Surgical Oncology 30 (2019) 1–5

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Node positive breast cancer: Concordance between baseline PET/CT and sentinel node assessment after neoadjuvant therapy

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A B S T R A C T

Introduction: Sentinel node biopsy for axillary staging in node positive patients after neoadjuvant treatment is controversial, mainly due to high false negative rates. We examined the concordance between the location of the hot nodes identified on PET-CT at presentation with the location of the sentinel nodes.

Materails and methods: Fifty-eight breast cancer patients undergoing neoadjuvant treatment between January 2013 and September 2018 who had positive regional lymph nodes on PET/CT, and a SPECT/CT lymphoscintigraphy completed before sentinel node biopsy were included. Patient, tumor and treatment characteristics were collected. Images of PET/CT were compared to images of SPECT/CT lymphoscintigraphy post treatment and concordance between location of the hot nodes on PET/CT with the sentinel nodes visualized on SPECT/CT was assessed. Association between patient, tumor and treatment characteristics and concordance between the sentinel node and the hot nodes was determined.

Results: Sentinel nodes were identified in 53 (91%) of the cases in surgery. In 25 (43%) patients, axillary nodes were positive after treatment. In 16 (28%; 95% CI 18, 40) the sentinel node was not one of the hot nodes seen on PET/CT at presentation. Twenty-three (40%) patients had excision of additional axillary nodes. In two patients with non-concordant sentinel nodes, the sentinel node was falsely negative.

Conclusions: In node positive patients who undergo neoadjuvant treatment, the sentinel node visualized on lymphatic mapping is not necessarily one of the hot nodes identified on PET/CT at presentation. These findings underline the importance of marking the pathologically proven lymph node and excising it as well as the sentinel nodes after treatment.

1. Introduction

Advancements in systemic therapy have led to increased rates of pathological complete response in the breast and regional lymph nodes. With increased rates of pathological complete response, the need for axillary dissection in all women with node positive disease at diagnosis is debatable. Alternatives to axillary dissection include sentinel lymph node biopsy, excision of the marked pathologically-proven lymph node, or a combination of both (targeted axillary dissection). Several studies examining the feasibility of sentinel node biopsy in women with regional lymph node involvement undergoing neoadjuvant treatment, have reported false -negative rates higher than 10% [1,2]. A key question is whether the sentinel nodes identified post neoadjuvant treatment and the nodes involved with tumor at diagnosis, are identical.

In the current study, we correlated the location of suspicious regional lymph nodes visualized on baseline PET/CT studies with the location of sentinel nodes visualized on SPECT-CT lymphoscintigraphy performed after neoadjuvant therapy.

Recent introduction of SPECT/CT combining single photon emission computed tomography lymphoscintigraphic data with CT have gained improved diagnostic accuracy compared to planar lymphoscintigraphy, with better visualization and localization of the sentinel nodes [3,4]. This technology is routinely used at our center for sentinel node mapping.

2. Methods

Institutional Review Board approval was obtained and informed consent was waived for this retrospective cohort study.

Based on data search of reports at the department of nuclear medicine, we identified patients with breast cancer who had nodal disease on baseline PET/CT study and a lymphoscintigraphy study done after neoadjuvant therapy between January 2013 and September 2018. We collected data on demographics, breast cancer characteristics, neoadjuvant treatment regimen, details of the operative procedure and final

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https://doi.org/10.1016/j.suronc.2019.05.006
Received 15 February 2019; Received in revised form 30 March 2019; Accepted 13 May 2019
0960-7404/

pathology results.

Patients were candidates for sentinel node biopsy after neoadjuvant treatment if at the end of neoadjuvant treatment they were clinically and radiologically node negative. In all cases, dual tracer mapping was used.

FDG-PET/CT Acquisition: After fasting for at least 4 hours, an intravenous injection of 5 MBq/kg body weight (0.14 mCi/kg) of ^{18}F-FDG was administered. Data acquisitions were performed 60 min after injection using an integrated PET/CT system (Discovery 690, GE Healthcare). A whole body PET/CT scan in supine position was obtained from the vertex of the skull to mid-thighs. For both PET/CT and SPECT/CT patients were positioned in a similar manner with their hands raised above their head. PET image datasets were reconstructed iteratively by using CT data for attenuation correction, and co-registered images were displayed on a Xeleris workstation (GE Healthcare).

Lymphoscintigraphy: a day prior to surgery, a dose of 74 MBq (2 mCi) ^{99m}Tc-nano-sized-albumin-colloid (Nanotop; ROTOP pharmaka GmbH) divided into four equal aliquots of 0.5 ml each, was injected by a nuclear medicine physician. Peri-tumoral injection was used in patients with a palpable breast mass. In patients undergoing image-guided needle localization, a peri-areolar injection or an injection at the site marked by the radiologist was used. Immediate planar dynamic acquisitions were acquired, followed by static planar anterior and lateral projections, and repeated as necessary up to 24 h post-injection, until a sentinel node was detected. At that time a^{57}Co flood source was placed between the patient and the camera to define the body contour and a SPECT/CT study of the chest was acquired using a hybrid system composed of a dual-headed gamma camera with a low-dose x-ray tube (120 kV, 30 mA) and LEHR collimators (Discovery 640, GE Healthcare). SPECT acquisition of the chest was performed with the following parameters: matrix size 128 × 128, 180° in the anterior L-mode rotation, 3° angle steps and 20- to 25-s time frame. Data were reconstructed on a Xeleris workstation (GE Healthcare).

Comparison between FDG-PET/CT and SPECT/CT: PET/CT and SPECT/CT data were automatically co-registered using the Xeleris workstation and retrospectively reviewed by a nuclear medicine physician. For each study, the axillary sentinel lymph node detected on SPECT/CT was identified on the baseline PET/CT and specified as showing increased ^{18}F-FDG uptake at diagnosis or not. Co-registration of the images, despite being acquired by different modalities at different times, was possible by correlating the topography on the CT part of the images, i.e. the location of lymph-nodes in relation to the pectoralis muscles and other structures. This is generally done automatically by the XELERIS workstation. Maximum standardized uptake value (SUV_{max}) was obtained for all lymph nodes.

Analyses: Association between patient, tumor and treatment characteristics and concordance between the hot lymph node(s) visualized on PET/CT and the sentinel node(s) visualized on SPECT/CT lymphoscintigraphy were examined using chi square test for parametric variables and the Student's t-test or Mann-Whitney test for continuous variables (according to their distribution). All analyses were completed using IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY). Binomial distributions were assumed and ninety-five percent confidence intervals (CI) were estimated using the Wilson procedure.

3. Results

After excluding patients with no uptake on the regional lymph nodes on PET/CT (N = 32), and those with no visualization of sentinel nodes on SPECT/CT (N = 24), the study cohort included 58 post neoadjuvant patients (one male). Patient and tumor characteristics are summarized in Table 1. The mean age of the patients was 52 (range 24, 76). Almost half of the patients had high-grade tumors (26, 45%). In 31 (53%) patients, a metastatic lymph node was biopsy proven at diagnosis, in 11 (19%) patients the needle biopsy was negative. SUV_{max} ranged between 0.38 and 20.7, with a median of 2.81. In almost three quarters of the patients (43, 74%) there were up to five hot nodes on PET/CT. In eight (14%) patients, one of the hot nodes was located in the internal mammary region. Most of the patients received chemotherapy (32, 55%) or a combination of chemotherapy with biological therapy (19, 33%). The remainder received hormonal treatment.

Comparing PET/CT and SPECT/CT data: hot nodes found at diagnosis appeared to be concordant with one of the sentinel nodes in 41 patients (71%, 95% CI 58; 81) (Fig. 1a,b). In one patient, it was impossible to determine if the nodes were identical, because of difficulty

Table 1
Characteristics of the study group.

Mean age, years (SD)	53 (14.3)
Cancer type	
IDC G1	7 (12)
IDC G2	21 (36)
IDC G3	26 (45)
ILC	3 (5)
Missing	1 (2)
Receptor classification, N (%)	
Luminal	22 (38)
HER positive	19 (33)
Triple negative	15 (26)
Multicentric, N (%)	
No	41 (71)
Yes	16 (28)
Missing	1 (2)
Lymph node status at diagnosis, N (%)	
Negative	11 (19)
Positive	31 (53)
NA or ND	16 (28)
Median SUV_{max}, (range)	2.81 (0.38; 20.7)
Neoadjuvant type, N (%)	
Chemotherapy	32 (55)
Chemotherapy and biological therapy	19 (33)
Hormonal therapy	7 (12)
Mean time between PET and lymphoscintigraphy, days (SD)	220 (50)
Sentinel node identified, N (%)	
No	3 (5)
Yes	53 (91)
Missing	2 (3)
Blue node identified, N (%)	
No	11 (19)
Yes	36 (62)
Unknown	11 (19)
Hot node identified, N (%)	
No	6 (10)
Yes	45 (78)
Missing	7 (12)
Frozen, N (%)	
Negative	39 (67)
Positive	13 (22)
Unknown	6 (10)
Final pathology axillary node (sentinel or non-sentinel), N (%)	
Negative	31 (53)
Positive	25 (43)
Missing	2 (3)
Final pathology tumor, N (%)	
IDC	29 (50)
ILC	6 (10)
DCIS	5 (9)
No residual	15 (26)
Missing	3 (5)
Tumor stage at surgery, N (%)	
T1	19 33)
T2	11(19)
T3	1 (2)
T4	1(2)
Missing	6 (10)

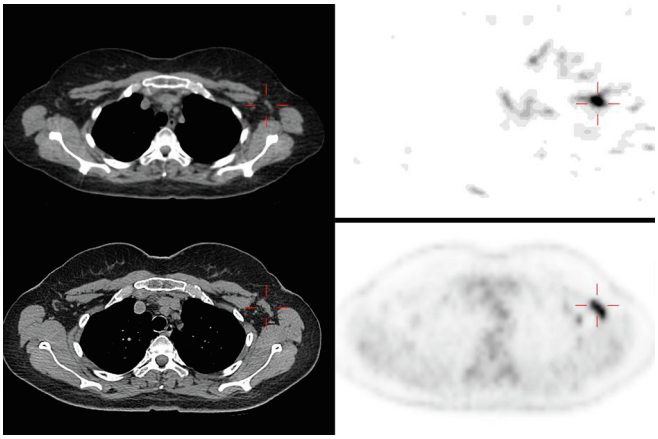

Fig. 1a. ^{99m}Tc-Nanotop SPECT/CT (top) and FDG PET/CT (bottom) images of a patient with concordant level-1 right axillary lymph a-axial.

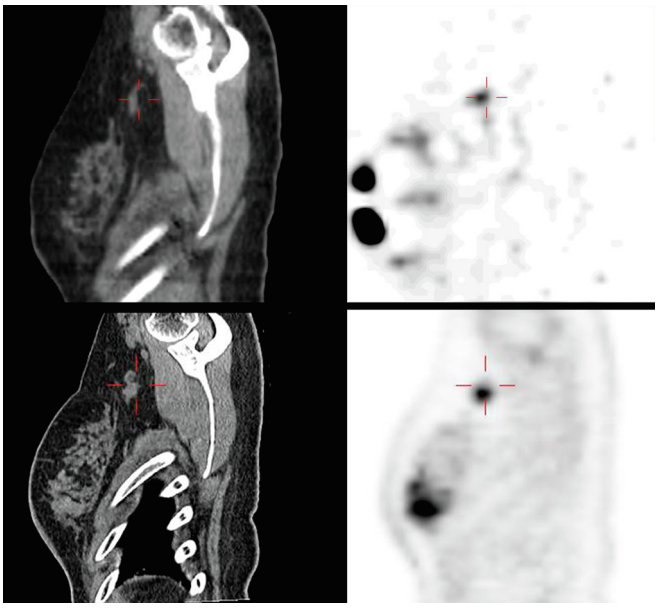

Fig. 1b. ^{99m}Tc-Nanotop SPECT/CT (top) and FDG PET/CT (bottom) images of a patient with concordant level-1 right axillary lymph b-sagittal.

in comparing the anatomy on both studies, as there were multiple hot nodes.

A sentinel node was identified at surgery in 53 (91%) of the patients. The median number of sentinel nodes removed was three (range 1–8). In 25 (43%) patients, the axillary nodes (sentinel and or non-sentinel) were metastatic after treatment. Twenty-three patients had non-sentinel nodes removed, either because the sentinel node was not identified (N = 3), the sentinel node was metastatic (N = 12), or for other reasons (macroscopically suspicious nodes or too few sentinel nodes identified). The median number of nodes removed in these 23 women was 10 (range 4–16). The sentinel nodes were the only nodes involved in seven (58%) of the patients undergoing removal of non-sentinel nodes. In three women that underwent removal of non-sentinel nodes the sentinel node was falsely negative, yielding a false negative rate of 14%. In two patients with non-concordance between the hot nodes on PET/CT and the sentinel nodes identified on SPECT/CT, the sentinel node was negative and a non-sentinel node was positive. In one patient with concordant PET/CT and SPECT/CT lymphoscintigraphy, the sentinel nodes were negative whereas a positive intra-mammary node was identified. In fifteen patients (26%), complete pathological response was documented. Table 2 summarizes the association between

Table 2
Association between patient, tumor and treatment characteristics and concordance between hot lymph node(s) on PET and CT-lymphoscintigraphy.

	Same lymph node		P
	No (16, 28%)	Yes (41, 71%)	
Mean age, years (SD)	55 (13)	51 (15)	NS
Multicentric, N(%)			
No	10 (24)	30 (73)	NS
Yes	6 (38)	10 (63)	
Receptor status classification, N(%)			
Luminal	8 (36)	14 (64)	NS
HER2 positive	4 (21)	14 (74)	
Triple negative	3 (20)	12 (80)	
Median SUV_{max} (SD)	3.57 (4.1)	4.36 (4.1)	NS
Number of suspicious nodes on PET			
Less than 5	13 (30)	29 (67)	NS
5 or more	3 (20)	12 (80)	
Previous Surgery, N(%)			
No	13 (31)	28 (67)	NS
Yes	1 (20)	4 (80)	
Neoadjuvant type, N(%)			
Chemotherapy	9 (28)	23 (72)	NS
Chemotherapy and biological therapy	4 (21)	14 (74)	
Hormonal	3 (43)	4 (57)	
Mean time between PET and surgery (days, SD)	237 (65)	214 (42)	NS
Sentinel node identified, N(%)			
No	0(0)	3 (100)	NS
Yes	16 (30)	36 (68)	
Frozen, N(%)			
Negative	11 (28)	27 (69)	NS
Positive	4 (31)	9 (69)	
Final pathology node, N(%)			
Negative	7 (23)	23 (74)	NS
Positive	9 (36)	16 (64)	

patient tumor and treatment characteristics and concordance of the hot nodes on PET/CT with the sentinel nodes on post neoadjuvant lymphoscintigraphy. There was no association between type of cancer, neoadjuvant treatment, response to treatment and concordance between the nodes on both studies. A case in which the location of the hot node on baseline PET/CT was not identical to the location of the sentinel node is shown in Fig. 2a,b.

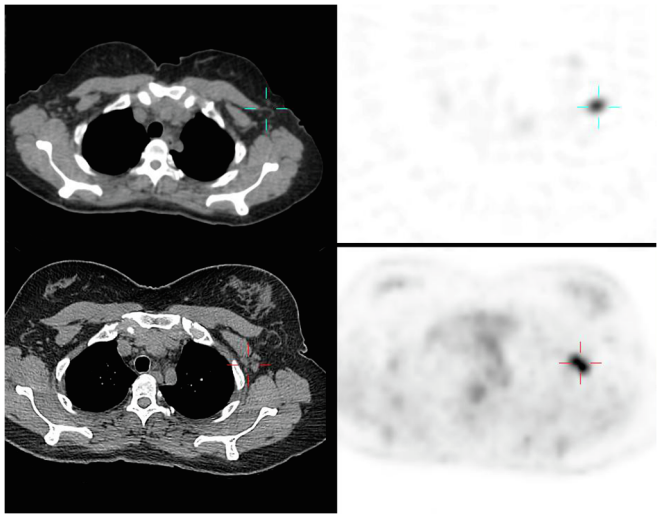

Fig. 2a. ^{99m}Tc-Nanotop SPECT/CT (top) and FDG PET/CT (bottom) images of a patient with non-concordant positive lymph nodes visualized in the left axilla. a-axial.

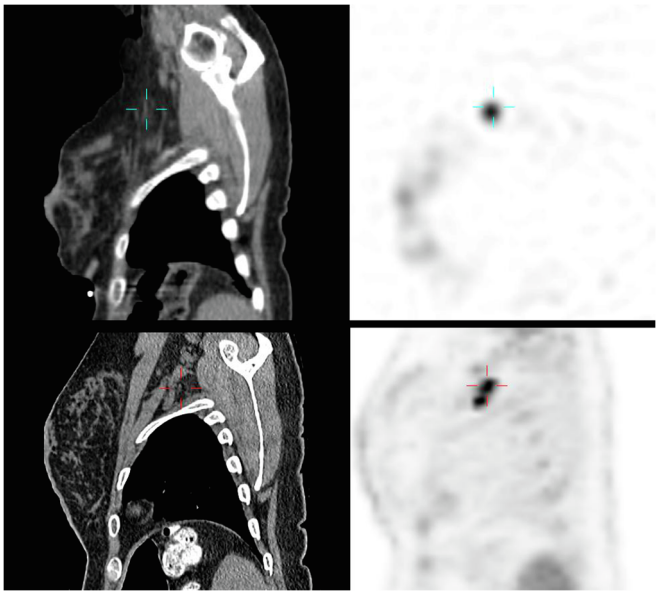

Fig. 2b. ^{99m}Tc-Nanotop SPECT/CT (top) and FDG PET/CT (bottom) images of a patient with non-concordant positive lymph nodes visualized in the left axilla. b-sagittal.

4. Discussion

In patients with breast cancer presenting with regional node involvement, accurate assessment of axillary node involvement after neoadjuvant treatment is of major clinical relevance. The post neoadjuvant status of the axilla is important for decisions regarding the need for regional radiation and further systemic treatment. Pathological complete response ranges between 35 and 68% [5]. Surveys of surgeons in the United States and the Netherlands report a wide variation in the management of the axilla in this setting [6,7].

Sentinel node biopsy has been shown to be accurate after neoadjuvant treatment in patients that are clinically node negative at presentation [8,9]. In node positive patients at presentation, sentinel node biopsy after neoadjuvant treatment is technically challenging [1,2,10,11], with identification rates of the sentinel node ranging between 80 and 93% [1,2,10]. No association was found between patient factors, tumor factors, response to treatment and rate of sentinel node identification [12]. In these trials, the false negative rate was higher than 10%. However, false negative rates were reduced when dual tracer was used and at least three sentinel nodes were removed [1,2]. There may be several explanations for the decreased sentinel node identification and/or increased false-negative rates after neoadjuvant treatment. These include fibrosis (due to response), blockage of the lymphatic channels by viable tumor (because of partial or no response), or non-uniform response of the tumor to treatment [13].

Several methods to mark a pathologically proven lymph node have been reported including clipping the node, use of radioactive iodine seeds (MARI), and charcoal injection [14,15]. Excision of the marked node after neoadjuvant treatment has been criticized for adding complexity and inconvenience to the procedure, especially if the clipped node needs to be localized by a needle prior to surgery [5]. Another concern is the reported false negative rate of 7% and negative predictive value of 83% [16]. Studies combining removal of the marked node and the sentinel nodes (targeted axillary dissection) report improved false negative and negative predictive rates [17–22].

In the current study, we compared the location of the hot nodes on PET/CT at diagnosis with the location of the sentinel nodes visualized on SPECT/CT post neoadjuvant treatment in order to examine the rate of concordance and identify predictors of non-concordance. Similar to other reports, a sentinel node was identified at surgery in 91% of the patients and a median of 3 sentinel nodes were removed. We found no association between patient, tumor and treatment characteristics and the likelihood of concordance between the location of the hot nodes on baseline PET/CT and the post treatment sentinel nodes. In only 71% of the cases, at least one of the hot nodes on the baseline PET/CT was found to be a sentinel node after neoadjuvant therapy. The finding that in more than a quarter of the cohort the sentinel node was not one of the hot nodes on PET is similar to reports on non-concordance between the pathologically proven marked node and the sentinel node, ranging between 9 and 24% of the cases [5], underlining the need to remove marked nodes together with the sentinel nodes in order to accurately stage the post-neoadjuvant axilla in this group of patients.

In two patients with non-concordant sentinel nodes with the original hot nodes, the sentinel nodes were found to be falsely negative. Additionally in one patient with concordant PET/CT and sentinel nodes, the sentinel nodes were negative whereas a biopsy proven intramammary node was still involved with cancer.

The study is limited by its retrospective design. Not all patients were treated at our center, and data were not available for all patients. The study group is heterogeneous with different tumor and treatment characteristics and a wide range of tumor load in the regional nodes. Concordance between FDG-avid lymph nodes and the sentinel nodes was based on comparing the location of the nodes in the two studies using the surrounding anatomy. As the studies were done at different times and using different modalities the accuracy of this method in some cases is limited. Criteria for axillary dissection were not uniform. The study group is small possibly limiting the power to detect association between different characteristics with concordance of the sentinel node with PET/CT hot nodes. However, to the best of our knowledge this is the first paper comparing PET/CT and SPECT/CT lymphoscintigraphy in post neoadjuvant patients.

In conclusion, comparison of SPECT/CT lymphoscintigraphy images post neoadjuvant therapy and nodal disease suggested on baseline PET/CT may assist in identifying patients in whom the sentinel nodes are not the known involved nodes found at presentation. The high rate of non-concordance between hot nodes at diagnosis and sentinel nodes identified after neoadjuvant therapy, underline the importance of marking pathologically-proven nodes prior to neoadjuvant treatment and removing them together with the sentinel nodes. In cases where the sentinel node does not appear to overlap with the baseline hot nodes, and no marking was performed prior to treatment, axillary dissection should be completed.

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