The Feasibility of Sentinel Lymph Node Biopsy Omission After Integrate ^{18}F -FDG Dedicated Lymph Node PET in Early Breast Cancer: A Prospective Phase II Trial

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Abstract

Purpose

Sentinel lymph node biopsy (SLNB) is currently the standard of care in clinically node-negative (cN0) breast cancer. The present study aimed to evaluate the negative predictive value (NPV) of ^{18}F -FDG dedicated lymph node positron emission tomography (LymphPET) in cN0 patients.

Methods

This is a prospective phase II trial divided into two stages (NCT04072653). In the first stage, cN0 patients underwent axillary LymphPET, followed by SLNB. In the second stage, SLNB was omitted in patients with a negative preoperative axillary assessment after integrating LymphPET. Here, we report the results of the first stage; the primary outcome was the NPV of LymphPET to detect macrometastases of lymph nodes.

Results

189 invasive breast cancer patients underwent LymphPET, followed by surgery, with definitive pathological reports. Forty patients had lymph node macrometastasis (LN-macro), and 16 patients had only lymph node micrometastasis (LN-micro). Of the 131 patients who had a negative LymphPET, 16 patients had LN-macro, the NPV was 87.8%. After combining axillary imaging evaluation with ultrasound and LymphPET, 100 patients were found to be both LymphPET and ultrasound negative, 9 patients had LN-macro, the NPV was 91%.

Conclusions

LymphPET can be used to screen potential patients to avoid SLNB with an NPV >90%. The second stage of the SOAPET trial is ongoing to confirm the safe omission of SLNB according to preoperational axillary evaluation when integrating LymphPET.

Introduction

Sentinel lymph node biopsy (SLNB) has replaced axillary dissection (AD) as the standard surgical procedure due to similar diagnostic accuracy and prognosis, and reduced surgical morbidity [1–3]. However, surgical morbidities still exist in patients with SLNB, with one-quarter occurring in the early postoperative period [4], and 4% occurring in the late period [5]. A recent review of seven trials involving 9426 participants found that the surgical complications of SLNB resulted in 4.8% cases of lymphedema, 4% of subjective arm movement impairment, 34% of paresthesia, 8.6% of pain, and 18.5% of numbness [6].

Due to the increased prevalence of screening mammography, early diagnose rate of breast cancer is increased [7], and about two-thirds of clinical node negative (cN0) patients were pathology node-negative after SLNB [3]. Therefore, it is of considerable interest to investigate the omission of SLNB in cN0 patients to avoid physical and emotional distress further. So far, the accuracy of physical examination combined with ultrasound, magnetic resonance imaging (MRI), and even ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) for preoperative axillary evaluation are not satisfactory (negative predictive value [NPV]<85%) [8, 9]. How to increase the NPV of axillary assessments to >90% in preoperative nodal staging is a key unmet need for clinicians when determining to omit SLNB.

Based on our previous study, a novel high-resolution dedicated axillary lymph node Positron Emission Tomography (LymphPET) could be used to identify and recognize more indolent axillary lymph nodes of the breast cancer because of more sensitivity and much higher negative predictive value, with NPV reached 90% [10]. Hence, we launched a prospective phase II study to investigate the NPV of LymphPET and to verify whether SLNB can be omitted in cN0 patients (SOAPET, NCT04072653).

Patients And Methods

Study design and patients

SOAPET (Sentinel node biopsy vs. Observation After axillary PET) is a prospective, open-label, phase II clinical trial conducted at Fudan University Shanghai Cancer Center and was divided into two stages. The study protocol is available in the DataSupplement (online only). In the first stage, cN0 patients were detected by clinical examination and underwent axillary imaging evaluation and LymphPET, followed by axillary surgery (SLNB or AD). In the second stage, SLNB was omitted for patients with the negative preoperative axillary assessment after integrating LymphPET. Here, we report the results of the first stage.

The eligibility criteria were: females ≥ 18 years old with newly diagnosed, histologically confirmed unilateral invasive breast cancer, with a negative axillary physical examination. The key exclusion criteria were: the presence of distant metastases; previous neoadjuvant therapy; previous axillary biopsy or axillary surgery 7 days before LymphPET; current pregnancy or lactating; and diabetes mellitus without bloodglucose management.

The study protocol was approved by independent ethics committees at Fudan University Shanghai Cancer Centre, and the study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before study participation.

Procedures

Patients with a negative axillary physical examination underwent routine breast and axillary imaging evaluation, and core needle biopsy in breast lesion to diagnose invasive carcinoma.

LymphPET system and examination

The LymphPET (PEMTECHTM, Shanghai, China) device contains movable double-planar confronted detectors with an axillary view and an adjustable distance between the two detector plates from 8 to 37 cm. The size of the sensitive detection area is 208×208 mm.

Patients were fasted at least 6 h prior to receiving a standardized injection of 4mCi 18F-FDG (injection in the contralateral arm to the breast lesion). Blood glucose levels were required to be lower than 10 mmol/L. After a resting period of 60 min to allow tracer distribution, LymphPET was performed and the acquisition duration was 3 minutes each region and both bilateral axillary regions were detected one by one. After acquisition, the images are reconstructed with a 3D standard maximum likelihood expectation maximization (MLEM 3D) algorithm, and be were checked immediately.

LymphPET image analysis

According to our previous study, LUV (LymphPET Uptake Value) has been used as a surrogate for SUV. The maximum single-voxel standardized LUV (maxLUV) was performed using commercial Medical Image Merge (version 6.5.4; MI M Software Inc, OH, USA), and two experienced nuclear medicine physicians were blinded to all study-related information (except breast cancer laterality) and analyzed the images separately. The maxLUV lymph node cut-off value was set at 0.27.¹⁰ ALNs were considered positive under the following three conditions: (1) the positive focus was located in the axillary region but not in skin, muscle, or bone; (2) 18F-FDG uptake was higher than the reference background (fat tissue); and (3) the physiological lymphatic uptake was excluded, such as symmetrically bilateral positive focus, like two funicular ropes.

Surgical procedure and pathological evaluation of lymph nodes

SLNB was performed in cN0 patients. Patients with ultrasound-detected lymph nodes would undergo ultrasound-guided fine-needle aspiration (FNA), if FNA was negative, SLNB was routinely performed.

The SLN was identified with blue dye and/or radio colloid. SLNs were defined as any blue-stained node, any node with blue-stained lymphatic channel directly leading to it, any node with radioactive counts $\geq 10\%$, or any pathologically palpable nodes. Touch imprint cytology was routinely applied on every SLN harvested. Also, slices were fixed formalin and paraffin-embedded for further evaluation. Serial sectioning with the HE staining was performed. The pathological results were classified as macrometastasis (>2 mm), micrometastasis (0.2–2.0 mm), and isolate tumor cells (<0.2 mm), according to the TMN staging system.

For patients with no more than two lymph node macrometastases (LN-macro), the decision to perform further axillary dissection was dependent on the operative type (breast-conserving therapy or mastectomy) and individual pathological characteristics.

Outcomes

LymphPET accuracy was evaluated by comparing results separately with the final histology. The results were classified as true positive (TP), true negative (TN), false positive (FP), and false-negative (FN). The evaluation of the results was on the calculation of sensitivity ($TP/[TP+FN]$), specificity ($TN/[TN+FP]$), and NPV ($TN/[TN+FN]$). The primary outcome was the NPV of LymphPET to detect macrometastases of lymph nodes, defined as the proportion of non-macrometastases lymph nodes in patients with negative LymphPET results.

Statistical analysis

As we expected, the NPV for LymphPET to be 87.5%, with a two-sided type I error of 2.5% and a power of 80%, 196 patients were needed for the present study. Assuming that 3% of patients would be lost to follow up, a total of 202 patients were needed in the first stage. For categorical variables, χ^2 -test calculated the difference or Fisher's exact test when necessary. Statistical analysis was performed with IBM SPSS version 20.0 software, and statistical significance was defined as two-sided $P \leq .05$.

Results

Patients

From September 9, 2019, to May 30, 2020, 224 patients were screened, and 189 patients with invasive breast cancer (180 invasive ductal carcinoma and 9 invasive lobular carcinomas) underwent LymphPET, followed by surgery, with definitive pathological reports. (Figure 1) The median age was 50 years, 36% underwent breast-conserving surgery. 53% o had T1-stage disease, 64% had grade I and II, and 58.7% had a ki67 $<30\%$. 63% were luminal type, 26% were HER2 positive, and 10% were triple negative. 40 patients had at least one LN-macro, and 16 only had lymph node micrometastasis (LN-micro). (Table 1)

Table 1
Patient demographics and clinical characteristics

Characteristics	n (%)
Age (years)	49.9 (28–75)
<50	97 (51.3)
≥50	92 (48.7)
Operation type	
Breast-conserving surgery	68 (36)
Mastectomy	121 (64)
Axillary evaluation	
SLNB	133 (70.4)
SLNB, then AD	40 (21.2)
AD	16 (8.4)
Node stage	
N0	133 (70.3)
N1mic	16 (8.5)
N1	32 (17)
N2	7 (3.7)
N3	1 (0.5)
T stage	
T1a	19 (10.1)
T1b	11 (5.8)
T1c	64 (33.9)
T2	89 (47.1)
Unknown	6 (3.1)
Histology	
IDC	180 (95.2)
ILC	9 (4.8)
Grade	
I	25 (13.2)
II	96 (50.8)
III	68 (36)
Subtype	
HR-positive & HER2 negative	120 (63.5)
HR-positive & HER2 positive	23 (12.2)
HR negative & HER2 positive	27 (14.3)
HR negative & HER2 negative	19 (10)
Ki67 ≥30%+	78 (41.3)
LVI positive	61 (32.3)
AD, axillary dissection; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; SLNB, sentinel lymph node biopsy.	

Efficacy Outcomes

According to the ultrasound reports, 124 patients had no lymph nodes detected (US-neg), 46 had lymph nodes detected (US-det), and 16 had suspected metastatic lymph nodes detected. Of the patients who had US-neg, 17 had LN-macro, and 12 had LN-micro. The NPV for US-neg was 86.3%. According to the

LymphPET reports, 131 patients were LymphPET negative (maxLUV<0.27). Of these patients, 16 had LN-macro, and 11 had LN-micro. The NPV of LymphPET was 87.8%. In 58 patients who LymphPET positive (maxLUV>0.27), 24 had LN-macro, and five had LN-micro. When combined clinical axillary evaluation with ultrasound and LymphPET, 100 patients were found to be both LymphPET and ultrasound negative. Of these patients, nine had LN-macro, the NPV was 91% (Table 2).

Table 2 Diagnostic performance of LymphPET and ultrasound in axillary staging							
Axillary imaging assessment	n	Macrometastases	Micrometastases	non-metastases	Sensitivity	Specificity	NPV
Ultrasound‡		40	16				
US-neg	124	17	12	95	57.5	71.8	86.3
US-det	46	14	4	28			
US-met	19	9	0	10			
LymphPET†							
Negative	131	16	11	104	60	77.2	87.8
Positive	58	24	5	29			
Combination*							
Negative	100	9	9	82	77.5	61.1	91
Positive	89	31	7	51			
‡ US-neg, no lymph nodes detected by ultrasound; US-met, suspected metastatic lymph nodes detected by ultrasound; US-det, lymph nodes detected by ultrasound.							
† maxLUV of LymphPET was set at 0.27 (negative <0.27, positive ≥0.27).							
* Negative, no lymph nodes detected by ultrasound and maxLUV in LymphPET <0.27; positive, lymph nodes detected by ultrasound and/or maxLUV in LymphPET ≥0.27.							
Sensitivity, specificity, and NVP were calculated according to lymph node macrometastases.							

The clinical characteristics of the nine patients with FN evaluation by ultrasound and LymphPET are listed in Table 3; seven patients had N1 disease, and two had N2 disease, one had invasive lobular carcinoma, and six had a lymphovascular invasion. Three patients were luminal A (patient ID: 83, 116, 129), three were luminal B (ID: 117, 128, 144), two were HER2 positive (ID: 57, 76), and one was triple-negative (ID: 147).

Table 3. Clinical characteristics of patients with a false-negative axillary node evaluation by LymphPET and ultrasound

Patient ID	Age (years)	Side	Operation	MG	Location	Size cm	Histology	Grade	LV	ER	PR	HER2	Ki67	SLN no.	No. lymph node macrometastases
57	44	Right	M	Mass	Center	1.5	IDC	III	+	80	60	+	15	4	1
76	67	Right	BCS	MC	Outer upper	3.7	IDC	II	–	80	10	+	20	3	1
83	41	Right	M	MC	Outer upper	1.5	IDC	II	+	80	80	–	15	5	2
116	67	Right	M	MC	Outer upper	2.8	IDC	II	+	80	80	–	10	6	3
117	41	Right	BCS	Mass	Outer upper	3	IDC	II	+	80	80	–	30	3	2
128	69	Right	M	Mass	Inner upper	2	ILC	II	–	80	20	–	30	3	2
129	47	Left	M	Mass	Outer	2.2	IDC	II	+	80	80	–	10	4	2
144	57	Left	M	Mass	Outer lower	3.5	IDC	II	+	80	80	–	30	3	1
147	61	Right	M	Mass	Outer upper	1.2	IDC	II	–	0	0	–	80	4	1

AD, axillary dissection; BCS, breast-conserving surgery; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LV, lymphovascular invasion; M, mastectomy; MC, mass with calcification; MG, mammography.

Efficacy Outcomes

After a median follow-up 14 months, no side-effects related to LymphPET scan were reported.

Discussion

The SOAPET study is the first prospective trial to investigate the accuracy of LymphPET in evaluating axillary status in cN0 patients detected by clinical examination. Its primary endpoint of an NPV of 87.8% for LymphPET was met. According to our results, in patients with a negative axillary physical examination, approximately 21% will have LN-macro after SLNB, even when combined with preoperative ultrasound, 13.7% of patients with no lymph nodes detected by preoperative ultrasound, still had LN-macro. Importantly, after combining ultrasound and LymphPET, we were able to screen potential patients who may avoid axillary evaluation with an NPV >90%.

Currently, in primary cN0 breast cancer, SLNB is the gold standard for regional axillary staging, with better physical function of the upper limb when compared with AD; however, it can also lead to specific axillary morbidity in both the early and late postoperative periods. In patients treated with SLNB alone, the rate of wound infections, axillary seromas, and paresthesia was 25% in Z0011 [11], and long-term postsurgical complications were recorded as 4% lymphoedema, 13% sensory neuropathy, and 13% motor neuropathy in IBCSG 23-01 [12]. Higher rates of lymphedema and an arm circumference increase of >10% were recorded after SLNB followed by axillary radiotherapy in AMAROS [13]. Therefore, screening cN0 patients to avoid surgical evaluation is an essential focus of current research. Several ongoing prospective randomized trials, such as SOUND trial and BOOG 2013-08 trial, are comparing SLNB with observation in cN0 patients treated with breast-conserving therapy [4, 14]. The key technical indicators for such trials are the NPV of preoperative assessment, as a higher number of FN means LN-macro remain in the axillary, which may lead to a higher local failure rate.

Initial data of the SOUND trial showed that 13.4% of patients in the SLNB group had LN-macro [15], the NPV of preoperative axillary assessment by physical examination and ultrasound was approximately 87%. It is still unclear whether 13% of FN with no lymph node surgical evaluation will influence outcomes. Our study had a similar finding, among patients with a negative axillary physical examination and no lymph nodes detected by preoperative ultrasound, 13.7% still had LN-macro. Therefore, it is essential to determine the omission of SLNB with increasing the NPV of preoperative axillary assessment.

Several studies have investigated axillary ultrasound in patients with early breast cancer. Retrospective data of 577 axillary ultrasounds demonstrated that a negative axillary ultrasound generally excludes the presence of pN2–3 disease, whereas ultrasound cannot accurately differentiate between pN1 and pN2-3 disease [16]. FN is relatively high, as in 118 patients with no node detected by ultrasound, 21% were ultimately found to be node-positive [17]; although these FN results did not significantly impact adjuvant medical decision-making, as patients with FN had recurrence-free survival equivalent to patients with pathological N0 disease [18].

Other studies have further evaluated whether metabolic imaging technology may increase accuracy in evaluating axillary status in early breast cancer. In 349 T1 patients who were preoperatively examined using ultrasound, MRI, and ¹⁸F-FDG PET/CT, the NPV was around 81.7–82.6%, suggesting that there are no definitive modalities for detecting node metastasis in T1 breast cancer to replace SLNB [8]. After combining ¹⁸F-FDG PET/CT and ultrasound, in 138 ultrasound-negative and ¹⁸F-FDG uptake-negative patients, 15% were found to have lymph node involvement [9]. Therefore, even with high specificity, ¹⁸F-FDG PET/CT demonstrated poor sensitivity in the detection of axillary metastases [19].

A possible explanation for this is that, currently, the whole-body ¹⁸F-FDG PET/CT system typically yields reconstructed images with a resolution of 5–15mm, depending on the injected dose, imaging time, post-reconstruction filtering, and intrinsic resolution of the scanner. This reduces the system's ability to detect small lesions (<1 cm) and/or lesions with low tracer uptake [20]. According to our previous study, the spatial resolution of LymphPET is much higher than whole-body PET/CT, with 88% sensitivity and 79% specificity [10].

In the current study, we found that the diagnostic accuracy of LymphPET was nearly equal to ultrasound. The sensitivity, specificity, and NPV for LymphPET were 60%, 77.2%, and 87.8%, respectively, and those for US-neg were 57.5%, 71.8%, and 86.3%. When combined LymphPET in the preoperative assessment, in the physical exam-negative and ultrasound-negative patients, we were able to further screen 80% of patients (100/124) with a 91% NPV for axillary lymph node macrometastases, and providing technical support for future studies looking at the omission of axillary evaluation.

Usually, FN rate of 10% for SLNB is acceptable. In Z0011, patients who underwent AD had 27% non-SLN positive, assuming patients with SLNB only still had around 30% with positive node remain in axillary, with the additional local treatment of radiotherapy, the local regional recurrence is less than 1% [11]. Similarly, in the AD group in AMAROS, 33% of patients had additional positive nodes; 5-year axillary lymph node recurrence was found to be 1.19% in SLNB group after axillary radiotherapy [13]. Therefore, we believe that LymphPET could be a reliable preoperative evaluation method, and axillary surgical evaluation can be omitted if both ultrasound and LymphPET are negative.

Limitations

Our study has several limitations. Firstly, isolated tumor cells (<0.2mm) and micrometastases (0.2–2 mm) were not calculated in the analysis. Currently, such small metastases are hard to detect by any imaging technique. Patients with micrometastatic tumor deposits, pN0(i+) or pN1mi, do not appear to have a worse 8-year disease-free survival or overall survival compared with SLN-negative patients [21]. Whether treatment recommendations for systemic therapy should consider the presence of a single micrometastatic lymph node identified during complete serial sectioning of sentinel node(s) is still controversial [22]. Axillary radiotherapy might reduce axillary lymph node recurrence, especially in patients following breast-conserving therapy with no axillary surgical intervention [23]. Secondly, in patients with FN detected by ultrasound and LymphPET, adjuvant systemic therapy may be inadequate without knowing the definitive node status. In our study, three patients who were HER2 positive and/or triple-negative would receive system adjuvant therapy in any case. For 5 patients with Luminal type N1 diseases, genomic signatures now represent an important progress in optimal selection of high risk patients that might benefit from the addition of chemotherapy to adjuvant endocrine therapy [24, 25]. One patient with invasive lobular carcinoma N2 disease (ID 128) might receive inadequate adjuvant treatment if the axillary node status is unknown. Due to these limitations, in the second stage of the SOAPET, we will select patients

ready for breast-conserving therapy who are both ultrasound and LymphPET negative, and genomic signatures will be recommended to patients with Luminal type, to assess the safety of omitting surgical axillary evaluation in such population.

In conclusion, the results of our study indicate that LymphPET can be used to identify cN0 patients, reducing the FN rate by <10%. The second stage of the SOAPET trial is ongoing to confirm the safety of omitting SLNB according to preoperational axillary evaluation when integrating LymphPET.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose

Authors contribution

Junjie Li: Conceptualization, Data curation, Methodology, Analysis, Investigation, Writing – original draft, Writing – review & editing;

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Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Fudan University Shanghai Cancer Centre (Aug 2019)

Consent to participate

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

Consent to publish: NA

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Figures

Figure 1

CONSORT diagram of patient disposition. *cN+: patients with a positive axillary physical examination