Is sentinel lymph node biopsy without frozen section in early stage breast cancer sufficient in accordance with ACOSOG-Z0011? A retrospective review from King Chulalongkorn Memorial Hospital.

Nattanan Treeratanapun
Chulalongkorn University
Bhoowit Lerttiendamrong
Chulalongkorn University
Voranaddha Vacharathit
Chulalongkorn University
Kasaya Tantiphlachiva
Chulalongkorn University
Phuphat Vongwattanakit
Chulalongkorn University
Sopark Manasnayakorn
Chulalongkorn University
Mawin Vongsaisuwon (mawin.v@chula.ac.th)
Chulalongkorn University

Research Article

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Abstract

Background: In 2021, increased implementation of the usage of permanent section (PS) without intraoperative frozen section (FS) for sentinel lymph node biopsy (SLNB) were evident worldwide. This pilot study conducted in Thailand will determine the re-operation rate in SLNB without FS technique.

Method: we retrospectively reviewed 239 cases of SLNB without FS in King Chulalongkorn Memorial Hospital from April 2016 to April 2021. These patients were diagnosed with primary invasive breast cancer with clinical node negative. The clinical nodal status was assessed from physical examination. The re-operation rate was evaluated by the number of positive SLNs; equal or more than 3 nodal metastases were subjected to second surgical procedure.

Result: Between April 2016 and April 2021, there are 239 patient who had undergone SLNB in accordance with ACOSOG Z0011 criteria with the use of PS alone. A total of 975 SLNs were removed from these 239 patients, with an average of 4.15 nodes per patient. Out of 239 patients, 21 (8.8%) and 6 (2.5%) had metastatic disease in 1 and 2 nodes, respectively. The remaining 212 (88.7%) patients had no nodal metastasis. None of the patients were subjected to a second surgical procedure.

Conclusion: With a re-operation rate of 0%, we concluded that the implementation of SLNB with PS analysis alone in patients who satisfied the ACOSOG Z0011 criteria do not altered the standard of care offered by additional FS analysis. With cessation of intraoperative procedure, operation cost, operation time and anesthetic side effect are projected to decrease.

Introduction

Breast cancer is one of the most common types of cancer worldwide with more than 2 million newly diagnosed cases in 2020 [1]. The treatment of choice for early-stage breast cancer was originally breast conservation surgery with axillary lymph node dissection (ALND) with consideration for postoperative radiation [2]. However, sentinel lymph node biopsy (SLNB) has been proposed as a standard diagnostic component in early breast cancer with clinically negative nodes in order to avoid ALND and its associated complications [3,4]. The evaluation of sentinel lymph nodes (SLNs) consists of 2 methods: intraoperative frozen sections (FS) and permanent section (PS) analysis. Intraoperative FS analyses were routinely done on SLNs to reduce the need for subsequent ALND, which was previously recommended when metastatic disease was found in SLNs on frozen sections regardless of the number of positive nodes[5–8].

However, in 2017, a study conducted by the American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) concluded that ALND was not always indicated even in patients with a positive SLN. Their inclusion criteria for the randomized control trial were as follows: 1) the patient must have undergone breast conserving therapy with tumor size of less the 5 cm in diameter 2) presence of 1 or 2 positive SLNs and no palpable axillary nodes. No significant difference in the 10 years overall survival for patients who had undergone SLNB and those who had undergone ALND was found [9]. With the implementation of ACOSOG Z0011, the benefit of FS will inevitably decline in early-stage breast cancer

patients, since ALND will be indicated only when FS show more than 2 nodal metastases. Moreover, FS is an expensive and time-consuming procedure which requires experienced pathologist interpretation [8]. Consequently, there has been a significant reduction of FS usage in SLNB procedures [10]. Research conducted in Korea in 2020 demonstrated that the benefit of FS in early node-negative breast cancer was questionable and that PS alone might be sufficient in these cases [11]. Importantly, the false negative rate of intraoperative FS ranged from 10% to up to 60%. Multiple studies suggested that the false negative rate of intraoperative FS was around 15–20% [8,12–16]. Although, the false negative rate of more than 2 lymph nodes on FS, which would require a second surgical procedure in accordance with ACOSOG Z011 was reported to be about 4% [8]. However, how this compares to the reoperation rate of PS alone is still unclear.

At King Chulalongkorn Memorial Hospital (KCMH), a tertiary care hospital in Bangkok, the capital city of Thailand, after the implementation of ACOSOG Z0011, we noticed that the majority of FS cases had less than 3 nodal metastases. Moreover, routine practice in many countries, such as Korea, FS is still the standard of care. Consequently, some surgeons performed PS alone for SLNBs while others still routinely performed intraoperative FS sending both FS and PS. Additional FS analysis at KCMH costs up to 1160 baht or approximately 37 US dollars per case (using an exchange rate from Bank of Thailand on 29th April 2021) and could cost even higher in private hospitals. We questioned this practice, prompting an in-depth cost-benefit analysis of conventional FS in early-stage breast cancer and whether sending PS alone altered the reoperation rate. We conducted a 5-year retrospective review from 2016 to 2021 to determine whether SLNB without FS in patients who meet the ACOSOG Z0011 criteria was non-inferior to SLNB with FS based on the re-operation rate (ALND) as well as reporting the epidemiological data of these patients. Knowing that the false negative rate of more than 2 lymph nodes on FS was about 4%, we hypothesized that the re-operation rate in selected patients would be less than 4%. If our hypothesis is proven correct, it would suggest that the re-operation rate of SLNB with FS is no better than that with PS alone. We hope to reduce FS usage on a national scale, which can reduce the average operative cost, operative time, and time under anesthesia without decreasing the quality of treatment.

Materials And Methods

In this study, we retrospectively reviewed all SLNB procedures which were preoperatively set at KCMH, from April 2016 to April 2021, accounting for 1104 cases. In accordance with the ACOSOG Z0011 protocol, exclusion criteria in our study were tumor size of larger than 5 cm (> T2), mastectomy cases, SLNB with FS, clinically positive nodal status, usage of preoperative neoadjuvant chemotherapy, non-invasive breast cancer cases such as ductal carcinoma in situ and cases that were converted to ALND perioperatively. One SLNB case where the surgeon failed to identify the SLNs which were converted to ALND was also excluded from the study. Only patients with early-stage breast cancer (T1 or T2 breast cancer) and clinical node negative status who underwent breast conservation surgery and SLNB without FS were included. As a result, there were 239 cases that were reviewed (shown in Figure. 1). The majority of SLNBs were performed using a single-agent mapping tracer (isosulfan blue dye), which is the current standard in KCMH and across Thailand. The re-operation rate was dependent on the number of positive

SLNs; patients with 3 nodal metastases or greater were subjected to a second surgical procedure in accordance with the ACOSOG Z0011 trial. The clinical nodal status was assessed by physical examination and radiological nodal status was assessed by breast ultrasonography and mammogram. For each patient, age, laterality, operation type, final pathological diagnosis, TNM staging classification of the tumor, Nottingham histologic grading, number of SLNs identified by PS, lymphovascular invasion, and HER-2 and hormonal receptor status were collected. Moreover, we compared the clinicopathology between patients with nodal metastases and the negative SLNB patients. Patient consent was not required for this retrospective chart review. All pathological diagnoses in this study were based on serial examination of SLNs using hematoxylin and eosin as the immunohistochemistry staining method. The primary outcome in this pilot study was to determine the re-operation rate for the practice of SLNB with PS alone technique. The secondary outcomes were to compare the tumor clinicopathology and radiological nodal status between patients with pathological nodal status N1 and pathological nodal status N0 in order to determine the nodal positivity of SLNB.

Statistical analysis

Data obtained from the medical records were analyzed using Microsoft Excel version 2019. Statistical analyses were performed using IBM SPSS Statistics ver. 26.0 (IBM Corp., Armonk, NY, USA). The categorical data in this study were described as numbers and percentages. Pearson Chi-square and Fisher exact tests were conducted to compare categorical variables. Statistical significance was defined as p-value < 0.05 in all tests.

Results

Between 10th April 2016 and 9thApril 2021, 513 SLNB were performed in breast conservative surgery operations. Two hundred and fifteen operations had an intraoperative FS while the remaining 298 operations were PS alone. A total of 239 out of 298 patients satisfied the ACOSOG Z0011 inclusion criteria and were included in this study.

As for patient demographics, patient age ranged from 26 to 89 years with a mean and median of 55.4 and 55.0 years, respectively. Two hundred and eighteen patients were 40 years of age or older (92.5%). Only 18 patients (7.5%) were under 40 yearsof age. Comparisons of clinicopathological features between patients with pathological N1 disease and those with pathological N0 disease are demonstrated in Table 1. Patients with nodal metastasis were two time more commonly found in the left side than the right side. There were 7 different histopathological diagnoses found in this study: invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ with micrometastasis, mucinous carcinoma, papillary carcinoma, tubular carcinoma and mixed invasive breast carcinoma. The majority of these cases were diagnosed with invasive ductal carcinoma which accounted for 195 patients (81.5%). As for the N stage, 212 (88.7%) patients had N0 while 27 (11.3%) patients had N1 disease on final pathologic analysis. Presence of lymphovascular involvement was found in 39 (16.3%) patients and absent in 200 (83.7%) patients. For 10 cases, the outcome of HER-2 immunohistochemistry was equivocal and did not

have fluorescence in situ hybridization (FISH) and was described as unknown HER-2 status. The percentage of patients who had positive SLNB (N1) in T2 and T1 stages were 14.8% and 11.9%, respectively. Radiological nodal status was found to be significantly correlated with nodal positivity ($p < 0.001$). Most patients (92.6%) with negative preoperative radiological nodal status were found to have nodes with no metastasis on final pathology. On the other hand, 45.0% of patients thought to have nodal metastasis based on radiographic findings were found to have no metastasis on final pathology. The association between lymphovascular invasion and nodal positivity was found to be statistically significant ($p < 0.001$). Every patient with evident of nodal metastasis was found to have invasive ductal carcinoma histopathology. Most patients without evidence of lymphovascular invasion were found to be negative for nodal metastases (95.5%). However, only 46.2% of patients with lymphovascular invasion also had nodal metastases. By the Nottingham histologic grading criteria, patients with pathological N1 disease had histologic grades 1, 2, and 3 at the rates of 2.1%, 13.7%, and 13.6%, respectively. However, none of the hormonal receptor statuses had a statistically significant correlation with SLN metastasis: up to 88.6%, 88.3%, and 87.8% of the patients with ER positive, PR positive and HER2 positive cancer were found to have pathological node N0.

Table 1

Comparison of Tumor Clinicopathology and Radiological nodal status between patients with Pathological nodal status N1 and Pathological nodal status N0

	Total	No. of Patient with Pathological node N1	No. of Patient with Pathological node N0	p-value
Location				0.189
Right	108	9 (8.4%)	99 (91.6%)	
Left	131	18 (13.8%)	113 (86.2%)	
Tumor size				0.095
T1 (< 2 cm)	150	13 (11.9%)	133 (91.1%)	
T2 (2-5 cm)	89	14 (14.8%)	75 (85.2%)	
Radiologic node				<0.001*
Positive/Borderline	20	11 (55.0%)	9 (45.0%)	
Negative	219	16 (7.4%)	203 (92.6%)	
Histologic grade				0.079
1	48	1 (2.1%)	47 (97.9%)	
2	132	18 (13.7%)	114 (86.3%)	
3	59	8 (13.6%)	51 (86.4%)	
Histopathology				0.333
IDC	195	27 (13.9%)	168 (86.1%)	
ILC	9	0 (0%)	9 (100%)	
DCISM	15	0 (0%)	15 (100%)	
Mucinous	10	0 (0%)	10 (100%)	
Papillary	6	0 (0%)	6 (100%)	
Tubular	1	0 (0%)	1 (100%)	
Mixed	3	0 (0%)	3 (100%)	
Lymphovascular Invasion				<0.001*
Yes	39	18 (46.2%)	21 (53.8%)	
No	200	9 (4.5%)	191 (95.5%)	
Estrogen receptor				0.961

Positive	185	21 (11.4%)	164 (88.6%)	
Negative	54	6 (11.1%)	48 (88.9%)	
Progesterone Receptor				0.834
Positive	155	18 (11.7%)	137 (88.3%)	
Negative	84	9 (10.8%)	75 (89.2%)	
HER-2				0.967
Positive	49	6 (12.2%)	43 (87.8%)	
Negative	180	20 (11.1%)	160 (88.9%)	
Not known	10	1 (10.0%)	9 (90.0%)	
Total	239	27	212	

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCISM, ductal carcinoma in situ with microinvasion; HER-2, human epidermal growth factor receptor 2

Sentinel lymph node biopsy

A total of 239 SLNB cases were stratified by the total number of retrieved SLNs into 1, 2, 3, 4, 5, 6, and more than 6 nodes removed, which accounted for 22, 45, 55, 36, 24, 36 and, 31 patients respectively (Table 2). Eighty-seven point two percent (208 in 239) of patients retrieved less than 7. Majority positive SLNs (24 in 27) were found in patients that retrieved SLNs between 1 to 6 nodes. However, at least 2 SLNs should be retrieved. On average, 4.15 SLNs were retrieved per patient. Twenty-one and six out of 239 (8.8%, 2.5%) patients had metastasis to only 1 node and 2 nodes, respectively, while the remaining 212 (88.7%) patients had no nodal metastases. Overall, none of the patients were subjected to a second procedure of ALND in accordance with the ACOSOG trial Z0011 since none of the patients had more than 2 nodal metastases.

Table 2

Number of cases and number of removed sentinel lymph nodes in metastatic lymph node

Total SLNs	Patients (N)	No. of patient with no nodal metastasis	No. of patient with 1 nodal metastasis	No. of patient with 2 nodal metastases
1	22	21	1	-
2	45	41	3	1
3	55	48	6	1
4	36	29	5	2
5	24	22	2	-
6	36	32	3	1
>6	31	29	1	1
975 (4.15)	239	212	21	6

Values are represented as number or number (mean).

SLNs, sentinel lymph nodes.

Discussion

The primary goal of intraoperative FS is to prevent reoperation for ALND. According to the ACOSOG Z0011 trial, an ALND is indicated only when the SLNB results in 3 or more nodes positive for metastatic disease [9]. Therefore, SLN intraoperative FS do not provide benefit in patients who have only 1 or 2 nodal metastases. Even with routine intraoperative FS, ALND as a second surgical procedure is still required if the intraoperative FS turns out to be a false negative. The false negative rate of having more than 2 SLNs on FS is still unclear. However, a study conducted at Imam Khomeini hospital, Iran, revealed a false negative rate of 20.6% when comparing intraoperative FS to PS [8]. Out of those cases, 4 cases (3.9%) were found with 3 or more diseased nodes. Therefore, using SLNB with FS resulted in a reoperation rate of up to 4%. Moreover, there were some limitations to the routine practice of sending FS. It is an expensive and time-consuming procedure which requires an experienced pathologist, additionally the preparation process could result in irreversible tissue loss which could ultimately alter the final pathological diagnosis such as understaging micrometastatic disease. Research have found that intraoperative FS was not sufficient to rule out micrometastases [17,18]. After the implementation of the ACOSOG Z0011 trial, other studies also recommended the usage of PS in early-staged breast cancer patients who meet the ACOSOG trial criteria and discouraged the routine use of intraoperative FS for similar reasons [8,11,19].

In this retrospective review, given that ALND is mandatory in patients with at least 3 SLNs with metastatic disease, we found that patients with early-staged breast cancer meeting the ACOSOG Z011 trial criteria

undergoing SLNB with PS alone had a reoperation rate of 0%. This matches findings from previous study which demonstrated that PS alone resulted in a small number of additional ALND (1.9%) [11]. Therefore, the practice of intraoperative FS does not necessarily prevent the second ALND operation compared to SLNB without FS. Three or more SLNs were detected in 72.0% of cases with an average of 4.15 nodes per case, which is comparable to the optimal yield of SLNs for SLNB (4 SLNs per case) [20]. When 2 or more SLNs are identified, the false negative rate can be decreased to an acceptable 5% level [20] as recommended by the American Society of Clinical Oncology (ASCO) guidelines [3].

In our descriptive retrospective series, the negative predictive value of a radiological negative node appears to be better than the positive predictive value of positive nodes, as up to 92.6% of patients with radiological negative nodes had no metastasis on final pathology. Furthermore, there was a statistically significant association between radiological nodal status and nodal positivity. This finding is consistent with prior studies which stated that ultrasonography and mammography (the imaging modalities in our study), have a strong predictive value for nodal positivity in early-staged breast cancer with non-palpable axillary nodes [21–23]. As for tumor clinicopathology, there was no statistically significant correlation between SLN metastasis and tumor size ($p = 0.095$) despite the percentage of patients with SLN metastasis in the T2 group was clearly higher than that of the T1 group. This is likely due to the fact that tumor sizes in the T2 group were close to the lower limit of 2 centimeters and likewise, the tumors in the T1 group were close to the upper limit of the T stage. This finding is inconsistent with a previous study which found that the rate of nodal metastases increased as the tumor size increased [24–27]. The percentage of patients with positive SLNs in the histologic grade 2 and 3 groups was higher than that in the histologic grade 1 group. Nodal positivity increased in accordance with histologic grading. However, there was no significant association between the higher histologic grade and nodal positivity in our study, even though Ding et al. previously found that histologic grade was one of the three independent predictive factors for positive SLN [22]. Our series also suggested that

lymphovascular invasion could be useful as a predictor for nodal positivity with a markedly significant association with SLN metastasis ($p < 0.001$). Moreover, the absence of lymphovascular invasion may be an indicator for nodal negativity, as 95.5% of patients without lymphovascular invasion were also found to be negative for nodal metastases. This is consistent with a systematic review and meta-analysis which found that lymphovascular invasion was a valuable predictor of lymph node metastasis [25]. The association of hormonal receptor status and SLN metastasis is still currently controversial. Prior studies suggested that estrogen receptor status may be useful as a predictor for nodal positivity and also discouraged the use of other hormonal receptors such as HER2 expression and histologic grading for predictive purposes [28,29] On the other hand, a study conducted in Germany suggested that progesterone receptor and HER2 status can correctly predict nodal metastasis [30]. However, we did not find any of these associations in our case series, as none of the hormonal receptor statuses were found to have any significant correlation with SLN metastasis.

Our study demonstrated that in certain well-selected cases, the practice of SLNB with PS alone was not inferior to SLNB with routine FS in terms of reoperation rate. Moreover, in terms of cost effectiveness, the

practice of PS alone could reduce the costs of up to 1160 baht or approximately 37 US dollars per case, which is a significant amount of money, especially in low to middle income countries (LMICS). Radiological nodal status and lymphovascular invasion of the main tumor can be used as predictors of nodal metastasis, which provide a better nodal positivity prediction compared to other clinicopathology. Limitations to this study are the small sample size with data from a single hospital. Additionally, this study was a retrospective review which could lead to selection bias. However, despite these limitations, this study is important because it is the first report to provide the reoperation rate in SLNB without FS in Thailand and suggested that such practice is not inferior to the current practice of routine intraoperative FS in patients with early-stage breast cancer and non-palpable axillary nodes. Finally, we encouraged a national data collection on tumor clinicopathology and radiological nodal statuses as associated tendencies for nodal metastasis need further study but can be incorporated into a SLNB with PS alone practice.

Conclusion

With a re-operation rate of 0%, we provide a proof of principle to all surgeons in Thailand and low to middle income countries that in cases that satisfied the ACOSOG Z0011 criteria, SLNB with PS alone was sufficient in terms of re-operation prevention. Utilization of PS alone can reduce the operative cost, operative time, and anesthetic side effects from prolonged operations.

Declarations

Data availability statement:

The Datasets generated and/or analyzed in the current study are not publicly available due to the individuals privacy issue but are available from the corresponding author on reasonable request

Conflicts of Interest:

The authors declare the they have no competing interests.

Funding statement:

No funding was available for this study.

Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Institutional review board of faculty of medicine, Chulalongkorn University on July 19, 2021, IRB approval number: 552/64. Individual consent for this retrospective analysis was waived.

Consent for publication: not applicable

Author statement

Nattanan Treeratanapun: Conceptualization, Data Curation, Validation, Formal analysis Investigation, Writing - Original Draft, Writing- Reviewing and Editing. Bhoowit Lerttiendamrong: Conceptualization, Data Curation, Formal analysis, Investigation, Validation, Writing- Reviewing and Editing. Voranaddha Vacharathit: Investigation , Writing- Reviewing and Editing. Kasaya Tantiphlachiva: Investigation. Phuphat Vongwattanakit: Investigation. Sopark Manasnayakorn: Investigation. Mawin Vongsaisuwon: Conceptualization, Methodology, Supervision, Validation, Writing - Review & Editing. All authors read and approved the final manuscript.

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Figures

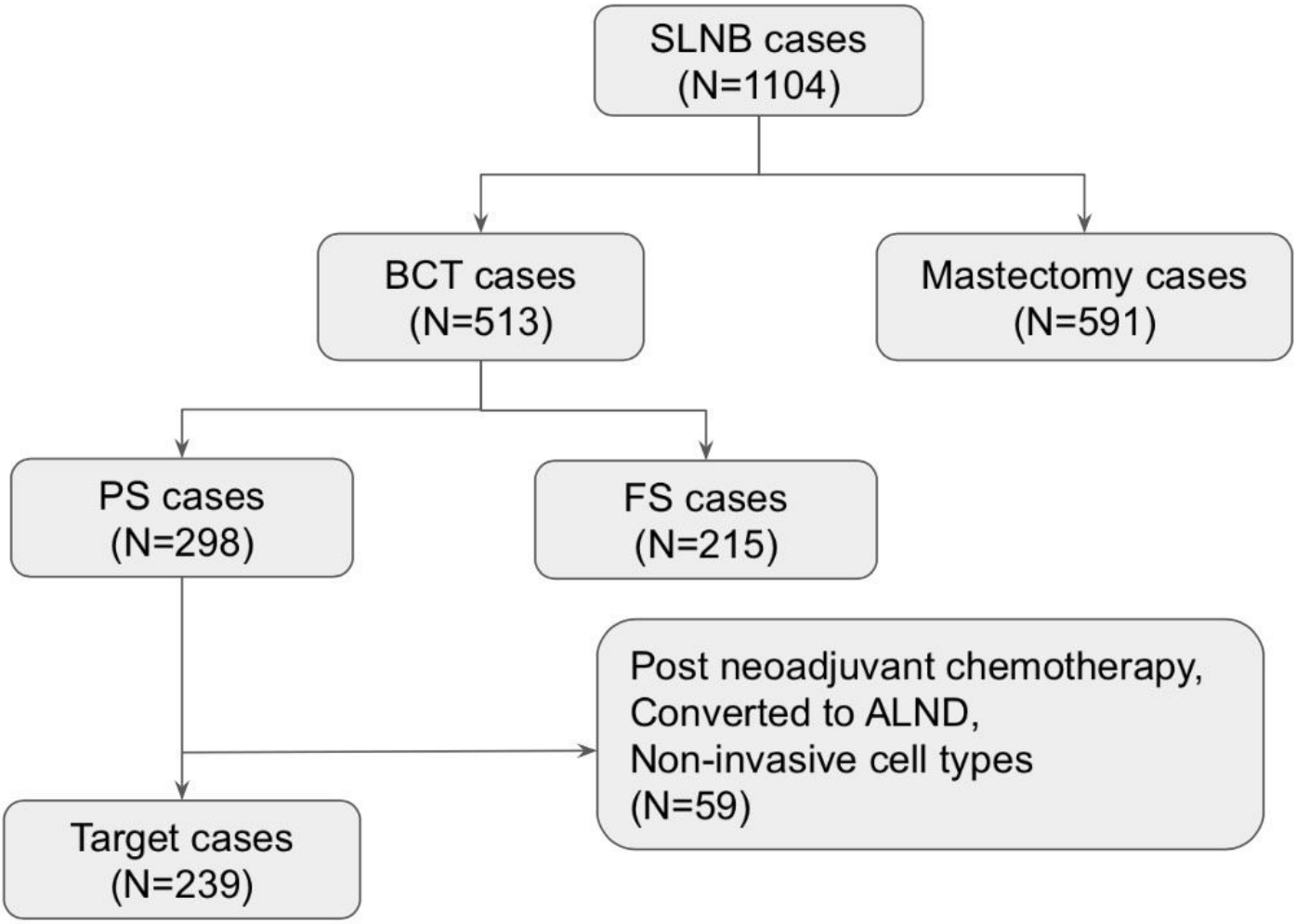

Figure 1

Patient selection flow chart. SLNB, sentinel lymph node biopsy; PS, permanent section; FS, frozen section; BCT, breast-conserving therapy; ALND, axillary node dissection.