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Therapeutic impact of 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography in the pre- and postoperative staging of patients with clinically intermediate or high-risk breast cancer

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Background: Positron emission tomography with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG–PET) is an accurate imaging modality for the staging of breast cancer. The aim of this study was to determine the potential therapeutic impact of pre- and postoperative FDG–PET in patients with clinically intermediate or high-risk breast cancer.
Patients and methods: One hundred and fourteen patients with newly diagnosed breast cancer were examined before (73) or after (41) surgery. Patient data were translated into three scoring sheets corresponding to information available before positron emission tomography (PET), after PET and after further diagnostic tests. Three medical oncologists independently reviewed the retrospectively acquired patient data and prospectively made decisions on the theoretically planed treatment for each time point, according to the recommendations of St Gallen Consensus Guidelines 2005.
Results: FDG–PET changed the planed treatment in 32% of 114 patients. In 20% of cases, therapeutic intention (curative versus palliative) was modified. Radiation treatment planning was changed in 27%, surgical planning in 9%, chemotherapy in 11% and intended therapy with bisphosphonates in 13% of all patients.
Conclusion: Based on current treatment guidelines, FDG–PET, as a staging procedure in patients with newly diagnosed clinically intermediate or high-risk breast cancer examined pre- and postoperatively, may have a substantial therapeutic impact on treatment planning.
Key words: breast cancer, FDG, patient management, positron emission tomography, primary staging, therapeutic impact

introduction

Breast cancer is the most frequently diagnosed malignant tumor among women in Europe, with 370 000 new cases estimated in Europe in 2004 [1]. Although there have been recent decline in breast cancer mortality rates in several European countries [2], breast cancer still ranks first among cancer deaths in women in Europe, with an estimated 129 900 cancer deaths in 2004 [1].

Primary staging of breast cancer most commonly consists of a chest X-ray, liver ultrasound and bone scan, and sentinel lymph node biopsy or axillary lymph node dissection for evaluation of lymph node involvement. Suspicious findings may be further investigated by computed tomography (CT) and magnetic resonance imaging (MRI).

2-[fluorine-18]fluoro-2-deoxy-D-glucose Positron emission tomography (FDG–PET) has proven to be an accurate imaging modality for the staging of breast cancer with sensitivities and specificities of 93% and 75% for primary staging [3] and in the range of 89%–100% and 72%–88%, respectively [4–8], for detection and restaging of recurrent breast cancer. Some studies have already addressed the impact of FDG–PET on the management of patients with recurrent or metastatic breast cancer and reported changes of the original therapeutic plans in overall 32% to 44% of cases [9–11]. However, data regarding the clinical impact of positron emission tomography (PET) in the primary staging of breast cancer are rare [12].

The purpose of our study therefore was to assess the potential clinical impact of FDG–PET in the pre- and postoperative staging of patients with newly diagnosed clinically intermediate or high-risk breast cancer based on current treatment recommendations [13].

patients and methods

patients

From 2002 to 2004, a total of 269 patients with breast cancer underwent an FDG–PET scan at our institution. All patients and PET scans were

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prospectively registered in a database according to national law. Inclusion criteria were clinically intermediate or high-risk breast cancer, whole body staging with FDG–PET pre- or postoperatively and availability of medical records. Two hundred and twenty-three patients assigned by a Department of Kantonsspital St Gallen or associated oncologists were evaluated. Forty-six patients did not meet the inclusion criteria because of nonavailability of medical records. A total of 114 patients (73 staged with FDG–PET before surgery, hereafter pre-OP group and 41 with FDG–PET before adjuvant therapy, hereafter post-OP group) fulfilled the inclusion criteria and were included in this study (Table 1). One hundred and eight patients scanned for suspicion or restaging of tumor relapse, or assessment of therapy response were not included. One patient with an initial diagnosis of breast caner was retrospectively excluded because further histological evaluation during follow-up revealed amelanotic melanoma.

clinical data

The clinical data of all patients were obtained through systematic review of all inpatient and outpatient medical records. Data included age, relevant comorbidities and previous treatments, date of initial diagnosis, histology, hormone receptor status, tumor marker level at time of diagnosis, results of mammography, chest X-ray, liver ultrasound, bone scan and further imaging modalities (MRI of the breast or other parts of the body, CT of the chest and/or abdomen) employed either before or after FDG–PET.

Table 1. Patient characteristics

	Pre-OP group ($n = 73$)	Post-OP group ($n = 41$)	All patients ($n = 114$)
Age (years)			
Range	38–83	32–80	32–83
Median	60	57	59
Mean	61	57	59
Ca 15–3[a] (kU/l)			
Range	5–944	5–78	5–944
Median	20	17	18
Mean	50	20	40
Histological subtypes (%)			
Ductal	53	76	61
Lobular	7	2	5
Mixed ductal–lobular	4	13	7
Large cell	6	2	4
Undifferentiated	4	0	3
Other subtypes	12	5	10
Not specified	14	2	10
Thereof clinically inflammatory subtype	12	2	9
Clinical stage grouping after conventional staging[b] (%)			
I	8	2	6
IIA	24	17	22
IIB	14	15	14
IIIA	10	25	15
IIIB	30	2	20
IIIC	3	32	13
IV	11	7	10
Diagnostic staging procedures before PET (%)			
Chest X-ray	47	81	59
Liver ultrasound	30	63	42
Bone scan	18	44	27
Computed tomography	16	7	13

[a]Reference value <27 kU/l.

[b]According to American Joint Committee on Cancer cancer staging manual 6th edition [14].

Pre-OP, FDG–PET before surgery; Post-OP, FDG–PET before adjuvant therapy; PET, positron emission tomography.

^{18}F-FDG–PET

FDG–PET was done using a dedicated full-ring Scanner (GE Advance NXi) with a transaxial resolution of 4.8–6.2 mm, 1–20 cm off center (National Electrical Manufacturers Association, Rosslyn, USA-1994). Patients fasted for at least 6 h before an i.v. injection of 370 MBq 2-fluoro-2-deoxy-D-glucose (FDG) into a vein contralateral to the tumor side. Blood glucose level was <10 mmol/l in all patients. Whole body data were obtained in supine position 45–60 min after injection in 2D-acquisition mode, with 5 min per bed position for emission and 2–3 min for transmission. In patients scanned preoperatively, and if axillary lymph node status was doubtful after whole body imaging, a second scan in prone position with elevated arms was carried out 130–140 min after injection. Image reconstruction was done with iterative 2D-OSEM algorithm. FDG–PET was interpreted by consensus of at least two experienced nuclear medicine physicians on clinical service at the time of acquisition. The mean time lag between diagnosis of breast cancer and FDG–PET was 1.9 weeks in the pre-OP group and 6.6 weeks in the post-OP group.

study design

The study was conducted as part of a quality assurance program of the Senology Center of Eastern Switzerland and the Department of Nuclear Medicine, Kantonsspital, St Gallen, Switzerland. Patient data was collected retrospectively and made anonymous. According to clinical practice with routine baseline staging, FDG–PET scanning in cases of lingering suspicion of metastases after negative conventional tests and occasionally further radiological tests (CT, MRI) in doubtful cases after PET, we categorized data as chronologically available. Diagnostic information was divided into data available before PET (time point pre-PET), after PET (time point PET) and after accomplishment of further diagnostic tests (time point post-PET). The data were finally translated into three scoring sheets using the categorization as mentioned above. The pre-PET scoring sheet included age, results of conventional diagnostic tests and resulting clinical stage grouping (Table 1), tumor–node–metastasis (TNM) classification (adapted) according to American Joint Committee on Cancer (AJCC) Cancer Staging Manual 6th edition [14], histology, hormone receptor status and previous treatments. Results of the FDG–PET scan and findings of subsequent diagnostic tests as well as updated TNM classifications were given in the PET and post-PET scoring sheets.

Three senior medical oncologists blinded to each other evaluated the scoring sheets independently and prospectively defined theoretical treatment decisions on the intention-to-treat (curative versus palliative), surgery, chemotherapy, endocrine therapy, therapy with trastuzumab, radiotherapy and bisphosphonates consecutively for each time point. Treatment decisions were made according to the recommendations of St Gallen Consensus Guidelines 2005 [13] and κ scores for the concordance of treatment decisions were calculated to measure interobserver agreement. Strength of agreement was classified as slight ($\kappa = 0.20$–0.40), moderate ($\kappa = 0.41$–0.60), substantial ($\kappa = 0.61$–0.80) or excellent ($\kappa = 0.81$–1.0).

In order to prevent ambiguity in the assessment of the anonymous patient data, following definitions were used. Breast-preserving surgery is intended if medically appropriate. In case of T2 classification (large operable), neo-adjuvant chemotherapy is offered to the patient with the intention to facilitate breast-preserving surgery. Locally advanced disease ($T \geq 3$ or $N \geq 2$) without distant metastases (M0) is treated by mastectomy and axillary clearance after neo-adjuvant systemic therapy in curative

intention. Supraclavicular and internal mammary lymph node metastases leads to an extended field of radiation therapy. Classification for distant metastases is M0 if chest X-ray, liver ultrasound and bone scan are negative, and if one or more tests have not been carried out, classification is MX. If tumor and lymph node classification is T1 N0, the absence of distant metastases (M0) is assumed even if all tests have not been carried out. In preoperatively staged patients, the detection of limited axillary lymph node involvement (N1) by FDG–PET is not assumed to affect treatment decision, as these lymph node metastases would be detected in histological work-up anyway.

results

changes of clinical stage grouping

Stage grouping according to AJCC 6th edition was changed in 48 of 114 patients (42%) after FDG–PET and in four patients after accomplishment of further diagnostic tests (4%). Rates of changes after PET based on clinical stage grouping before PET are given in Table 2.

T stage changed in two patients (2%) due to multifocal disease. PET revealed previously unknown regional lymphatic spread classified as N3 in 24 cases (21%), supraclavicular lymph node metastases in 15 (13%) and internal mammary lymph node metastases in 18 patients (16%). Distant metastases were diagnosed by FDG–PET in 22 cases. Distant metastases in FDG–PET were confirmed by other imaging modalities in 10 patients or during a follow-up of 39 ± 8 months in nine cases. In two patients with exclusively distant lymphatic spread according to PET metastases were not proved by other imaging modalities and patients remained clinically stable after adjuvant treatment during follow-up. In 59 patients previously classified as MX due to equivocal results or incomplete conventional staging procedures, PET confirmed staging as M0.

Post-PET examinations did not change T classification, but lead to a downstaging in one case with previously suspected lymph node metastases and in one patient with a false-positive PET finding in the vertebral column due to posttraumatic changes. Post-PET results defined unclear stage grouping after PET in three patients with sarcoidosis, an ovarian breast cancer metastases and a second primary in the lung.

impact on patient management

Results of FDG–PET changed the treatment plan in 32% of all patients (Table 3). The intention-to-treat was modified from a curative to a palliative approach or vice versa in overall 20% and surgical planning was revised in 9% of all patients. Radiation treatment planning was changed in a total of 27% of patients with omission of planed adjuvant radiation

Table 2. Changes of stage grouping and TNM classification according to conventional staging (time point pre-PET, Table 1) after FDG–PET (time point PET) or further diagnostic tests (time point post-PET)[a]

	Time point PET						Time point post-PET					
	Proportions			(%)			Proportions			(%)		
	Up	Down	All	Up	Down	All	Up	Down	All	Up	Down	All
Stage grouping												
I	2/7		2/7	29		29						
IIA	11/25		11/25	44		44		1/25	1/25		4	4
IIB	5/16		5/16	31		31		1/16	1/16		6	6
IIIA	6/17		6/17	35		35	1/17		1/17	6		6
IIIB	14/23		14/23	61		61						
IIIC	9/15		9/15	60		60						
IV		1/11	1/11		9	9		1/11	1/11		9	9
All	47/114	1/114	48/114	41	1	42	1/114	3/114	4/114	1	3	4
TNM classification												
Pre-OP group												
T stage	2/73		2/73	3		3						
N stage	22/73 35/73[b]	1/73	23/73 36/73[b]	30/48[b]	1	32/49[b]						
M stage	12/73	0/73 40/73[c]	12/73 52/73[c]	16	0/55[c]	16/71[c]						
Post-OP group												
T stage												
N stage	9/41		9/41	22		22		1/41	1/41		2	
M stage	9/41	1/41 20/41[c]	10/41 29/41[c]	22	2/49[c]	24/71[c]	1/41	2/41 3/41[c]	3/41 4/41[c]	2	5/7[c]	7/9[c]
All patients												
T stage	2/114		2/114	2		2						
N stage	31/11444/114[b]	1/114	32/114 45/114[b]	27/39[b]	1	28/40[b]		1/114	1/114		1	1
M stage	21/114	1/114 60/114[c]	22/114 81/114[c]	18	1/53[c]	19/71[c]	1/114	2/114 3/114[c]	3/114 4/114[c]	1	2/3[c]	3/4[c]

[a]According to American Joint Committee on Cancer cancer staging manual 6th edition [14].

[b]Including nodal upstaging from N0 to N1 in 13/114 patients.

[c]Including downstaging from MX to M0 in 59/114 patients.

TNM, tumor–node–metastasis; PET, positron emission tomography; FDG–PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography; Pre-OP, FDG–PET before surgery; Post-OP, FDG–PET before adjuvant therapy.

Table 3. Treatment modifications after FDG–PET and concordance of treatment decisions between three medical oncologists

Changes of treatment plans (%)	Pre-PET group			Post-PET group			All patients			
	More	Less	All	More	Less	All	More	Less	All	κ score
Overall			28			37			32	0.96
Intention-to-treat			17			24			20	0.98
Stage I–IIB			6			14			8	
Stage IIIA–C			29			29			29	
Surgery	1	10	11	5	1	6	3	6	9	0.82
Radiotherapy	8	14	22	12	23	35	10	17	27	0.96
Chemotherapy	2	4	6	4	16	20	3	8	11	0.75
Endocrine therapy			1			1			1	0.33
Bisphosphonates			11			12			13	0.97

FDG–PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose Positron emission tomography; PET, positron emission tomography.

treatment after diagnosis of distant metastases in 17% and enlargement of the radiation treatment field after detection of previously unknown internal mammary and supraclavicular lymph node metastases in 10% of patients. Diagnosis of internal mammary node involvement alone accounted for changes in 6% of cases. Changes of the surgical treatment were due to omission of planned breast and axillary surgery after diagnosis of distant metastases, detection of breast cancer in the breast contralateral to the known primary and diagnosis of axillary lymph node metastases remaining *in situ* after axillary dissection. Intended chemotherapy was changed in 11% of all patients, endocrine therapy was modified in 1% and treatment with bisphosphonates was started for previously unknown bone metastases in 13% of patients. Diagnostic tests and surgical exploration carried out after PET modified treatment plans by confirmation of metastases, revealing false-positive findings and detection of PET-negative metastases in overall 5% of cases.

Kappa analysis showed substantial or excellent concordance of treatment decisions between three medical oncologists except for endocrine therapy, which was changed in only one percent of cases.

use of conventional staging procedures

The number of diagnostic tests carried out before FDG–PET declined during the investigation period from an average 5.2 tests per patient in 2002 to 1.8 in 2004. Likewise, the number of investigations accomplished after FDG–PET fell from an average 1.1 tests per patient in 2002 to 0.3 in 2004.

discussion

FDG–PET is a valuable imaging modality for detection and restaging of recurrent breast cancer, and is more accurate than conventional staging methods in screening for lymph node metastases [7, 15], especially for the detection of internal mammary and mediastinal nodes [16, 17], as well as in the detection of distant metastases [3, 18] and proved to have a major clinical impact in this context [9–11]. In contrast, data defining the role of PET in the primary staging of breast cancer are rare [12]. In the absence of prospective studies it is not entirely clear, which patients may benefit from a PET scan as part of the primary staging and under which circumstances staging with FDG–PET might be a cost-effective approach.

In this study, we intended to analyze the potential value of FDG–PET in a collection of patients of a single center, which were referred for staging clinically intermediate or high-risk breast cancer. Focusing on patients defined as mentioned above, we found that based on PET results, changes of the planed treatment would be required in 32% of all patients. This number is comparable to what was reported in studies investigating patients with recurrent or metastatic disease [9–11]. Eubank et al. [9] retrospectively reviewed the medical records of 125 consecutive patients with recurrent and advanced disease and found documented changes in the therapeutic plan in 32% of the patients. Yap et al. [10] and Grahek et al. [11] evaluated the impact of PET on the management of patients referred for restaging through questionnaires sent to the referring physician before and after the PET study, and reported changes of treatment in 60% and 44% of the cases. Response rates of the questionnaires were relatively low (31% and 56%, respectively), making it likely, that a responder bias lead to an overestimation of the rate of management changes. Van der Hoeven et al. [12] evaluated FDG–PET in the primary staging of patients with locally advanced breast cancer referred for participation in a trial on chemo- and immunotherapy. The authors detected unexpected distant metastases leading to a palliative treatment strategy in 8% of 48 patients, compared with 17% in the corresponding pre-OP group in our trial. However, Van der Hoeven [12] reported that five of nine patients, who were PET positive for distant metastases, were treated as planed according to the study protocol when conventional imaging was negative. In our study, nearly half of the PET positive distant metastases were also negative in the initial conventional imaging and proved to be true positive in follow-up examinations. Carr et al. [19] presented data of a multimodality breast imaging study designed to evaluate multimodal local staging. The authors reported that FDG–PET added little additional information and detected distant metastases in only 3% of all patients. In fact, the study population consisted of only 69% of patients with invasive cancers and overall <10% with tumors classified as stage IIB or higher. These results therefore do not contradict

our own findings, but highlight the importance of an appropriate patient selection for PET staging.

Recently, Gil-Rendo et al. [20] published a prospective study focusing on the role of FDG–PET in the axillary staging of 275 patients with stage I and stage II diseases. The authors found a change of treatment in overall 33% of patients, when taking into account sparing of sentinel lymph node biopsy in cases of positive FDG uptake in the axilla.

According to our results, FDG–PET necessitated changes of radiation treatment planning in 27% of the patients, which is consistent with previously reported results [21]. In 6%, the planed radiation field was extended because of unexpected internal mammary lymph node metastases. The detection of internal mammary metastases is of particular importance as metastases to the internal mammary chain are associated with a poor prognosis [16, 17, 22]. The rate of internal mammary metastases in our study is lower than previously reported for patients with advanced or recurrent disease, presumably due to smaller average tumor size and lower percentage of inflammatory breast cancer [16, 17, 23].

Surgical planning and chemotherapy were mainly revised after detection of distant metastases, resulting in the omission or reduction of planned treatments in 6% and 8% of patients, respectively. Treatment with bisphosphonates was intended in cases of multifocal bone involvement. Endocrine therapy is indicated in all our patients with hormone receptor-positive tumors irrespective of whether classified as intermediate or high risk. Changes of stage grouping therefore lead to additional chemotherapy with no major modifications of endocrine treatment.

A certain limitation of our study is the retrospective collection of clinical data. As a consequence, not all conventional staging procedures were carried out as part of the primary staging in every patient. Hence, a certain number of metastases detected by FDG–PET possibly would also have been detected by conventional procedures, if carried out. The standard algorithm at a given institution for staging breast cancer will also influence the additional value of FDG–PET which may be less pronounced in sites where CT instead of chest X-ray and liver ultrasound is routinely carried out. As the exact rate of expected treatment changes and the potential therapeutic impact and usefulness of FDG–PET depends on the prevalence of lymphatic and distant metastatic spread, an appropriate patient selection based on the clinical experience of the referring physician is of particular importance. Patient referral by experienced medical oncologists therefore might lead to a certain selection bias in our study.

According to our experience, considering patients with intermediate or high-risk breast cancer as candidates for PET staging leads to a reasonable rate of treatment modifications and showed substantial or excellent concordance of treatment decisions between three medical oncologists. A preselection of patients with clinically stage III disease may change the intention-to-treat in up to one-third of all patients.

The impact of FDG–PET on patient management ultimately depends on the confidence in the accuracy and validity of PET among clinicians. The declining number of additional conventional imaging procedures carried out before and after FDG–PET during the study period in our institution reflects the latter aspect and underlines the impact of FDG–PET in and for daily clinical practice. The introduction of integrated PET/CT systems leads to a further improved diagnostic accuracy [24] and adds incremental diagnostic confidence in PET in >50% of patients and regions with increased FDG uptake [25].

conclusions

FDG–PET in the primary staging of patients with clinically intermediate or high-risk breast cancer has a substantial impact on patient management. PET not only influences individual treatment decisions but also impacts on clinical and diagnostic workflows, as redundant staging procedures tend to be omitted and tumor staging is more straight forward. Implementation of FDG–PET in the staging of breast cancer leads to improved stage grouping in a significant number of patients, hence facilitating appropriate treatment and avoiding straining and dispensable therapies. Our results give reason to investigate whether modified clinical workflows with FDG–PET, when implemented in the primary staging of advanced breast cancer, might be a cost-effective approach under certain conditions.

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