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Published in:
Breast Cancer Research and Treatment

DOI:
10.1007/s10549-020-05929-3

Publication date:
2021

Document version:
Accepted manuscript

Citation for pulished version (APA):
Vogsen, M., Jensen, J. D., Christensen, I. Y., Gerke, O., Jylling, A. M. B., Larsen, L. B., Braad, P.-E., Søe, K. L., Bille, C., Ewertz, M., & Hildebrandt, M. G. (2021). FDG-PET/CT in high-risk primary breast cancer: a prospective study of stage migration and clinical impact. *Breast Cancer Research and Treatment*, *185*(1), 145-153. https://doi.org/10.1007/s10549-020-05929-3

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Download date: 11. Jan. 2025

FDG-PET/CT in high-risk primary breast cancer – a prospective study of stage migration and clinical impact

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Abstract

Purpose To investigate the clinical impact of FDG-PET/CT for staging and treatment planning in high-risk primary breast cancer.

Methods Women with high-risk primary breast cancer were enrolled between September 2017 and August 2019 at Odense University Hospital, Denmark. Conventional mammography with/without MRI was performed before staging by FDG-PET/CT. We studied the accuracy of FDG-PET/CT for the detection of distant metastases, the effect on the change of treatment, and the prevalence of incidental findings. Biopsy and follow-up were used as a reference standard for the accuracy analysis.

Results Of 103 women, 24 (23%) were diagnosed with distant metastases by FDG-PET/CT. Among these, breast surgery was omitted in 18 and could have been spared in six. Another sixteen (16%) patients were upstaged to more advanced loco-regional disease, leading to more extensive radiotherapy. Sensitivity and specificity for diagnosing distant metastases were 1.00 (95% confidence interval: 0.86-1.00) and 0.95 (0.88-0.99), respectively. Twenty-nine incidental findings were detected in 24 women (23%), leading to further examinations in 22 and diagnosis of eight (8/22, 36%) synchronous diseases: cancer (n=4), thyroiditis (n=2), aorta aneurysm (n=1), and meningioma (n=1).

Conclusions FDG-PET/CT had a substantial impact on staging and change of treatment in women with high-risk primary breast cancer, and further examination of incidental findings was considered clinically relevant. Our findings suggest that FDG-PET/CT should be considered for primary staging in high-risk primary breast cancer to improve treatment planning.

Keywords Breast cancer; FDG-PET/CT; stage migration; clinical impact; incidental findings

Introduction

Correct staging of breast cancer is of paramount importance in the planning of the optimal treatment for breast cancer. Staging is based on TNM guidelines from the American Joint Committee on Cancer Staging (AJCC) and is associated with prognosis. [1] However, the choice of imaging modality for staging is not provided in the staging guidelines.

International clinical guidelines [2,3] make no clear recommendations on diagnostic procedures in high-risk primary breast cancer, and imaging modalities varying between conventional computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI), ultrasound of the abdomen, and various bone scans. Different diagnostic modalities have different diagnostic accuracies which may lead to variable results in staging. [4,5]

In recent years, 18F-fluoro-deoxy-glucose-positron emission tomography / computed tomography (FDG-PET/CT) is more accurate than conventional imaging for the examination of high-risk primary breast cancer in stage IIB or higher regardless of age, malignancy grade, and receptor status. [6-8] Compared to conventional imaging, more metastases are detected by FDG-PET/CT to the internal mammary lymph nodes, infra- or supraclavicular nodes, and distant sites. [5,6,8,9]

Stage migration from an initial less advanced stage into a more advanced stage of the disease could have the potential to improve stage-specific survival in early-stage breast cancer due to a more correct allocation into stages. [7] Apart from stage-specific prognosis, the correct staging of patients implies optimal treatment planning of surgery, radiotherapy, and medical treatment.

It is well-known that FDG-PET/CT has the potential to detect incidental findings. We lack information on the extent and clinical implications of such incidental findings among patients with primary breast cancer.

While FDG-PET/CT remains an optional modality in international clinical and staging guidelines, [2,3,1] we aimed to investigate the overall clinical impact of using FDG-PET/CT in women with high-risk primary breast cancer. We studied 1) the accuracy of FDG-PET/CT for diagnosing distant metastasis, 2) the impact on staging and effect on the change of treatment, and 3) the extent and consequences of detecting incidental findings.

Methods

Women with high-risk primary breast cancer were referred for additional staging with FDG-PET/CT. We examined the extent of stage migration, impact on treatment planning, accuracy for staging distant metastases, and the extent and consequences of detecting incidental findings.

Study design

We conducted a prospective diagnostic study of the accuracy of FDG-PET/CT for diagnosing distant metastases. The STARD guideline [10] was used for reporting accuracy results.

Patients

The study was carried out at a single institution (Odense University Hospital, Denmark) over a two-year period from September, 1st, 2017 to August, 31st, 2019.

To be eligible, women had to be older than 18 years with biopsy-verified primary breast cancer at high risk of metastatic spread and to sign an informed consent. High-risk was defined as either: i) inoperable locally advanced breast cancer (LABC), ii) tumor size ≥ 50 mm, iii) ≥ 4 tumor positive axillary lymph nodes after surgery, or iv) tumor size ≤ 49 mm with the addition of either: specific symptoms, changes in blood tests, aggressive subtype (triple-negative breast cancer (TNBC) or human epidermal growth factor receptor-2 (HER2) positive breast cancer), or other findings in the initial staging raising suspicion of metastatic spread. Women were excluded if they were diagnosed with primary metastatic breast cancer (MBC) before referral for FDG-PET/CT, pregnant, in treatment for other invasive cancers, or suffered from conditions that precluded the patient's understanding of the study.

All women had prior conventional mammography with/without MRI, blood test, and chest x-ray. All breast tumors and suspected axillary lymph nodes were verified by biopsies at diagnosis and before FDG-PET/CT. Knowledge of performed biopsies was taken into account in the FDG-PET/CT assessment. FDG-PET/CT was performed before treatment and at the latest after surgery in the group of women with unexpected high lymph node involvement. Information on histopathologic characteristics derived from the primary core needle biopsy for women who had FDG-PET/CT before surgery. For women who had surgery before FDG-PET/CT, the histopathologic characteristics were obtained from the pathology report. Patients were allocated into immune-histochemical subtypes according to St. Gallen consensus guidelines 2011. [11]Patients with oligometastatic disease or clinical doubt about the diagnosis had a biopsy taken from a suspected metastatic lesion, while patients with unambiguous metastases did not undergo biopsies. No patients had confirmatory biopsies from regional

lymph nodes metastases outside the axilla.

Data collection

The secure electronic systems: Research Electronic Data Capture (RedCap) and Sharepoint were used for data collection. We collected patient and disease-specific characteristics regarding age, the reason for referral to FDG-PET/CT, pathology, as well as scan and medical reports. TNM classification was performed before and after information from the FDG-PET/CT.

FDG-PET/CT image technique

Based on intravenous injection of 4 MBq [^{18}F]-FDG per kg bodyweight, PET imaging was performed 60 ± 5 min p.i. from the top skull to mid-thigh on the GE PET/CT system Discovery MI or Discovery 710 (GE Healthcare, Waukesha, WI, USA) according to standard guidelines from the European Association of Nuclear Medicine.[12] Before [^{18}F]-FDG injection patients fasted for at least four hours. Blood sugar levels were measured routinely. Immediately following the low-dose PET/CT a diagnostic CT was acquired with in-vivo contrast (ultravist 370 I/ml) over the PET scan field-of-view using a standard CT protocol.

FDG-PET/CT image interpretation

As part of daily clinical practice, all scans were visually assessed by two experienced physicians in nuclear medicine and radiology, respectively. A combined image interpretation was available for clinical and research assessment and was used for further clinical workup. In cases of uncertainty, a consensus was reached in multidisciplinary conferences.

For staging distant metastases, the result from the scan report was ranked by an oncologist (MV) in a Likert scale: 0 – "no suspected metastatic lesions"; 1 – "assumingly no metastatic lesion"; 2 – "lesions could be as well benign as malignant"; 3 – "suspected metastatic lesions" was present; and 4 – "highly suspected metastatic lesions".

Outcome measures

Stage classification was conducted following AJCC staging in breast cancer 8th edition. [1] The TNM stage was either determined from the medical report, if available from the multidisciplinary team conference, or assessed by an oncologist (MV). The stage was first assessed as clinical TNM (cTNM) stage before FDG-PET/CT based on conventional mammography with/without MRI, and then again after FDG-PET/CT based on the scan report.

Change of treatment included surgery, radiotherapy, and medical treatment. Incidental findings were registered as well as further examination procedures and the final diagnosis of these.

For the staging of distant metastases, a 5-point Likert scale as described above was used. A cut-off at the Likert scale between 2 and 3 was used for dichotomizing the Likert scale into "no metastatic lesions" and "suspected metastatic lesions" for accuracy analysis. Assessment of area-under-the-Receiver operating curve (AUC-ROC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy was performed. The reference standard was biopsy from a suitable suspected metastatic lesion or 6 months of follow-up. If distant metastases were detected within the first 6 months after FDG-PET/CT the scan result was considered false negative.

Incidental findings, not known before FDG-PET/CT, were registered, and the clinical consequence and final diagnosis were obtained. Only incidental findings that required further examinations were taken into account.

Statistical analysis

Descriptive statistics were performed according to data type, i.e. categorical variables were summarized as frequencies and respective percentages. Point estimates for AUC-ROC and accuracy parameters of dichotomized data (sensitivity, specificity, and so on) were supplemented by 95% confidence intervals (95% CIs). All analyses were performed with Stata/IC 15.0 (StataCorp, College Station, Texas 77845 USA).

Results

Of 145 referred women with high-risk primary breast cancer, we excluded 42 patients according to exclusion criteria (Figure 1), leaving 103 patients eligible for the study. The patients were referred to additional FDG-PET/CT due to: inoperable LABC (n=47, 46%), tumor size ≥ 50 mm (n=6, 5.8%), ≥ 4 tumor positive lymph nodes in the axilla after primary breast surgery (n=31, 30%), and tumor size ≤ 49 mm with other high-risk characteristics or symptoms leading to FDG-PET/CT in our institution (n=19, 18%).

Clinical characteristics of the 103 women with a median age of 69 years (range 28–91) appear in Table 1. The pattern reflected our high-risk population with 20% having more than 10 tumor positive lymph nodes, 31% malignancy grade III, 21% being estrogen receptor (ER) negative, and 19% HER2 positive.

Stage migration

Figure 2 illustrates stage migration in 40 out of 103 women (39%) who were upstaged to more advanced disease

by FDG-PET/CT compared to cTNM staging by conventional mammography with/without MRI before FDG-PET/CT. Among women initially staged as early-stage primary breast cancer, 24 (23%) were upstaged to metastatic breast cancer and 16 (16%) to more advanced loco-regional disease i.e. involvement of internal mammary, infra-, or supraclavicular lymph node levels.

In the group of women with inoperable LABC, 15 of 47 (32%) were upstaged to metastatic breast cancer. For the remaining groups, the numbers of women who were upstaged to MBC were 0/6 (0.00%), 6/32 (19%), and 3/17 (18%) for the groups: ≥ 50 mm, ≥ 4 lymph nodes, and ≤ 49 mm + characteristics, respectively.

The distribution of metastatic disease according to molecular subtypes was for Luminal A 2/13 (15.4%), Luminal B (HER2-) 13/53 (24.5%), Luminal B (HER2+) 2/11 (18.2%), Basal-like 2/13 (15.4%), and Erb-B2 overexpression 3/9 (33.3%). Four patients had Luminal (HER2-) disease with unknown Ki67, and 2/4 (50.0%) had metastatic disease.

Clinical impact

As seen in Figure 3, 40 patients (39%) had changes in treatment after FDG-PET/CT. Surgical treatment was changed in 24 (23%) women due to MBC. Of these 18 were diagnosed before surgery, leading to the omission of surgery. The remaining six patients were diagnosed after surgery, implying that surgery with curative intent could have been spared. Medical treatment was changed in 26 patients (25%) due to a change of medical treatment strategy for all women diagnosed with MBC (24, 23%) and a more extensive neoadjuvant treatment protocol in two patients, upstaged to a more advanced loco-regional stage. Radiotherapy was altered in 39 patients (38%); i.e. radiotherapy was omitted in 23 patients diagnosed with MBC, who should have had radiotherapy according to the initial stage. The remaining 16 patients had more extensive radiotherapy due to more lymph node involvement mainly in the internal mammary level.

Accuracy

Sensitivity, specificity, PPV, NPV, and accuracy with 95% confidence intervals (CI) for detection of distant metastasis in 103 patients were 1.00 (0.86–1.00), 0.95 (0.88–0.99), 0.86 (0.67–0.96), 1.00 (0.95–1.00), and 0.96 (0.90–0.99), respectively. AUC-ROC was 0.99 (0.98–1.00), Figure 4. The reference standard used for diagnosing MBC was a biopsy from a metastatic lesion, MRI, and clinical follow-up in 11/24 (46%), 3/24 (13%), and 10/24 (42%), respectively. Figure 5 illustrates a patient with LABC who was upstaged to MBC due to unambiguous bone metastases at FDG-PET/CT assessed at a multidisciplinary team conference without a confirmatory biopsy.

Incidental findings

FDG-PET/CT detected 29 incidental findings: thyroid- or parotid gland (n=9), colon (n=7), gynecological (n=6), lung (n=2), and other (n=5) in 24 patients. Further diagnostic examinations were performed due to malignant suspicion: 13 ultrasounds, 2 MRI, 7 gastroscopy/colonoscopies, 15 biopsies, and 6 surgeries, leading to four (3.8%) synchronous cancers. The detected cancers were: two endometrial cancers, a lung cancer, and a gastrointestinal stromal tumor in the stomach. Figure 6 illustrates a patient with triple-negative stage II primary breast cancer and an incidental synchronous endometrial cancer (FIGO1a). FDG-PET/CT detected four non-malignant diseases, which needed treatment or follow-up: one case of meningioma, a large aorta aneurysm, and two cases of Hashimoto thyroiditis.

Discussion

This study demonstrated that adding FDG-PET/CT to staging led to stage migration in 40% of women with high-risk primary breast cancer, resulting in changes in surgery, radiotherapy, and medical treatment. About a fourth of all women were upstaged to metastatic disease, which rules out curative, surgical treatment. FDG-PET/CT was highly accurate in diagnosing distant metastases. Incidental findings were detected in approximately a fourth of the women, and clinically relevant diagnoses were confirmed in one-third of patients undergoing further examination.

Prognosis and treatment for breast cancer depend on initial staging. A recent review [5] on evidence-based recommendations for initial staging of primary breast cancer with FDG-PET/CT reported changes in the stage in 5–52% of women with primary breast cancer which agrees well with our finding of 40%. Stage migration from non-metastatic breast cancer to MBC increases with increasing stage with: 2%, 11%, 18%, 37%, and 47% in stage IIA, IIB, IIIA, IIIB, and IIIC, respectively [13]. Upstaging from early-stage breast cancer to MBC would not be expected to impact the survival of women with MBC. However, FDG-PET/CT has the potential to more accurately sort out the patients with metastatic disease, hence leading to a potentially improved stage-specific survival among women with high-risk primary breast cancer. [7,14,15]

Treatment strategy was changed after FDG-PET/CT in around 40% of the patients in this study. Others have found the impact on treatment less pronounced with a 7–14% change in treatment strategy after FDG-PET/CT among women with LABC. [4,5,9] However, these data come from earlier days, where the PET-technology was less developed and where FDG-PET/CT might not have been as integrated in daily clinical practice as it has become of today. Today the treatment strategy for early breast cancer has become more individualized

with more neoadjuvant systemic treatment, optimizing breast and axilla sparing surgery, and more advanced targeted radiotherapy. Therefore, optimal treatment planning is warranted and correct staging leads the way for initiating the optimal surgical procedure or refrain from surgery with curative intent if distant metastases are detected.

FDG-PET/CT was highly accurate in diagnosing distant metastases in our cohort, which is in line with previous studies. [4,5,16]. Our data illustrate daily clinical practice and patients were enrolled consecutively before initial treatment. Confirmatory biopsies from metastatic lesions were performed in cases of clinical or radiological doubt.

FDG-PET/CT has the potential to reveal unexpected findings. This may have created a reluctancy to perform FDG-PET/CT to avoid further examinations of the patients. To our knowledge, no other studies have examined the extent and consequences of incidental findings in breast cancer patients. We detected incidental findings in one third (29/103) of FDG-PET/CT scans, which corresponds well with findings from other studies of head and neck and ovarian cancer patients. They detected incidental findings in 21-35% of patients referred for FDG-PET/CT. [17,18] We found additional malignancies in 4/103 (3.8%) of the patients, leading to a substantial impact on the patients' prognosis and treatment for breast cancer. Previous studies have found incidental malignancies in between 1–8% of various cancer patients who were examined by FDG-PET/CT. [17-21]

In this study, patients had FDG-PET/CT with diagnostic contrast-enhanced CT (CE-CT), which exposes them to a somewhat higher radiation dose of 12-16 mSv, compared with CE-CT alone (approximately 10 mSv). However, the conventional examination program for metastases detection comprises the combination of CE-CT and bone scintigraphy. [2] This combination has the same radiation dose as FDG-PET/CT of approximately 14 mSv.

The major strengths of this study are the prospective design and enrollment of patients with high-risk primary breast cancer from the daily clinic with a novel illustration of incidental findings . Therefore, the results reflect a common clinical dilemma in the initial staging of breast cancer patients.

Limitations of our study are the single-center set-up and the lack of confirmatory biopsies from extra-axillary lymph nodes based on non-feasibility. This makes a possible overestimation of positive lymph nodes to the internal mammary, infra- and supraclavicular levels possible. However, all women in this study had a change in radiotherapy and few cases also in the medical treatment due to unequivocal signs of spread. This study was not performed to compare findings on FDG-PET/CT and CT alone, and the question of whether some of the metastases

found on FDG-PET/CT would have been visualized in CT alone remains open.

FDG-PET/CT has already been implemented as the standard diagnostic workup for breast cancer patients with stage III or higher in our institution as well as in the Dutch guidelines. [22] Even though we acknowledge the shortage of FDG-PET/CT scanners in some other countries, we wish to increase the awareness of FDG-PET/CT in high-risk primary breast cancer to offer the patients the most efficacious treatment up-front and to spare unnecessary treatment modalities.

More prospective studies are needed to address the accuracy of FDG-PET/CT in the detection of extra axillary lymph nodes, preferable with biopsy verification. Further, the impact of FDG-PET/CT in lower stages of breast cancer and the impact of incidental findings needs more research attention.

In conclusion, FDG-PET/CT has a substantial impact on staging and change of treatment in women with high-risk primary breast cancer, and further examinations of incidental findings were considered clinically relevant. Along with existing evidence, our findings suggest that FDG-PET/CT should be considered for implementation in future clinical guidelines for staging high-risk primary breast cancer to improve treatment planning.

Acknowledgements Two patient representatives, Marie Lykke Rasmussen and Susanne Geneser have served as co-researchers in this study. We want to share our deepest acknowledgments for a highly valuable impact on the design and conduct of the study.

Funding The work has been financially supported by Mrs. Astrid Thaysens grant, Qvesehls grant, The Independent Research Fund Denmark (DFF – 7016-00359), by University of Southern Denmark (Ph.D. grant), Odense University Hospital (Ph.D. grant) and by Centre for Personalized Response Monitoring in Oncology (PREMIO), Odense University Hospital, Odense, Denmark.

Author contributions All authors contributed to the study concept and design. Material preparation, data collection, and analysis were performed by Marianne Vogsen, Jeanette Dupont Jensen, Ivar Yannick Christensen, Oke Gerke, Anne Marie Bak Jylling, Lisbet Brønsro Larsen, Katrine Lydolph Søe, Camilla Bille, Marianne Ewertz, and Malene Grubbe Hildebrandt. The first draft of the manuscript was written by Marianne Vogsen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest

Ethics approval

The study was approved by the Danish Ethics Regional committee (S-20170019) and conducted following the Helsinki declaration. The study was registered at ClinicalTrials.gov (NCT03358589).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Patients consented to publish their data and photographs.

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TABLES

Title: **Table 1** Clinical characteristics of 103 Danish women with high-risk primary breast cancer, 2017-2019

Characteristics	N (%)
Age	
at diagnosis, median (range)	69.3 (27.9-91.3)
Bilateral disease	
Yes	7 (6.80)
No	96 (93.2)
Type of surgery	
Mastectomy	24 (23.3)
Breast conserving	9 (8.74)
No surgery*	69 (67.0)
Other#	1 (0.97)
Surgical margins	
Free	31 (30.1)
Not free	3 (2.91)
No surgery*	69 (67.0)
Tumor size	
≤10 mm	2 (1.94)
11-20 mm	5 (4.85)
21-50 mm	20 (19.4)
≥50 mm	6 (5.83)
No surgery*	70 (68.0)
Lymph node involvement	
0	1 (0.97)
1-3	2 (1.94)
4-9	10 (9.71)
≥ 10	21 (20.4)
No surgery*	69 (67.0)
Histology	
Ductal carcinoma	40 (38.8)
Lobular carcinoma	22 (21.4)
Carcinoma NOS	41 (39.8)
Grade of malignancy	
I	10 (9.71)
II	45 (43.7)
III	32 (31.1)
Unknown/Not graded	16 (15.5)
ER status	
Negative (0%)	22 (21.4)
Positive (1-9%)	2 (1.94)

Positive (10-100%)	79 (76.7)
HER-2 status	
Normal	83 (80.6)
Positive	20 (19.4)
Total	103 (100)

*No surgery at the time of enrollment, #Axillary surgery without breast surgery, ER: estrogen receptor, HER2: human epidermal growth factor receptor-2

FIGURE LEGENDS

Figure 1

Title: Fig1. Flowchart of 103 Danish women referred for additional FDG-PET/CT according to reasons for referral, 2017-2019

Footnotes: FDG-PET/CT: 18F-flouro-deoxy-glucose-positron emission tomography / computed tomography, MBC: metastatic breast cancer, LABC: locally advanced breast cancer, LN: lymph nodes, TNBC: triple-negative breast cancer, ER: estrogen receptor, HER2: human epidermal growth factor receptor-2

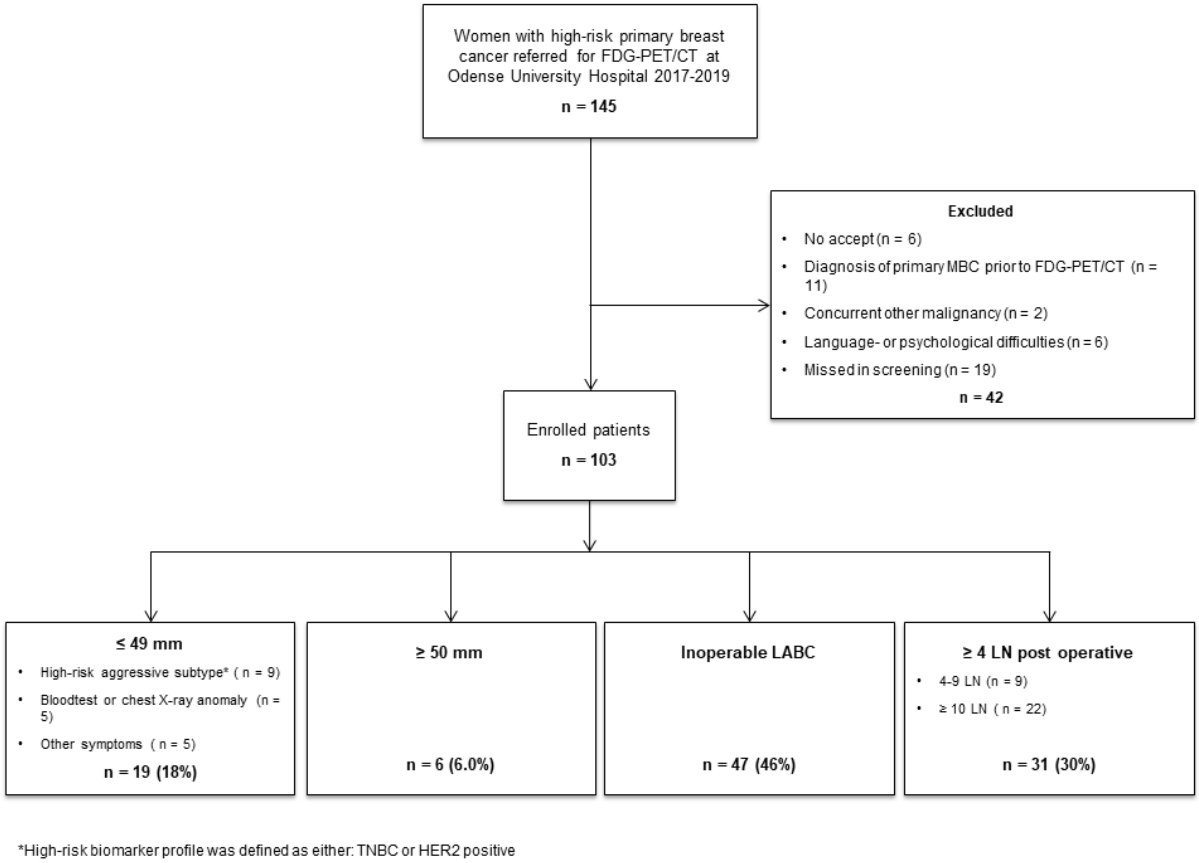

Figure 2

Title: Fig.2 Stage migration in 40 women with high-risk primary breast cancer upstaged to more advanced disease by 18F-flouro-deoxy-glucose-positron emission tomography / computed tomography (FDG-PET/CT). TNM staging before and after FDG-PET/CT. Initial cTNM staging was performed by conventional ± magnetic resonance imaging (MRI) mammography. Solid line boxes indicate stage migration to a higher N-stage and dashed boxes stage migration to metastatic disease. The thickness of the arrow lines reflects the number of patients migrating from one stage to another

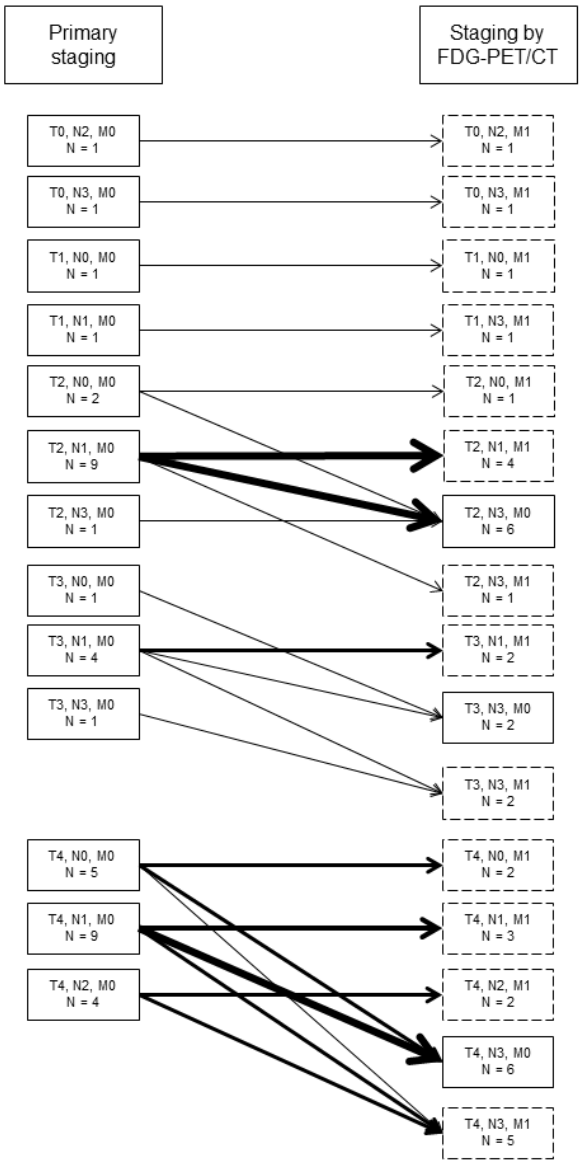

Figure 3

Title: Fig.3 Change of treatment in 103 patients with high-risk primary breast cancer after additional 18F-flouro-deoxy-glucose-positron emission tomography / computed tomography (FDG-PET/CT). Changes of treatment were divided into surgery, radiotherapy, and medical treatment

Footnotes: MBC: metastatic breast cancer, LN: lymph nodes

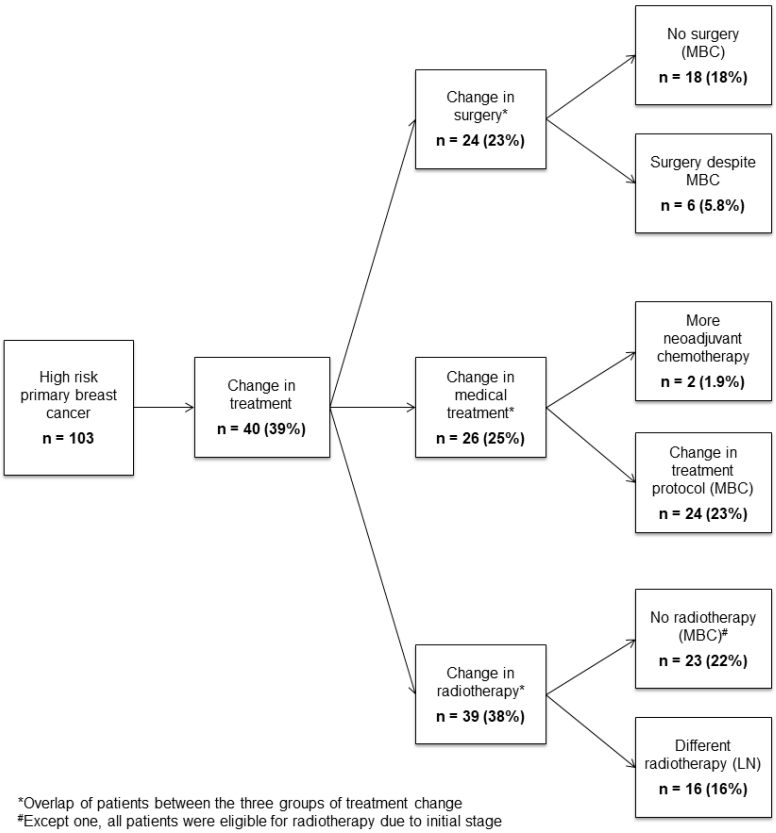

Figure 4

Title: Fig.4 Receiver operating characteristic (ROC) curve and area under the curve (AUC) derived from 18F-flouro-deoxy-glucose-positron emission tomography / computed tomography (FDG-PET/CT) scans in 103 high-risk primary breast cancer patients

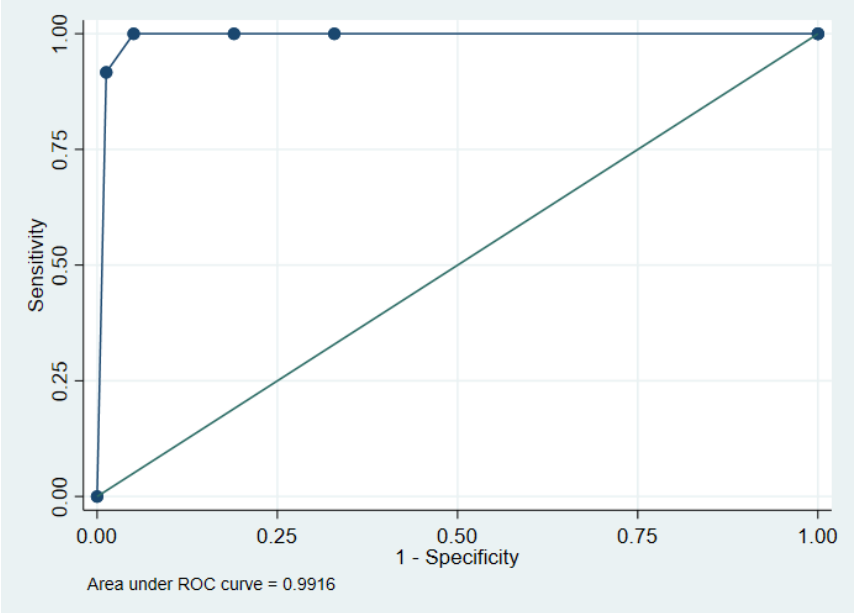

Figure 5

Title: Fig.5 An illustration of a patient with locally advanced breast cancer upstaged to metastatic breast cancer by 18F-flouro-deoxy-glucose-positron emission tomography / computed tomography (FDG-PET/CT). The final diagnosis confirmed without a confirmatory biopsy due to unambiguous bone metastases

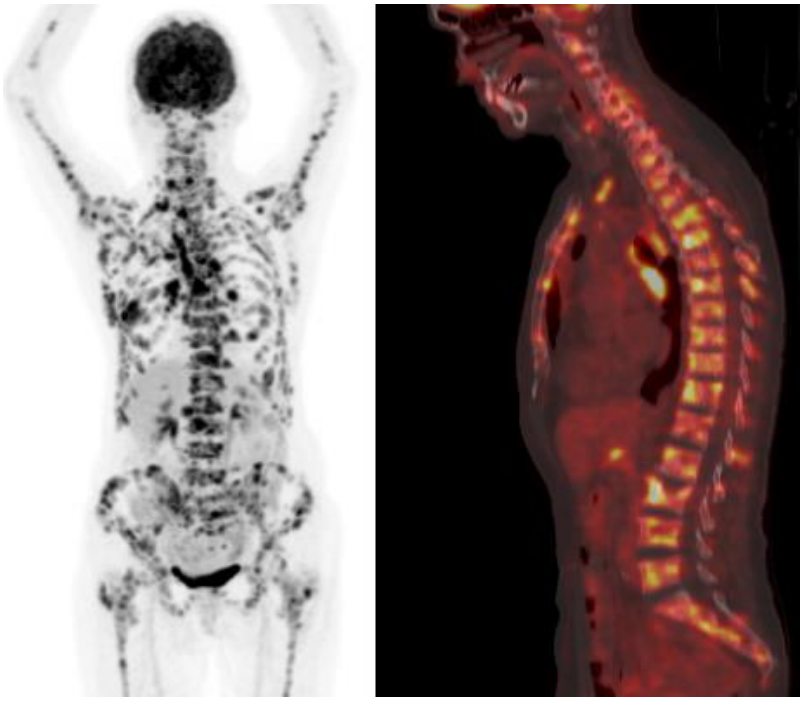

Figure 6

Title: Fig.6 An illustration of a patient with triple-negative stage II primary breast cancer with an incidental synchronous endometrial cancer (FIGO1a) detected at 18F-flouro-deoxy-glucose-positron emission tomography / computed tomography (FDG-PET/CT)