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Sentinel node biopsy after primary systemic therapy in node positive breast cancer patients: Time trend, imaging staging power and nodal downstaging according to molecular subtype

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ABSTRACT

Background: The management of axilla after Primary Systemic Therapy (PST) for breast cancer is a highly debated field. Despite the proven axillary downstaging occurring after PST, there is still some degree of reluctance in applying sentinel node biopsy (SNB) in the neoadjuvant setting.

Patients and methods: We performed a retrospective analysis on 181 PST patients with axillary positive nodes at presentation treated between 2005 and 2017 at San Raffaele Hospital in Milan. The aim was to observe the application time trend of SNB, to determine the imaging staging power and the axillary downstaging according to molecular subtypes.

Results: Median follow-up after surgery was 32.5(IQR: 12–59) months. After PST, 119 (65.7%) patients had no clinically palpable nodes, 72 (39.7%) converted to N0 on final imaging and 34 (18.8%) underwent SNB with an increasing application trend. Axillary-US showed the highest accuracy (69.3%) in re-staging axilla after PST. Staging power of preoperative testing varied with tumour biology: Positive Predictive Value was higher in Luminal A (80% for clinical examination and 100% for axillary-US) and Luminal B (72% and 70.5%) tumours, whilst Negative Predictive Value was higher in HER2 positive (100% and 93.3%), and triple negative (71.4% and 93.3%) tumours. Ninety five (52.5%) patients experienced axillary downstaging after PST, by molecular subtype 15% (3/20) in Luminal A, 46.4% (45/97) in Luminal B, 90.9% (20/22) in HER2+ and 70.3% (26/37) in triple negative breast tumours.

Conclusion: SNB application after PST for breast cancer in node positive patients at presentation is increasing. Pre-operative axillary imaging and tumour biology help identify patients who might be candidates for SNB as a single staging procedure.

Introduction

The Primary Systemic Therapy (PST) has become a common strategy in the multimodal treatment of breast cancer in order to facilitate breast conservation, to assess *in vivo* response and potentially downstage axillary disease [1,2]. Just as breast disease downstaging translates into an increased breast conservation rate, axillary downstaging in patients with clinically positive nodes, may similarly translate into higher "axillary node conservation" rate [2,3].

It has been widely demonstrated that PST downstages involved axillary lymph nodes in a considerable proportion of patients

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[4–6], although the accuracy and timing of SNB in this setting remains a point of concern due to early studies reporting identification rates ranging from 63 to 100% as well as false negative rates of 0–33% [7–10]. However, the 2017 National Comprehensive Cancer Network (NCCN) guidelines have recommended SNB for most breast cancers, even after PST [11,12].

Currently, the nodal status at diagnosis remains crucial to guide the axillary treatment. For patients presenting with clinically node-negative disease at diagnosis, SNB before or after PST is the standard of care; the greatest controversy concerns SNB after PST in women with positive axillary lymph nodes at diagnosis, who can potentially be spared from the morbidity of axillary dissection (AD) as is the case for primary surgery [13]. The NCCN guidelines state that when axillary lymph nodes are positive at diagnosis, the axilla may be re-staged after PST and AD should be performed if the axilla is still clinically positive, whilst either SNB or AD can be performed if the axilla becomes clinically negative.

We carried out a retrospective analysis of all consecutive breast cancer patients who underwent PST at the San Raffaele Research and University Hospital in Milan in the last thirteen years, focusing on the application trend of SNB, staging power of standard imaging tools and axillary response to PST in patients being node positive at diagnosis.

Patients and methods

All patients having node positive breast cancer who underwent surgery following PST at the San Raffaele University and Research Hospital in Milan between January 2005 and December 2017 were included in this study. The inclusion criteria were: histologically proven invasive breast cancer with a clinical stage of T1-4, node positive axilla and chemotherapy as primary treatment. Exclusion criteria were node negativity and/or distant metastases at diagnosis, incomplete medical data (<50% of data required), inflammatory breast cancer, previous breast cancer, previous surgery on indexed axilla.

Initial work-up

Both a surgical oncologist and a medical oncologist evaluated all patients who were candidate to PST at diagnosis. Prior to be examinated, all underwent mammography, breast and axillary ultrasound (US), together with breast core needle biopsy. Systemic staging was performed with thoracic X-ray and abdominal ultrasound or 18-FDG PET or total body-CT associated to bone scan.

Oncological treatment

Once the indication for PST was confirmed, the medical oncologist chose the most appropriate regimen according to patient and tumour characteristics. The selected regimens generally included anthracyclines and taxanes, unless clinical trials were available. Anti-HER-2 agents were associated whenever indicated. At the end of chemotherapy a local and eventually systemic re-staging was performed through clinical surgical evaluation, mammography, breast and axillary US and eventual breast contrast-enhanced MRI or 18-FDG PET.

Surgical treatment

The type of breast surgery was decided according to the residual tumour to breast ratio. When breast conservation was not feasible, nipple-sparing mastectomy with immediate reconstruction was performed provided that the tumour did not involve the nipple-areola complex at diagnosis or intraoperative examination of retro-areolar ducts was negative. Axillary surgery was generally AD due to the initial N+ status, however more recently SNB was offered to selected N+ patients having a major or complete response on clinical examination and imaging. ^{99}Tc-labeled colloid was injected sub-dermally close to the areola; then lymphoscintigraphy was performed to ascertain the presence, the location and the numbers of SNs draining the breast. Surgery was performed the next day or, occasionally, on the same day. The sentinel lymph node was detected intraoperatively by using a wireless gamma probe to identify the axillary hotspot and guide its surgical removal. The identified sentinel lymph nodes were removed and, when possible, examined intraoperatively. AD was completed when positive sentinel node was found.

Adjuvant treatment and follow-up

Each clinical case was discussed in a multidisciplinary meeting in order to decide the most appropriate adjuvant treatment. Adjuvant treatments were administered according to the NCCN guidelines. Follow-up visits were performed every six months for five years and then yearly. Patients who were not followed-up in our hospital were contacted by phone and asked about their health status and clinical exams. Physical examination was recommended every six months, mammography, breast and axilla US was recommended yearly for a period related to the age at diagnosis whilst chest X-ray, abdominal US and bone scan were requested yearly for five years.

Study design

Data were retrospectively collected from a prospectively maintained database of electronic medical records. Breast cancer molecular subtypes were defined according to the immunohistochemical classification by the 2013 St. Gallen Expert Panel [14]. In patients having a bilateral breast cancer, for the purpose of the study, we reported the data on the two breasts separately. All patients with overt palpable pathological nodes on clinical examination, cortical thickness and absence of fatty hilum on axillary US or eventual positive biopsy (58 patients had positive citology, 24 micro-histology) or positive nodes on 18-FDG PET were considered node positive and included in the study [15]. A population of 326 patients underwent PST and then surgery during the study period. A total of 57 patients had a N0 disease at diagnosis and 88 patients fulfilled other exclusion criteria and were not included in the analysis. A total of 181 (55.5%) patients with positive nodes at baseline represented the study population. At diagnosis 74.7% (n = 135) of these patients had clinically overt nodal involvement, the remaining percentage had at least two positive axillary testing results among US, fine needle citology or core biopsy, MRI or PET.

The time trend of axillary surgery was analysed according to the axillary status at diagnosis and after PST. Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity, specificity and accuracy of preoperative clinical examination, axillary US, contrast-enhanced breast MRI, 18-FDG PET and percentage of axillary downstaging according to molecular subtype were calculated. Additionally, axillary and breast cancer recurrence were reported.

Statistical analysis

Categorical variables were described as number and percentage, mean and standard deviation were calculated for normally distributed continuous variables, median and interquartile range (IQR) for other continuous variables.

Results

The median age of the whole population was 49 (IQR: 42–56) years. Table 1 shows patient and tumour characteristics. The median follow-up after surgery was 32.5 (IQR: 12–59) months (mean 38.7 ± 31.6 months). Tables 2 and 3 show the tumour response to PST and the type of surgery performed on breast and axilla.

After PST 64.7% (n = 117) of patients had no clinically palpable nodes, 39.7% (n = 72) patients converted to cN0 on final imaging (all axillary exams were negative), however only 34 (18.8%) patients underwent SNB, the median number of removed sentinel nodes was 3 (IQR: 2–4). Of these, two (5.9%) patients had ITCs or micrometastasis in the sentinel node and no further surgery was performed. Seven (20.6%) patients had macrometastases and underwent AD, four of these having one positive node only. The tumour response to PST was complete (both breast and axilla) in 51 (28.2%) patients, single breast and axillary pathological response are reported in Table 3.

Fig. 1 shows the increasing application of SNB in node positive PST patients who become clinically/imaging node negative before surgery, particularly in the last three years. The percentage of patients treated with SNB increased from 16.7% in 2015 to 46.5% in 2017. Completion AD was necessary in 11.1% (1 out of 9) and 25% (5 out of 20) of cases in the last two years.

Table 4 shows the outcomes of clinical evaluation, axillary US, breast MRI and 18-FDG PET after PST. PPV and NPV are most easily understood in clinical practice as they indicate the chance of a correctly positive or negative answer respectively, and so they were also calculated according to tumour biology, as shown in Table 5. There was a notable variation in NPV and PPV according to phenotype, which is most evident for US only. The PPV being highest in luminal breast cancer and NPV highest in HER2 positive and triple negative breast cancer. Test accuracy was more homogenously distributed in all phenotypes.

Table 1
Patients' characteristics at diagnosis.

	Study population (n = 181)
	n (%)
Age (years)	
<35	13 (7.2)
35–49	85 (47.0)
50–69	69 (38.1)
>70	15 (8.3)
Side	
Left	99 (54.7)
Right	82 (45.3)
Histologic type	
Ductal	170 (93.9)
Lobular	8 (4.4)
Other	3 (1.7)
Molecular subtype	
Luminal A	20 (11.0)
Luminal B	97 (53.6)
HER-2	22 (12.2)
Triple-negative	38 (21.0)
Unknown	5 (2.8)
Grade	
G1	1 (0.6)
G2	36 (19.9)
G3	82 (45.3)
Unknown	65 (35.9)
Focality	
Unifocal	137 (75.7)
Multifocal	33 (18.2)
Multicentric	8 (4.4)
Unknown	3 (1.7)

Table 2
Clinical and radiological outcomes.

	Pre-PST Staging (n = 181)	Post-PST Staging (n = 181)
	n (%)	n (%)
Clinically palpable nodes		
Yes	135 (74.7)	58 (32.0)
No	33 (18.3)	117 (64.7)
Unknown	13 (7.0)	6 (3.3)
Positive Axillary nodes on US		
Yes	155 (85.6)	79 (43.7)
No	15 (8.3)	84 (46.4)
Unknown data	12 (7.1)	18 (9.9)
Positive Axillary nodes on MRI		
Yes	91 (50.3)	43 (23.8)
No	12 (6.6)	56 (30.9)
Unknown data	78 (43.1)	82 (45.3)
Positive Axillary nodes on PET		
Yes	99 (54.7)	17 (9.4)
No	6 (3.3)	33 (8.2)
Unknown data	76 (42.0)	131 (72.4)

Table 3
Type of surgery and final pathology.

	Study population (n = 181)
	n (%)
Breast surgery	
BCS	100 (55.2)
Mastectomy	81 (44.8)
Axillary surgery	
SNB	34 (18.8)
AD	147 (81.2)
Breast pathology	
ypT0(excluding DCIS)	43 (23.8)
ypT0(includingDCIS)	16 (8.8)
ypT1-3	122 (67.4)
Axillary pathology	
ypN0(excluding ICT, micrometers)	86 (47.5)
ypN1-3	86 (47.5)
ypN_{ITC}	4 (2.2)
ypN_{mic}	5 (2.8)
pCR for both breast and axilla	51 (28.2)

The percentage of pathological axillary downstaging after PST was 52.5% (n = 95 patients) across all patients. Stratification by phenotype revealed a downstaging of 15% (3/20) in Luminal A, 46.4% (45/97) in Luminal B, 90.9% (20/22) in HER2+ and 70.3% (26/37) in triple negative breast tumours.

Two patients were lost to follow-up. Two (1.1%) patients had an ipsilateral breast recurrence after a mean recurrence-free interval of 24.5 ± 9.2 months. Four (2.1%) patients had contralateral breast cancer, one (0.5%) patient had both ipsilateral and contralateral breast recurrence. No isolated axillary recurrence occurred, six patients (four treated with AD and two converted to cN0 and treated with SNB) developed both locoregional node and distant recurrence, four of these patients died.

Discussion

In the last few decades the surgical treatment of breast cancer has experienced a progressive de-escalation both for the breast and the axilla [16,17]. What is now well established as "minimum effective" for primary surgery however, remains challenging for surgery following PST [4,5,18–21]. In particular, the management of the axilla in this setting is still controversial.

At diagnosis axillary status acts as one of the main drivers in selecting the best candidates for PST. PST represents an effective

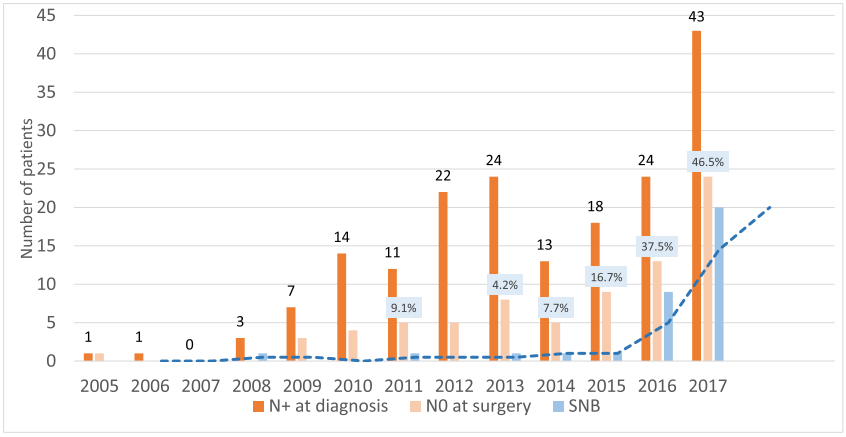

Fig. 1. Details on patient distribution per year (red columns), patients being N+ at diagnosis who converted to cN0 after PST (pink columns), SNB performed distributed per year (blue columns), percentage of N+ patients undergoing SNB (blue rectangles) and increasing mean of SNB performed (blue dotted line).

Table 4
Staging power of clinical evaluation, US, MRI and FDG-PET after PST.

	Clinical examination	Axillary US	Breast MRI	18-FDG PET	US + MRI + PET
PPV(%)	60.3	64.6	53.5	70.6	61.8
NPV(%)	59.8	73.8	73.2	48.5	70.9
Sensitivity (%)	42.7	69.9	41.8	41.4	71.6
Specificity (%)	75.3	68.9	67.2	76.2	60.9
Accuracy (%)	60.0	69.3	64.6	56.0	65.9

Table 5
Outcomes of clinical evaluation, US, MRI and FDG-PET in N+ cohort after PST according to molecular subtype.

	Clinical examination	Axillary US	Breast MRI	18-FDG PET
PPV(%)				
Luminal A	80.0	100.0	100.0	–
Luminal B	72.0	70.5	72.8	90.9
Her2-positive	40.0	16.7	–	100.0
Triple negative	31.0	41.2	23.1	20
NPV(%)				
Luminal A	11.1	42.9	16.7	20
Luminal B	54.4	66.0	71.4	50
Her2-positive	100	93.3	100.0	100.0
Triple negative	71.4	93.3	100.0	28.6
Accuracy(%)				
Luminal A (20)	47.4	76.5	50.0	20.0
Luminal B (99)	59.4	65.7	50.0	25.0
Her2-positive (22)	86.4	71.4	66.7	100
Triple negative (38)	59.5	65.7	50	25.0
Total (n)				
Luminal A (20)	19	17	10	5
Luminal B (97)	93	91	57	27
Her2-positive (22)	22	21	12	6
Triple negative (37)	37	32	20	12

opportunity to avoid AD and related morbidities (lymphedema, sensory changes, wound infection, arm dysfunction), in particular in patients with either triple-negative or HER-2 positive tumours [22,23]. The de-escalation of surgery should be based on tumour biology. The need for AD was reported to be lower in patients receiving PST than in primary surgery if they had triple-negative or HER-2 positive tumours, hence for these PST should be preferred [22]. In fact, even in our series the best responses, particularly in the axilla, were seen in Her-2 positive and triple negative tumours (90.9% and 70.3%, respectively). Hence, in the challenging situation of node positivity at diagnosis, the final decision for axillary surgery should be deferred until the post-PST axillary status is assessed. As shown in our population, despite 64.7% of axillae being negative on preoperative clinical examination and 46.4% on axillary US after PST, SNB was performed in 18.8% of patients, which is encouraging but certainly not enough considering that axillary pCR was 52.5%, which is very similar to the imaging CR on axillary US (negative preoperative axillary US: 46.4%, US accuracy: 69.3%).

The axillary status after PST plays a key role in the surgical choice between SNB and AD in place of initial axillary status. On one hand the idea of avoiding AD in previous cN + patients who converted to cN0 is supported by studies showing a downstaging in up to 74% of patients [4,6,24–26]. On the other hand the concern to leave residual disease in the axilla after SNB only, persists due to

several issues: 1) the doubtful accuracy of SNB after PST in previous positive axillae, 2) the lack of an objective imaging assessment of axillary status before surgery, and 3) the paucity of data on long-term outcomes in N+ patients who converted to N0 and were treated with SNB only.

Firstly, the new techniques and recommendations have dramatically reduced the false negative rate to less than 10%, as for primary axillary surgery [27–30]. Secondly, in our study PPV of clinical examination was 60.3% and for axillary US was 64.6%, while breast contrast-enhanced MRI and 18 FDG-PET had a PPV of 53.5% and 70.6%, respectively, when compared to final pathology. This data is partially consistent with the literature and suggests AD in non-responder patients that can be detected clinically or on imaging [31–33]. Nevertheless, the published data on axillary US following PST is heterogenous. Data from SENTINA trial and Z1071, showed lower sensitivity of both palpation and axillary US after PST when compared with retrospective single center cohorts, like ours [31,34–36]. Schwentner et al. have already explained these differences between small and large studies by the interobserver variability, the experience of the centers and the bias of results from other imaging tools [35]. However, the power of axillary US in guiding axillary surgery and reduce the false negative rate after PST is undoubted [36]. Data on PET and MRI are very limited to derive any meaningful conclusions, the well-known low sensitivity of both tests and the highest specificity of PET were confirmed (see Tables 4 and 5). Axillary US, being a non-invasive and less expensive method, is the most commonly used for axillary re-staging after PS. In fact, US shows the best accuracy as well as PPV and NPV among analysed diagnostic tools, even better than the combination of axillary US, MRI and PET. Our results, despite being limited by a small sample size, confirm previous data on the accuracy of axillary US according to tumour biology. Peppe et al. [37] reported that HER2 negative breast cancer patients have the highest PPVs, so if positive on axillary US they are more likely to be positive on final pathology, while HER2 positive tumours indeed, show the highest NPV and if their US testing is negative they are more likely to be truly negative. Nevertheless, in our data triple negative breast tumours behave more like HER2 positive disease, while Luminal A and B follow the trend described for HER2 tumours. In particular, axillary US seems to be very reliable in Luminal A and B tumours when positive (PPV: 100% and 70.5%), in HER2 and Triple negative tumours when negative (NPV: 93.3% for both). This data could be hypothesis-generating for larger studies on this topic, eventually supporting the surgical decision based on tumour biology. Kuhn et al. have recently reported on the relevance of a multiparametric nomogram in predicting the axillary status after PST, our data supports the strength of tumour biology and goes even further considering the staging power of imaging in the light of tumour biology [38]. Ideally the surgeon could be encouraged to directly proceed to AD in Luminal tumours when preoperative axillary US is positive and offer SNB in HER2 and triple negative tumours when negative.

Thirdly, these data beg the question: should we really chase single residual tumour cells in the axilla? Considering that ITC and micrometastases after PST are still an indication to completion of AD according to the NCCN guidelines, it is difficult to find any sign of such a low disease burden on imaging. In fact, even 18-FDG PET, showing the highest PPV, has a limited capacity of detecting small residual tumour deposits, probably due to the low metabolic activity of microscopic disease. What is the prognostic value of removing such a limited tumour burden? Mamtani et al. [30] reported that since 2013 at the Memorial Sloan Kettering Cancer Center AD is omitted in patients presenting with axillary nodal metastases who received PST and have no palpable nodes the end, physical examination is the single tool used to decide between SNB and AD (preoperative axillary US is not routinely performed). Their axillary pCR rate was 49%, which is very similar to the 50% of our N+ cohort. To date, data on long-term outcomes in such N+ patients who are managed with SNB alone are limited. A small single-institution experience of 79 cN0-2 patients who underwent PST, around 50% being N+ at diagnosis, and then SNB reported no axillary recurrence at a median follow-up of 62 months [39]. The Italian studies by Galimberti [40] and Martelli [41] supported the feasibility and accuracy of SNB after PST, regardless of axillary status at diagnosis. At a median follow-up of 61 months, axillary failure occurred in one (0.7%) cN1/2 patient who had already undergone completion AD for positive sentinel node [40], which is comparable with our data (0%). Martelli et al. [41] found no difference in survival between ypN0 patients treated with SNB + AD and those treated with SNB only. Furthermore, survival difference between the cN0 and cN1 (before PST) subgroups of the SNB group was not statistically significant [41].

Our experience with SNB after PST follows the trend reported in the literature. We never used dual-mapping and after a short phase of validation we started to use SNB after PST when major clinical response both on axilla and breast occurred. Our data collection starts from a time when the safety of SNB after PST was still highly debated even in cN0 patients, so it is not surprising that only 18.8% of patients underwent SNB. The application of SNB in the study population has grown from 2012 to 13 in parallel with axillary downstaging, thus suggesting a more selective and tailored use of PST in time. This is an encouraging trend, showing that something is changing and despite the lack of data on long-term outcomes, the concept of axillary surgery as a staging procedure only is being slowly imported from primary surgery to the PST setting too. Of course, the residual tumour means worse prognosis, but considering that a recent study by Van Nijnatten et al. [42] showed that prognosis of ITC and micrometastases after PST was more comparable to prognosis of ypN0 than that of ypN+, our approach to the management of the axilla should change further. Provided that no imaging tool is currently able to detect ITC or micrometastases in the axilla and considering that such amounts of residual disease do not affect outcomes, dedicated axillary imaging may ideally identify residual macrometastases, which are “prognosis-relevant”, rather than any extent of residual disease. We expect that, as for primary surgery [43], even after PST, local control does not rely on surgery alone, but surgery plus radiotherapy and eventual adjuvant systemic treatment (i.e. hormonal therapy or targeted therapy) will act together and be effective. Ongoing NSABP B51 and Alliance A11202 trials recruiting patients being node positive before PST will help determine which patients can benefit from regional node RT as well as from axillary RT only, rather than AD according to the axillary response.

Conclusion

Despite several limitations due to the retrospective nature, population size, short follow-up and single institution data, our study suggests that SNB application in the neoadjuvant setting is increasing and may have a promising role as a single axillary staging procedure in node positive patients who become node negative on imaging after PST. The biology of the tumour predicts the downstaging rate in the nodes and the performance of the imaging procedures. These data should be considered in order to recommend proper surgical treatment after PST.

Conflict of interest

All authors (Rosa -Di Micco, Veronica Zuber, Enrico Fiacco, Federica Carriero, M. Ilaria Gattuso, Ludovica Nazzaro, Pietro

Panizza, Luigi Gianolli, Carla Canevari , Nadia Di Muzio, Marcella Pasetti, Isabella Sassi, MilviaZambetti, Oreste D.Gentilini) declare that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-fi financial interest (such as personal or professional relationships, affiliation liations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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