Value of [18F]FDG PET/CT in the work-up to neoadjuvant systemic therapy in breast cancer

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Abstract

The utility of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) in the initial staging of stage I-IIA breast cancer remains unclear. No firm recommendations on its applicability in these low stages can be drawn from previous research. This single-institution retrospective cohort study was designed to assess the addition of [^{18}F]FDG PET/CT to ultrasonography (US) and magnetic resonance imaging (MRI) in the initial staging of breast cancer patients in work-up to neoadjuvant systemic therapy (NST). Data of 304 patients newly diagnosed with breast cancer between 2018 and 2021 who underwent US, MRI, and [^{18}F]FDG PET/CT for initial staging of breast cancer were evaluated. Our aim was to assess the impact of preoperative [^{18}F]FDG PET/CT on staging, alteration of treatment strategy, incidental findings, and delay in starting NST. Alteration of initial staging occurred in 16.1%, and alteration of breast cancer treatment plan in 19.3% of cases. Multicentricity (OR 3.2; 3.0) and a cN+ status (OR 3.9; 3.2) were significant risk factors for alteration. A total of 99 incidental findings occurred, resulting in 157 additional investigations by which 4.0% of findings were proven malignant. The performance of an [^{18}F]FDG PET/CT did not lead to a significant delay in starting NST. [^{18}F]FDG PET/CT is of added value alongside US and MRI in the initial staging of advanced and low stage multicentric, cT3-4, or cN+ breast cancer. In all other breast cancer cases, it may be worth contemplating omitting [^{18}F]FDG PET/CT.

Introduction

Breast cancer is the most common type of cancer among women worldwide. Neoadjuvant systemic therapy (NST) is increasingly applied in its treatment due to the ability to evaluate response of therapy to guide postoperative treatment decisions (1,2) and its benefit of allowing less extensive surgery. Initial staging of breast cancer is a precondition for determining treatment strategy and accurate response evaluation. Staging is carried out according to the TNM staging system of the American Joint Committee on Cancer (3).

Ultrasonography (US) and magnetic resonance imaging (MRI) of the breast and axilla are commonly performed for assessing the primary tumour extent and spread to regional lymph nodes. In locally advanced breast cancer, screening for distant metastasis is recommended because the probability of metastasis is substantially increased (4,5). For this purpose, ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography ([^{18}F]FDG PET/CT) is the first choice as it has been proven to be more accurate in detecting distant metastases than a conventional multimodality imaging algorithm including chest X-ray, abdominal US and bone scintigraphy (6,7). Additionally, it provides information about regional lymph nodes, including those extra-axillary, which may be missed when imaging with US and MRI exclusively. However, of the diagnostic modalities US, MRI, and [^{18}F]FDG PET/CT, none can be considered most reliable for determination of the N status (7-9). Consequently, a combination of US, MRI, and [^{18}F]FDG PET/CT is often executed in initial staging. Several studies have pointed out the utility of [^{18}F]FDG PET/CT in stage ≥IIB, as it leads to significant restaging and alteration of treatment (10-13). Still, its contribution in stage I-IIA breast cancer remains debatable (14-16). The high sensitivity of an [^{18}F]FDG PET/CT harbours the potential for detecting incidental findings. Only 1.2-2.0% of incidental findings are clinically relevant (pre)malignant lesions, of which the gastrointestinal tract, lungs, and thyroid are the most common sites (17,18). Such unexpected findings might result in additional investigations, treatment delays, and unwarranted patient concerns.

This study investigates the impact of performing an [^{18}F]FDG PET/CT in stage I-II breast cancer patients eligible for NST with respect to change of initial staging, treatment plan and the occurrence of incidental findings.

Material and Methods

Study Design

Patients diagnosed with breast cancer between January 2018 and December 2021 who had US, MRI, and [^{18}F]FDG PET/CT performed within six weeks of diagnosis at the Jeroen Bosch hospital (JBZ, 's-Hertogenbosch, The Netherlands) were identified through a search in the hospital's electronic health records (EHR). The performance of an [^{18}F]FDG PET/CT in patients eligible for NST, independent of staging, was local standard practice. Subjects were excluded if the [^{18}F]FDG PET/CT was performed for other reasons than the work-up to NST, or if systemic treatment had commenced before the [^{18}F]FDG PET/CT. Subjects were excluded from specific delay analysis when a deviation from normal practice occurred that affected the outcome of interest.

Data Collection and Verification

Variables of the subjects extracted from the EHR included sex, age at diagnosis, oncological history, localization of the primary tumour, histological subtype, grading, oestrogen, progesterone, HER2neu expression, clinical TNM using TNM version 8 stage after US and MRI, clinical TNM stage after [^{18}F]FDG PET/CT performance, number and sites of suspected lymph nodes and metastases, treatment plan after US and MRI, treatment plan after [^{18}F]FDG PET/CT performance, number and sites of incidental findings, additional investigations and procedures due to FDG PET scan results, and the dates of diagnosis, multidisciplinary team meetings (MDTM's), and the start of NST. Metastases were preferably verified by histology. When histology or cytology was not possible, highly suspicious abnormalities were considered malignant based on characteristic features observed on imaging. Incidental findings were reported when noted in the [^{18}F]FDG PET/CT report and discussed in either an MDTM or consultation with the patient. Deviations from the normal course of events in the work-up to, or implementation of, NST were noted.

Primary and Secondary Outcomes

The two primary outcomes investigated in this study are the occurrence of alteration in initial staging and the occurrence of alteration in treatment strategy of breast cancer resulting from the performance of an [^{18}F]FDG PET/CT. In addition, the contribution of different patient and tumour characteristics possibly influencing these outcomes was examined. Secondary outcome measurements are the occurrence, sites, ensuing investigations, presence of malignancy and effects on treatment strategy of incidental findings on the [^{18}F]FDG PET/CT. Moreover, delay in starting NST treatment attributable to performance of an [^{18}F]FDG PET/CT or subsequent incidental findings were also investigated.

Statistical Analysis

Frequencies and percentages were used to express categorical variables, and medians and ranges were used to express continuous variables. The association between clinical parameters and alteration in staging and treatment strategy was assessed using risk ratios and odds ratios after logistic regression with a 95% confidence interval (CI). Bivariate regression analyses were conducted to identify input variables for multivariate logistic regression. A threshold of more than a 10% deviation in the target variable coefficient in bivariate regression determined variable inclusion. Subgroups were combined to meet the one-in-ten rule. The cN status, the parameter most influencing stage classification, was set as the target variable.

Software and Tests

Statistical analyses were performed using IBM SPSS version 27. The Chi-Square test was used for crosstab analyses when its requirements were met, otherwise, the Fisher's Exact test was used. The model test was used for the regression analyses. For analysing the differences in delay, the Mann-Whitney U test was used. A p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

A flowchart depicting the data extraction and exclusion process is illustrated in figure 1. The search resulted in a list of 344 patients, of which 40 were excluded. A total of 307 primary tumours were detected in the 304 eligible patients. Characteristics of the patients and tumours are summarized in table 1.

Alteration of Staging and Treatment Strategy

A total of 302 patients with 305 primary tumours were selected for this analysis. In the two not included cases, regional lymph node status could not be assessed on [^{18}F]FDG PET/CT because a sentinel node procedure was carried out shortly before the imaging. The performance of an [^{18}F]FDG PET/CT led to the detection of unknown lymph node metastases in 16.7% (51/305), and unsuspected distant metastases in 5.9% (18/305) of tumours. In one case, an enhancing lesion described on MRI as a lymph node was corrected to a satellite lesion of the primary tumour on the [^{18}F]FDG PET/CT, causing downstaging. These new findings subsequently resulted in alteration of staging in 16.1% of cases and to alteration of treatment strategy in 19.3% of cases.
The changes in treatment strategy included 5 planned modified radical mastectomies (4 executed), 15 planned axillary lymph node dissections (14 executed), 30 expansions of the radiation field, 1 narrowing of the radiation field, and in 10 cases the switch from curative to palliative treatment intent.

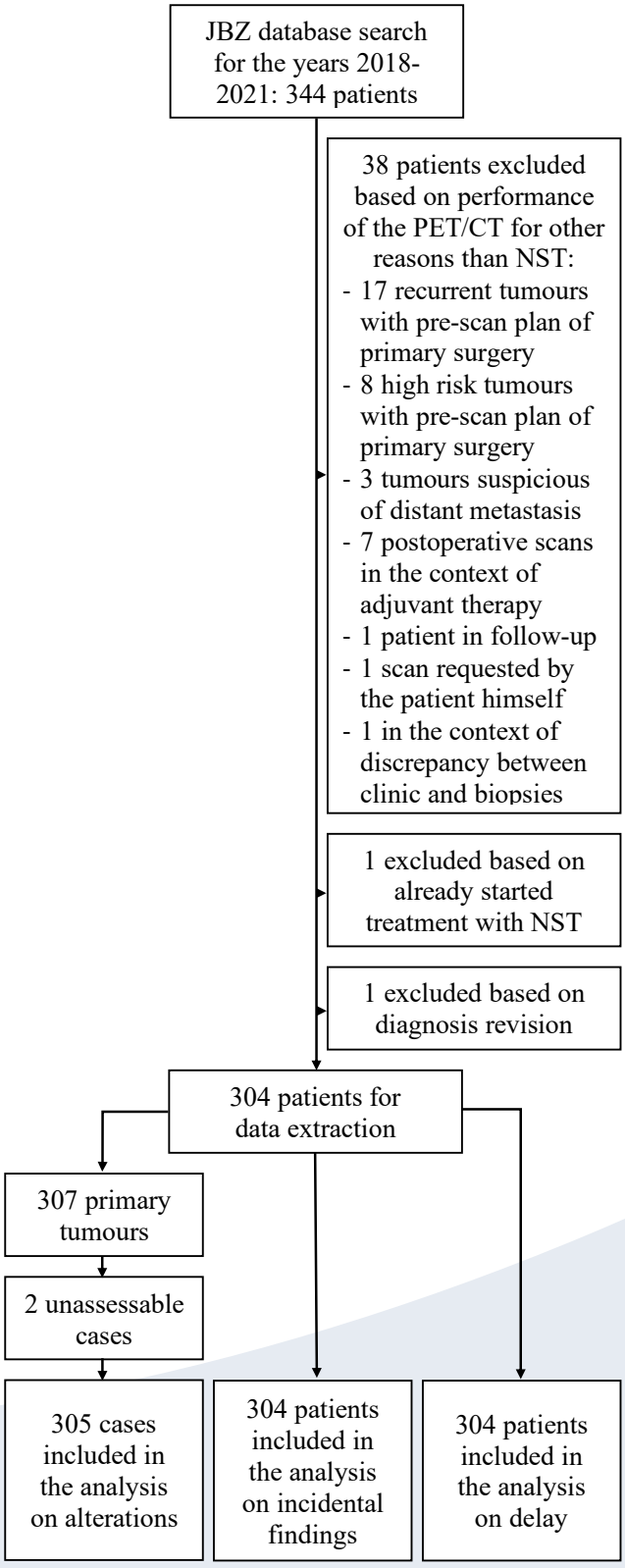

Figure 1. Flow-chart of the data collection and exclusion process.

Table 1. Characteristics of patients and tumours.

patient characteristic	N=304
female sex – no. (%)	298 (98.0)
median age (IQR) – yr	53.0 (44.0-61.0)
range	23 to 84
history of cancer – no. (%)	26 (8.6)
history of breast cancer	16 (5.3)
tumour characteristic	**N=307**
median diameter (IQR)* – mm	30.0 (22.0-43.5)
range	8 to 130
quadrant localisation* – no. (%)	
lateral quadrant	217 (70.7)
medial quadrant	84 (27.4)
other***	6 (2.0)
focality* – no. (%)	
unifocal	137 (44.6)
multifocal	79 (25.7)
multicentric	87 (28.3)
unknown	4 (1.3)
histological type** – no. (%)	
invasive ductal carcinoma	270 (87.9)
invasive lobular carcinoma	26 (8.5)
other**** or unknown	11 (3.6)
differentiation** – no. (%)	
grade 1	28 (9.1)
grade 2	159 (51.8)
grade 3	111 (36.2)
unknown	9 (2.9)
unknown	9 (2.9)
receptor profile** – no. (%)	
ER+/HER2neu+	69 (22.5)
ER+/HER2neu-	140 (45.6)
ER-/HER2neu+	23 (7.5)
ER-/HER2neu-	75 (24.4)
tumour status* (cT) – no. (%)	
T0	3 (1.0)
Tis	1 (0.3)
T1	57 (18.6)
T2	170 (55.4)
T3	49 (16.0)
T4	27 (8.8)
regional lymph nodes* (cN) – no. (%)	
N0	122 (39.7)
N1	102 (33.2)
N2	46 (15.0)
N3	37 (12.1)
distant metastasis* (cM) – no. (%)	
M0	279 (90.9)
M1 oligometastatic	10 (3.3)
M1	18 (5.9)
staging* – no. (%)	
stage I	26 (8.5)
stage IIA	102 (33.2)
stage IIB	58 (18.9)
stage III	93 (30.3)
stage IV	28 (9.1)
FDG avidity PET/CT – no. (%)	
good	270 (87.9)
moderate	28 (9.1)
poor	9 (2.9)

*as determined on US/MRI/[18F]FDG PET/CT; **as determined on surgical resected tumour tissue and if not available tumour biopsy; ***T0 or retro-areolar; ****medullar, tubular, mucinous, metaplastic, ductal carcinoma in situ, or low-grade basal-like

Table 2 provides an overview of the patient and tumour characteristics influencing staging and treatment due to performance of [18F]FDG PET/CT. Multicentricity of the tumour and suspected lymph node metastasis before the [18F]FDG PET/CT scan are statistically significant risk factors after multivariate logistic regression analysis for both alteration of staging and alteration of treatment strategy. cN+ status after US and MRI had the highest effect with an OR of 3.9 (95% CI, 1.6-9.3) on alteration of staging and an OR of 3.2 (95% CI, 1.4-7.1) on alteration of treatment strategy compared to cN0 status, both with a significance of $p<0.01$. Multicentricity of the tumour had an OR of 3.2 (95% CI, 1.5-7.0) on alteration of staging and an OR of 3.0 (95% CI, 1.5-6.1) on alteration of treatment strategy compared to unifocal and multifocal tumours, both with a significance of

p<0.01. Tumours with a HER2neu+ profile had a statistically significant RR of 1.7 (95% CI, 1.0-2.9) with p=0.04 on alteration of staging compared to a HER2neu- profile, but did not experience more often a significant alteration of treatment strategy (p=0.10). Between the subgroups within the clinical parameters of age, quadrant localization, histological type, oestrogen hormone status, cM status, and after correction in the logistic regression analysis, grade of differentiation and cT status, no statistical difference in alteration of either staging or treatment strategy was found.

When comparing the equivalent outcomes in stage I-II breast cancer to these outcomes, shown in table 3, similar trends of proportions and risk ratios are found, with less significance because of the smaller study population. Noteworthy, invasive lobular carcinoma (ILC) has an RR of 3.0 (95% CI, 1.1-8.3) with p=0.08 for alteration of staging and an RR of 3.3 (95% CI, 1.2-9.2) with p=0.06 for alteration of treatment strategy compared to invasive ductal carcinoma (IDC). This derived from alteration of staging and treatment strategy in 33.3% (3/9) of cases with ILC, compared to alteration of staging in 11.1% (21/190) and alteration of treatment strategy in 10.0% (19/190) of cases with IDC.

Incidental Findings

Incidental findings occurred in 27.0% (82/304) of [^{18}F]FDG PET/CT scans. In 5.6% (17/304) of the scans, two incidental findings were found, leading to a total of 99 incidental findings. Most common sites were the lymph nodes (19.2%) followed by the thyroid/parathyroid glands (14.1%), the lungs (13.1%), the

Table 2. Patient and tumour characteristic analysis on the primary outcomes.

	staging alteration [^{18}F]FDG-PET/CT			treatment strategy alteration [^{18}F]FDG-PET/CT		
characteristic	**no. events/ total no. (%)**	**risk ratio (95% CI)**	***p*-value**	**no. events/ total no. (%)**	**risk ratio (95% CI)**	***p*-value**
total	49/305 (16.1)			59/305 (19.3)		
age						
< 50y	16/119 (13.4)	1.0	0.32	19/119 (16.0)	1.0	0.23
≥ 50y	33/186 (17.7)	1.3 (0.8-2.3)		40/186 (21.5)	1.3 (0.8-2.2)	
localisation*						
LQ	30/216 (13.9)	1.0	0.16	39/216 (18.1)	1.0	0.63
MQ	17/83 (20.5)	1.5 (0.9-2.5)		17/83 (20.5)	1.1 (0.7-1.9)	
focality*						
unifocal	11/137 (8.0)	1.0	<0.01	13/137 (9.5)	1.0	<0.01
multifocal	11/78 (14.1)	1.8 (0.8-3.9)		11/78 (14.1)	1.5 (0.7-3.2)	
multicentric	25/86 (29.1)	3.6 (1.9-7.0)		33/86 (38.4)	4.0 (2.3-7.2)	
histol. type**						
IDC	44/269 (16.4)	1.0	1.00	50/269 (18.6)	1.0	0.29
ILC	4/25 (16.0)	1.0 (0.4-2.5)		7/25 (28.0)	1.5 (0.8-3.0)	
diff. grade**						
grade 1	9/28 (32.1)	1.0	0.01	9/28 (32.1)	1.0	0.01
grade 2	26/157 (16.6)	0.5 (0.3-1.0)		35/157 (22.3)	0.7 (0.4-1.3)	
grade 3	10/111 (9.0)	0.3 (0.1-0.6)		11/111 (9.9)	0.3 (0.1-0.7)	
horm. status**						
ER-	13/98 (13.3)	1.0	0.36	15/98 (15.3)	1.0	0.22
ER+	36/207 (17.4)	1.3 (0.7-2.4)		44/207 (21.3)	1.4 (0.8-2.4)	
HER2neu**						
HER2neu-	28/213 (13.1)	1.0	0.04	36/213 (16.9)	1.0	0.10
HER2neu+	21/92 (22.8)	1.7 (1.0-2.9)		23/92 (25.0)	1.5 (0.9-2.4)	

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cT*,***						
T1	7/56 (12.5)	1.0	0.31	7/56 (12.5)	1.0	<0.01
T2	24/169 (14.2)	1.1 (0.5-2.5)		22/169 (13.0)	1.0 (0.5-2.3)	
T3	12/49 (24.5)	2.0 (0.8-4.6)		17/49 (34.7)	2.8 (1.3-6.1)	
T4	4/27 (14.8)	1.2 (0.4-3.7)		11/27 (40.7)	3.3 (1.4-7.5)	
cN*						
N0	7/129 (5.4)	1.0	<0.01	9/129 (7.0)	1.0	<0.01
N+	42/176 (23.9)	4.4 (2.0-9.5)		50/176 (28.4)	4.1 (2.1-8.0)	
cM*						
M0	49/295 (16.6)	1.0	0.37	56/295 (19.0)	1.0	0.41
M1	0/10 (0)	-		3/10 (30.0)	1.6 (0.6-4.2)	
staging*						
stage I	3/29 (10.3)	1.0	<0.01	3/29 (10.3)	1.0	<0.01
stage IIA	5/105 (4.8)	0.5 (0.1-1.8)		5/105 (4.8)	0.5 (0.1-1.8)	
stage IIB	16/72 (22.2)	2.1 (0.7-6.8)		14/72 (19.4)	1.9 (0.6-6.1)	
stage III	25/89 (28.1)	2.7 (0.9-8.3)		34/89 (38.2)	3.7 (1.2-11.1)	
stage IV	0/10 (0)	-		3/10 (30.0)	2.9 (0.7-12.1)	

multivariate logistic regression analysis (N=296)

	staging alteration [^{18}F]FDG-PET/CT			treatment strategy alteration [^{18}F]FDG-PET/CT		
characteristic	**coefficient (SE)**	**odds ratio (95% CI)**	**adjusted *p*-value**	**coefficient (SE)**	**odds ratio (95% CI)**	**adjusted *p*-value**
focality* MC vs UF-MF	1.2 (0.4)	3.2 (1.5-7.0)	<0.01	1.1 (0.4)	3.0 (1.5-6.1)	<0.01
diff. grade** G3 vs G1-2	-0.6 (0.4)	0.6 (0.3-1.2)	0.15	-0.7 (0.4)	0.5 (0.2-1.1)	0.08

* as determined on US/MRI; ** as determined on biopsy; *** T0 excluded from this analysis (n=3)
Abbreviations: LQ= lateral quadrant; MQ= medial quadrant; histol. type = histological type; IDC= invasive ductal carcinoma; ILC= invasive lobular carcinoma; diff. grade = differentiation grade; horm. status = hormonal status; MC= multicentric; UF-MF= unifocal and multifocal; G3= grade 3; G1-2= grade 1 and grade 2

Table 3. Patient and tumour characteristics analysis on the primary outcomes in the subgroup stage I-II breast cancer.

	staging alteration [^{18}F]FDG-PET/CT			treatment plan alteration [^{18}F]FDG-PET/CT		
characteristic	**no. events/ total no. (%)**	**risk ratio (95% CI)**	***p*-value**	**no. events/ total no. (%)**	**risk ratio (95% CI)**	***p*-value**
total	24/206 (11.7)			22/206 (10.7)		
age						
< 50y	8/86 (9.3)	1.0	0.39	7/86 (8.1)	1.0	0.37
≥ 50y	16/120 (13.3)	1.4 (0.6-3.2)		15/120 (12.5)	1.5 (0.7-3.6)	
localisation*						
LQ	14/144 (9.7)	1.0	0.23	14/144 (9.7)	1.0	0.46
MQ	10/60 (16.7)	1.7 (0.8-3.6)		8/60 (13.3)	1.4 (0.6-3.1)	
focality*						
unifocal	9/111 (8.1)	1.0	0.04	8/111 (7.2)	1.0	0.06
multifocal	6/55 (10.9)	1.3 (0.5-3.6)		6/55 (10.9)	1.5 (0.6-4.1)	
multicentric	9/38 (23.7)	2.9 (1.3-6.8)		8/38 (21.1)	2.9 (1.2-7.2)	
histol. type**						
IDC	21/190 (11.1)	1.0	0.08	19/190 (10.0)	1.0	0.06
ILC	3/9 (33.3)	3.0 (1.1-8.3)		3/9 (33.3)	3.3 (1.2-9.2)	
diff. grade**						
grade 1	3/19 (15.8)	1.0	0.05	3/19 (15.8)	1.0	0.04
grade 2	16/96 (16.7)	1.1 (0.3-3.3)		15/96 (15.6)	1.0 (0.3-3.1)	
grade 3	5/89 (5.6)	0.4 (0.1-1.4)		4/89 (4.5)	0.3 (0.1-1.2)	
horm. status**						
ER-	5/76 (6.6)	1.0	0.11	5/76 (6.6)	1.0	0.17
ER+	19/130 (14.6)	2.2 (0.9-5.7)		17/130 (13.1)	2.0 (0.8-5.2)	
HER2neu**						
HER2neu-	13/137 (9.5)	1.0	0.25	11/137 (8.0)	1.0	0.10
HER2neu+	11/69 (15.9)	1.7 (0.8-3.6)		11/69 (15.9)	2.0 (0.9-4.3)	
cT*,***						
T1	5/50 (10.0)	1. 0	0.45	5/50 (10.0)	1.0	0.84
T2	19/145 (13.1)	1.3 (0.5-3.3)		17/145 (11.7)	1. 2 (0. 5-3.0)	
T3	0/9 (0)	-		0/9 (0)	-	
cN*						
N0	6/120 (5.0)	1.0	<0.01	6/120 (5.0)	1.0	<0.01
N+	18/86 (20.9)	4.2 (1.7-10.1)		16/86 (18.6)	3.7 (1.5-9.1)	
staging*						
stage I	3/29 (10.3)	1.0	<0.01	3/29 (10.3)	1.0	<0.01
stage IIA	5/105 (4.8)	0.5 (0.1-1.8)		5/105 (4.8)	0.5 (0.1-1.8)	
stage IIB	16/72 (22.2)	2.1 (0.7-6.8)		14/72 (19.4)	1.9 (0.6-6.1)	

* as determined on US/MRI; ** as determined on biopsy; *** T0 excluded from this analysis (n=3)
Abbreviations: LQ= lateral quadrant; MQ= medial quadrant; histol. type = histological type; IDC= invasive ductal carcinoma; ILC= invasive lobular carcinoma; diff. grade = differentiation grade; horm. status = hormonal status; MC= multicentric

skeleton (12.1%), colon and rectum (7.1%), the upper GI tract (7.1%), the kidneys/adrenal glands (7.1%), and the gynaecologic tract (6.1%). The remaining 14.1% of the abnormalities were located at other sites, including the ENT site, skin, soft tissues, liver, cardiovascular system, brain, and the breast. Of all 99 incidental findings, 78 needed further investigations and led to the performance of 49 US examinations, 1 X-ray, 26 CT scans, 6 MRI scans, 3 PET/CT scans, 3 endobronchial US scans, 12 endoscopies, 52 biopsies/punctures, 5 polypectomies, and to 4 resections: 1 mastectomy, 2 hemithyroidectomies, and 1 partial nephrectomy. For the other 21 abnormalities, a reassuring conclusion could be derived by anamneses, physical examination, or by combining expertise in an MDTM. In figure 2A, B and 3 some examples of findings with [^{18}F]FDG PET/CT.
Of all incidental findings 4.0% (4/99) was proven malignant, which involved 1 sigmoid carcinoma, 1 stomach carcinoma, 1 renal cell carcinoma, and 1 thyroid carcinoma. In two other patients, further investigation to an incidental finding with high suspicion of malignancy was waived due to the prognosis of the breast cancer. In 3.0% (3/99) of cases, the treatment for breast cancer was altered due to the incidental finding. These alterations included a mastectomy instead of a lumpectomy, an expansion of the adjuvant radiation fields, and combined surgery of the breast cancer and the sigmoid carcinoma followed by adjuvant chemotherapy instead of receiving NST.

Delay

The number of included subjects for each analysis together with their corresponding results is noted in table 4. The median lead time of the performance of an [^{18}F]FDG PET/CT was 3 workdays, equivalent to the lead time of the performance of an MRI that is executed in the same time window. The median lead time between the performance of the [^{18}F]FDG PET/CT and starting NST was 9 workdays. There was no significant delay in lead time of starting NST after [^{18}F]FDG PET/CT performance with occurring incidental findings, whether they had additional investigations performed or not.

Discussion

In this study, alterations of initial staging and treatment strategy of breast cancer resulting from the performance of an [^{18}F]FDG PET/CT were significantly more common in multicentric tumours and cN+ status on US and MRI. Alteration of staging was also significantly more common in HER2neu+ breast cancer patients, representing the aggressive nature of this subtype (19). However, the effect of HER2neu status on alteration of staging and alteration of treatment strategy differs. Also, the proportion of new findings on the [^{18}F]FDG PET/CT does not differ between HER2neu- and HER2neu+ subgroups. Therefore, the significant difference between the HER2neu profile statuses on initial staging appears to be a distorted outcome.
Similarly, there is a difference in the effect on alteration of staging and alteration of treatment strategy of cT status. This could be the result of less frequent restaging in cT3-4 tumours compared to cT1-2 tumours. However, cT status does not retain its significant effect on alteration of treatment strategy in the logistic regression analysis. This shift is at least partly attributable to the significantly higher proportion of cN+ status co-occurring

Table 4. Analysis on delay resulting from the performance of [^{18}F]FDG PET/CT.

lead time of interest	no. patients	time in working days			
		median (IQR)	modus	range	*p*-value difference
order of imaging – performance of imaging					
MRI	296	3 (2-5)	3	0-14	
[^{18}F]FDG PET/CT	300	3 (2-5)	2	1-10	
[^{18}F]FDG PET/CT performance – start NST					
total	240	9 (7-12)	9	2-23	
[^{18}F]FDG PET/CT without incidental findings	177	9 (7-12)	9	2-20	R
[^{18}F]FDG PET/CT with incidental findings	63	9 (7-12)	9	4-23	0.56
[^{18}F]FDG PET/CT with incidental findings needing further investigation	53	9 (8-12)	9	4-23	0.26

Abbreviations: R= reference group

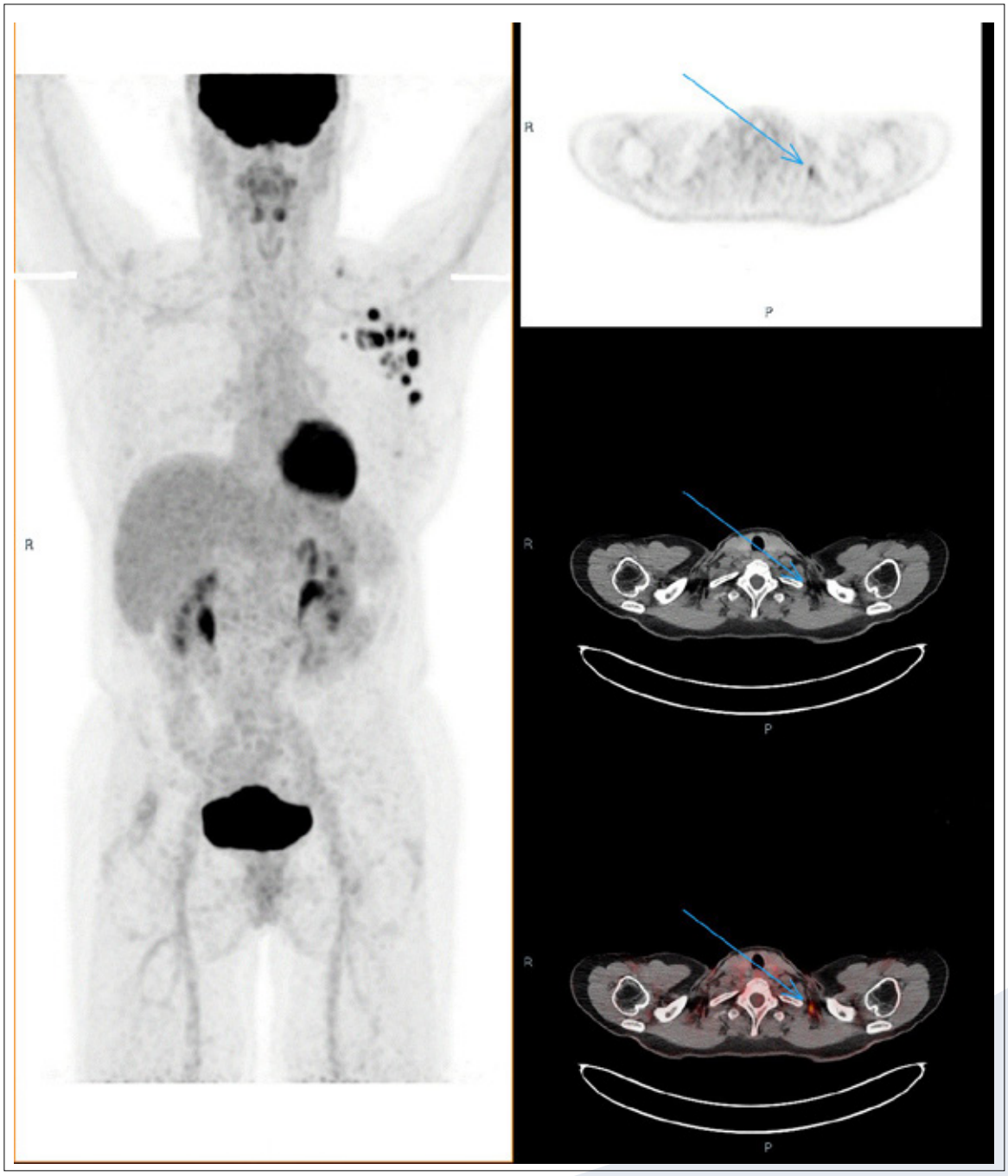
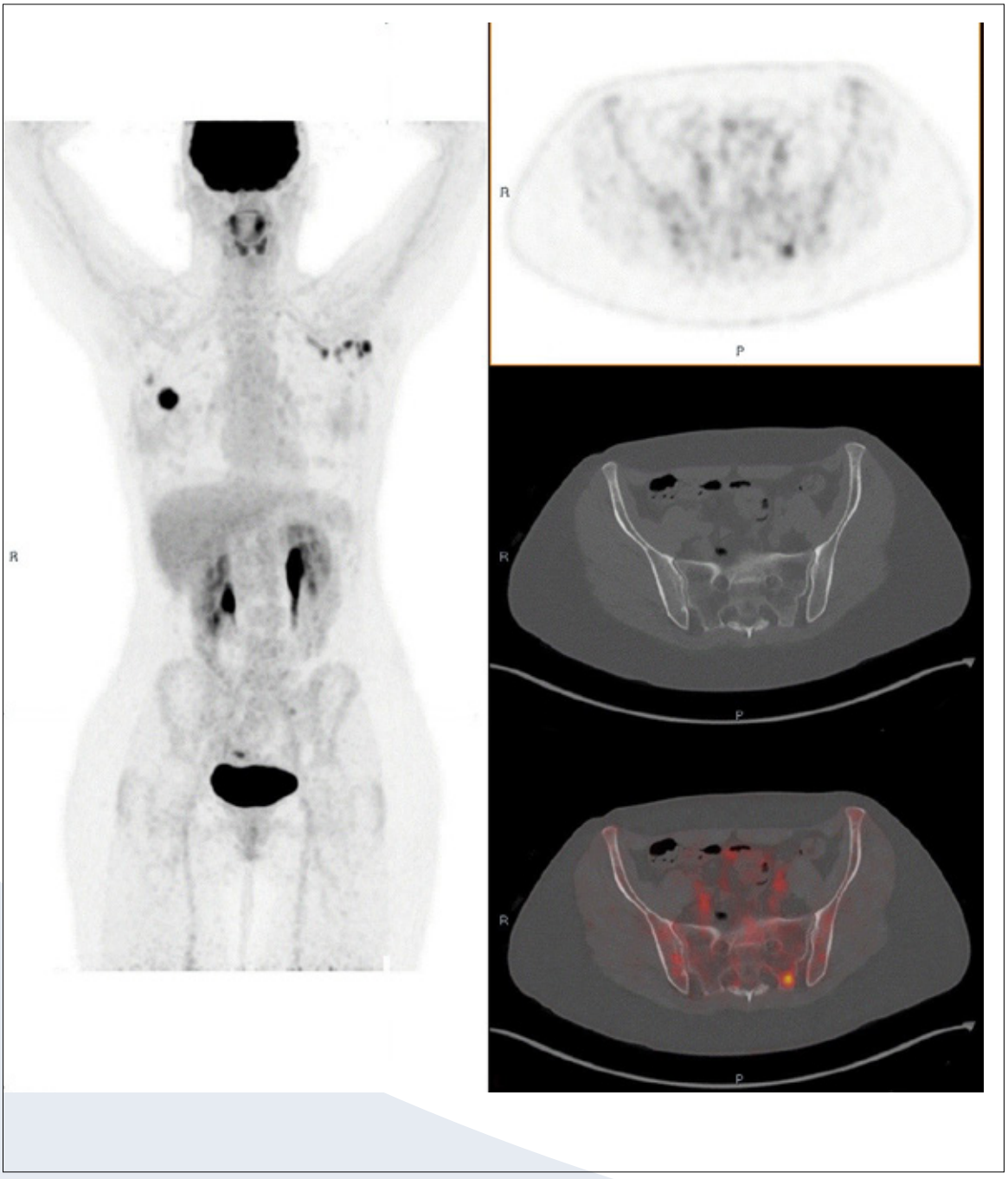


Figure 2. Two patient examples with relevant findings on [^{18}F]FDG PET/CT affecting tumour staging and treatment **A**: an FDG-avid supraclavicular lymph node, ipsilateral to the breast tumour and axillary lymph node metastases, resulted in upstaging of the breast cancer from stage IIIA (cT1c N2a Mx) to stage IIIC (cT1c N3c M0) and expansion of the radiation field for adjuvant radiotherapy. **B**: an FDG-avid, biopsy-proven sacral bone metastasis led to upstaging of the breast cancer from stage IIB (cT2 N1) to stage IV (M1, oligometastatic). The lesion was included in the radiotherapy treatment. Notably, FDG uptake was also observed in several left axillary lymph nodes, which was not due to metastatic involvement, but attributed to a reactive response following recent administration of a COVID-19 vaccine in the left upper arm.

TvNG 2025 47(2)



B

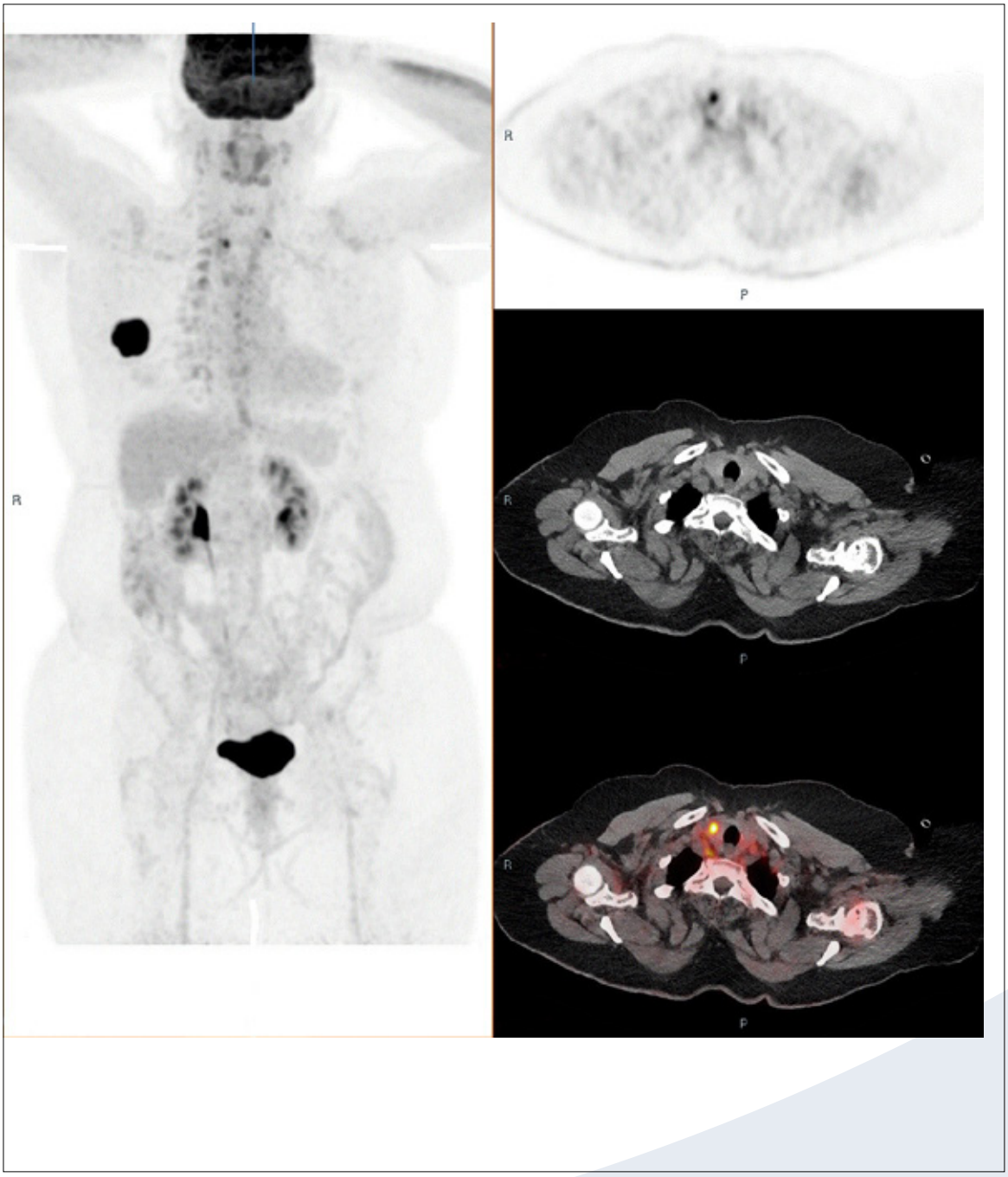


Figure 3. Example patient case with an encountered incidental finding.
[^{18}F]FDG PET/CT showed, in addition to the breast tumour without lymph node or distant metastasis, a suspected thyroid lesion. This lesion appeared to be a follicular adenoma after an inconclusive biopsy and later diagnostic hemithyroidectomy.

with cT3-4 tumours. Inference from this logistic regression analysis suggests that lymph node involvement confers a higher risk of additional regional and distant metastases than increasing tumour volume, consistent with results of earlier studies (4,5). Also, most patients presenting with a large cT3 of cT4 tumour will be planned for mastectomy irrespective of the [^{18}F]FDG PET/CT outcome. Therefore, in these patients upgrading of the treatment plan to more extensive local treatment after the [^{18}F]FDG PET/CT scan is less likely than in patients with a smaller tumour. Incidental findings are inevitable with additional imaging in patient populations. This becomes especially relevant with low-value investigations regarding a certain purpose, as evaluated in this study. A total of 99 incidental findings occurred in the executed [^{18}F]FDG PET/CT scans. These findings led, in the observed period, to the execution of 161 additional investigations, which did not result in a significant delay in initiation of NST. Of the incidental findings, four were proven malignant, and treatment strategy regarding the breast cancer was altered in three patients.

The median lead time to the performance of an [^{18}F]FDG PET/CT of three workdays did not differ from the lead time of an MRI in this study. However, logistics may vary significantly among hospitals, affecting the delay in initiating treatment following the [^{18}F]FDG PET/CT. In this study, roughly half of the inclusion period was during the COVID pandemic. In this time, regular care was scaled down and more room was made for urgent oncological investigations. Now regular care is back, facilitating extra diagnostics within three workdays will be much more challenging.

When assessing the utility of [^{18}F]FDG PET/CT in initial staging of breast cancer patients eligible for NST, statistical significance needs to be related to clinical relevance. Even in the most favourable circumstances, some findings will always be missed if not everyone is screened. This also applies to stage I-II breast cancer as confirmed in the results of this study. The consideration that must be made is what is considered acceptable to miss and which under- and overtreatment is allowable. Our results indicate that [^{18}F]FDG PET/CT certainly should be performed in case of multicentricity of the tumour and cN+ status. Furthermore, although no significant effect of cT status is found in these results, the effect of this described in other studies cannot be rejected entirely either (4,5). In context of individualized patient care and cost-effectiveness, it may be worth contemplating omitting [^{18}F]FDG PET/CT diagnostics in non-multicentric cT1-2N0 breast cancer, which covers over one-third of the NST population. The present study is not without limitations. First, cN status was often simply notated as cN+ without subdivision into cN1-3 status, leading to potential ambiguity in categorization. Criteria used for cN2a status was explicitly mentioning of retropectoral positioning, connected or confluent lymph nodes, six or more suspected axillary lymph nodes, and when a modified radical mastectomy or lymphadenectomy was performed. Furthermore, the sample size was not large enough for assessment of rare characteristics such as other histological types of carcinomas, for example metaplastic carcinoma. Moreover, there is a presumed limited value of the [^{18}F]FDG PET/CT scan in ILC tumours due to reduced FDG-avidity (20). Given the insufficient numbers of ILC tumours in this study, no firm recommendation can be made about the value of [^{18}F]FDG PET/CT for these tumours. Lastly, due to the retrospective cohort design of our study, data gathering was limited to specific time frames, impacting the long-term accuracy of the collected data. Therefore, it is not possible to draw conclusions about the impact of [^{18}F]FDG PET/CT performance on long-term oncological outcomes, cosmetic outcomes due to more limited surgery, or the modification of radiotherapy fields.

Conclusions

[^{18}F]FDG PET/CT in the work-up to NST led to alterations in staging in 16.1% and alterations in treatment strategy in 19.3% of breast cancer cases. Evident risk factors for these alterations include multicentricity of the tumour and a cN+ status, irrespective of the stage or histologic subtype of the breast cancer. We recommend an [^{18}F]FDG PET/CT before NST only in patients with a multicentric tumour, cT3-4, or cN+ breast cancer, irrespective of the tumour subtype.

Ethics

This is an observational study. The Medical Ethics Review Committee (METC) Brabant issued a non-MWO Declaration on April 15th, 2024; METC nr NW2024-28.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. ♦

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