/CT/MRI, %	
Reference, year	**Patients**	**sensitivity**	**specificity**	**sensitivity**	**specificity**
Uematsu, 2005[b]	15	17	100	85	99
Abe, 2005[b]	44	100	97	79	100
Nakai, 2005[b]	55	80	88	78	82
Gallowitsch, 2003[b]	62	92	92	92	82
Dose, 2002[b]	50	83	89	89	92
Yang, 2002[b]	48	95	–	93	–
Ohta, 2001[b]	51	78	98	78	81
Cook, 1998[b]	23	–	–	–	–
Bender, 1997[a, b]	75	100	98	46	98

^{18}FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; ^{99m}Tc-scintigraphy = ^{99m}technetium-scintigraphy; CT = computed tomography; MRI = magnetic resonance imaging.
a) Comparison of PET and CT/MRI; b) For a full list of references, please contact the authors.

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ACCEPTED: 15 May 2011
CONFLICTS OF INTEREST: none

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