Review

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The Adventure of Axillary Treatment in Early Stage Breast Cancer

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ABSTRACT

Axillary lymph node dissection (ALND) which was an essential part of breast cancer treatment and the gold standard in evaluation of the status of axillary lymph node had notorious with increased arm morbidity and reduction of quality of life. Sentinel lymph node biopsy (SLNB) accurately stages the axilla in early breast cancer and ALND is omitted in SLNB negative patients. In patients with positive SLNB the omission of ALND with or without replacement of axillary radiotherapy has also been recommended by guidelines. The neoadjuvant chemotherapy (NAC) which has been increasingly used for large breast cancers to downstage the tumours for allowing breast conserving surgery and decreasing mastectomy rate has also been used in axillary node positive patients to reduce the need for ALND. The issues surrounding the treatment of axilla in patients treated with NAC; application and false negative rate of SLNB, number of identified sentinel lymph nodes, and axillary radiotherapy instead of ALND are currently the discussed and practiced hot topics. The quests for decreasing arm morbidity without compromising outcome in breast cancer treatment which have begun with the invention of SLNB continue for axilla conserving surgery. This article reviews the adventure of axillary treatment in breast cancer patients treated with or without NAC.

Keywords: Breast cancer, axillary treatment, axillary lymph node dissection, sentinel lymph node dissection, neoadjuvant chemotherapy

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Introduction

Axillary lymph node dissection (ALND) was an essential part of breast cancer treatment and erstwhile for a lengthy period was the sole gold standard in evaluation of the status of axillary lymph node. The benefits of ALND were staging the axilla, providing important prognostic information, improving of axillary regional control, and the probable improvement of survival and disease-free survival (DFS) (1-3). As to the harms of ALND; they are known as increased arm oedema, restrictions in the arm movements, and reduction of quality of life. Arm oedema which is the most known complication after ALND could sometimes be very severe, increase by axillary radiotherapy and may even lead to the disability of arm (4-7).

Larson et al. (8) reported that extent of ALND (full ALND vs lower or level 1, 2 ALND) was a significant predictor of subsequent lymphoedema. In that study, in addition to level 1, 2 ALND, the stripping of axillary vein was described as full ALND and the dissection of axillary content between latissimus muscle, axillary vein and pectoralis minor muscle was described as lower or level 1, 2 ALND. Lymphoedema rate was reported as 37% for full ALND, and 8% for level 1, 2 ALND. In reference to the article by Larson et al. (8), other articles claimed that the risk of lymphoedema is directly related to the extent of axillary surgery as level 1, 2 ALND vs full ALND (7, 9). The approval of full ALND as level 1-3 ALND based on the description of Larson et al. (8) is misleading, because level 1-3 ALND does not include the stripping of axillary vein which was known as a major cause of lymphoedema by disrupting the lymphaticovenous anastomoses (10, 11).

The extent of axillary dissection had been argued and whether level 1-2 axillary dissection instead of level 1-3 axillary dissection could decrease the arm morbidity had been investigated (12, 13). The two randomised studies showed that the extent of ALND (level 1, 2 or level 1 versus level 1-3) was not associated with arm morbidity in cT1-3cN0-1 invasive breast cancer (12, 13). In the study by Kodama et al. (12), level 1 was compared with level 3 dissection and 58% and 68% were clinically and histologically axillary node negative,

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respectively. Tominaga et al. (13) compared level 1, 2 with level 1-3 dissection, and 74% were clinically and 65% were histologically axillary node negative. These studies proved that the 10-year survival, DFS or axillary recurrence-free survival were not significantly different for level l and level 1, 2 or level 1-3 ALND. Arm oedema and restrictions in arm movements were also not significantly different for level 1 or level 1-3 in the study by Kodama et al. (12). Tominaga et al. (13) reported that there were no significant differences for level 1 or level 1-3 ALND in regard to arm pain, motor function or social functioning. In both of these trials patients were randomised to level 1, level 1, 2 or level 1-3 ALND without performing sentinel lymph node biopsy (SLNB). While it was clear that ALND has no benefit for axillary recurrence or survival in patents with negative axillary lymph node, the power of these studies was also not sufficient to evaluate the advantage of level 1-3 ALND over level 1 or level 1, 2 ALND. Although the extent of ALND has been shown to be not effective for survival, DFS, axillary recurrence and arm morbidity in breast cancer, arm morbidity continued to remain high after either level 1, 2 or full (level 1-3) ALND (4-6). Findings from a systematic review and meta-analysis suggest that more than one in five women with breast cancer will develop arm oedema (4). The quests for decreasing arm morbidity without compromising outcome in breast cancer treatment which began with the invention of SLNB continue for axilla conserving surgery. This article reviews the adventure of axillary surgery in breast cancer patients treated with or without NAC.

Clinical and Research Consequences

Sentinel lymph node biopsy in clinically axillary node negative patients

Following the first successful report of SLNB (14, 15), this technique was rapidly introduced to clinical practice in cT1-2 patients with clinically axillary node negative (16-21). Overall identification rate of SLNB and the false negative rate (FNR) of SLNB are over 90% and under 10%, respectively (Table 1) (22-30). High FNR is of clinical concern because of probability of higher axillary recurrence and inappropriate staging. Therefore, surgeons who perform SLNB are recommended to have figures close to or not worse than these.

Long term results of studies in patients with negative SLNB who did not undergo ALND, demonstrated that axillary recurrence rate was low and less than 2% (range, 0.4-1.7%) (Table 2) (31-38) and there was not significant difference between SLNB without ALND and with completion ALND in respect to axillary recurrence, DFS or survival (Table 2) (28, 31, 32, 34, 37, 39). Arm morbidity and/or quality of life were also shown to be improved significantly in patients with SLNB alone compared with completion ALND (Table 2) (4, 25, 28, 31, 32, 40-45). However, one study reported that SLNB is not associated with a better quality of life than ALND (46). SLNB was associated with low risk of arm oedema compared with ALND (47). As the results of sentinel node trials revealed no difference in terms of survival and axillary recurrence between SLNB and ANLD (23), SLNB has been accepted as a standard procedure for early-stage breast cancer with cT1-2 clinically axillary node negative patients (21, 48). The American Society of Clinical Oncology (ASCO) guideline updated on 2014 recommended that women without SLNB metastases should not receive ALND (21).

Axillary treatment in patients with metastasis on sentinel lymph node biopsy

Until 2011, axillary lymph node dissection (ALND) had been the standard treatment in breast cancer patients with metastasis on SLNB (32, 49). However, ALND stood on to be associated with high arm morbidity (5, 50).

Many retrospective studies which reported the outcomes in patients with positive SLNB have observed no axillary recurrences (51-54) or between 0.2% and 1.7% in patients with SLNB alone (Table 3) (34, 55, 56). The others which compared the outcomes after SLNB alone with completion ALND demonstrated that the axillary recurrence rate was ≤2% (Table 3) (43, 57, 58). However, in a cohort study from the Netherlands, 1,028 patients with sentinel lymph node (SLN) micrometastases who did not undergo ALND were shown to have a significantly higher risk of axillary recurrence of 5,6% at 5 years follow-up compared with 0% in 94 patients who received axillary radiotherapy after SLNB or 1.1% in 793 patients who underwent ALND ($p<0.001$) (Table 3) (59, 60). All patients in that study had a tumor size of ≤1 cm and only 52% of the patients with no axillary therapy received systemic therapy. Two retrospective studies with metastasis on SLNB reported that axillary recurrence was 0% with a median follow-up of 30 months and 48% and 32% of patients had radiotherapy for breast and 22% and 29% of patients received additional radiotherapy for nodal fields, respectively (Table 3) (52, 53).

Naik et al. (57) reported that 210 SLNB-positive/no ALND patients had either refused completion ALND or were felt to be at low risk of having residual axillary disease. In the study by Naik et al. (57) although axillary recurrence was higher in 210 SLNB positive/no ALND patients compared with SLNB positive/ALND group, it was not significant and of the 149 patients who underwent breast conserving surgery (BCS) 53 had radiotherapy. In this group, 43% (23/53) had radiotherapy for the breast only, and 57% (30/53) received additional radiotherapy for the axilla. No patients in this subset developed axillary recurrence (58).

In the study by Park et al. (58) which included an expanded number of patients from Memorial Sloan Kettering Cancer Center (MSKCC), among 287 SLNB positive/no ALND patients, none of the 6 patients who developed axillary recurrences had radiotherapy for axilla and/or supraclavicular region.They reported that in SLNB (+)/no ALND patients, axillary recurrence was significantly higher compared with SLNB (+)/ALND group (2% vs 0.4%, $p=0.004$). However, 31% of their patients underwent mastectomy, and only 15% of all patients with SLNB (+)/no ALND had additional radiotherapy for axilla or supraclavicular region.

These show that uncontrolled omission of ALND could result in increased rate of axillary recurrence and the importance of radiotherapy as part of BCS and/or as additional tangent fields to axilla in patients treated with BCS or mastectomy. Although, none of the retrospective trials and meta-analyses revealed any significant difference in survival or DFS in patients with positive SLNB/no ALND compared with ALND, the impact of axillary recurrence should never be overlooked. The Early Breast Cancer Trialists' Collaborative Group reported that for every 4 locoregional recurrences avoided, about 1 breast cancer death over the next 15 years is prevented (61). Harris and Morrow (62) reported that with increasing use of chemotherapy this ratio changed from 4:1 to 2:1.

The meta-analysis by Bilimoria et al. (63) showed that axillary recurrence and survival were not significantly different for patients who underwent SLNB alone versus SLNB with completion ALND for microscopic nodal disease and, in selected patients, for macroscopic nodal metastases. On the other hand meta-analysis by Yi et al. (64) reported that axillary recurrence was significantly higher in patients with SLNB alone compared

Table 1. Identification and false negative rates of SLNB in clinical node negative patients

Study	Patient numbers	SLNB identification rate %	False negative rate%*
Before adjuvant chemotherapy			
Veronesi et al. (1999)	371	98.7	6.7
Tafra et al. (2001)	535	87	13
		Surgeon experience	Surgeon experience
		<10 cases: 82	<30 cases: 15.5
		≥10 cases: 92	≥30 cases: 4
			1 node: 20.8
			≥2 nodes: 9.2
McMasters et al. (2000)	806	Single agent: 86	Single agent: 11.8
		Dual agent: 90	Dual agent: 5.8
ALMANAC trial (2006)	815	96	6.7
		Single agent: 85.6	
		Dual agent: 96	
Kim et al. (2006) Meta-analysis of 69 studies	8059	96 (41-100)	7.3 (0-29)
NSABP B-32 (2007)	5536	97.2	9.8
Sentinella/GIVOM (2008)	697	95	16.7
Hunt et al. (2009)	3171	98.7	4.1
Kuru et al. (2011)	232	91	7
After neoadjuvant chemotherapy			
Tafra et al. (2001)	29	93	0
NSABP B-27 (2005)	343	85	10.7
		Lymphazurin: 78	Lymphazurin: 14
		Radioisotope: 89	Radioisotope: 8
Xing et al. (2006) Meta-analysis of 21 studies	1273	90 (72-100)	12 (0-33)
Hunt et al. (2009)	575	97.4	5.9
Classe et al. (2019)	589	97.6	11.9
Kelly et al. (2009) Meta-analysis of 24 studies	1799	89.6 (63-100)	8.4 (0-33)
Fontein et al. (2013) Meta-analysis of 21 studies	1738	95	11.4
Geng et al. (2016) Meta-analysis of 16 studies	1456	96	6

*Detected by axillary lymph node dissection after SLNB
NSABP: National Surgical Adjuvant Breast and Bowel Project; SLNB: sentinel lymph node biopsy

with those with ALND in macroscopic nodal disease. However, axillary recurrence rate of 0.2% in selected patients with SLNB alone is very low and an acceptable figure. Yi et al. (64) considering the axillary radiotherapy as an alternative to ALND in SLNB-positive patients, noted that patients who underwent BCS were more likely to undergo SLNB alone. Because patients who underwent BCS would have already been candidate for adjuvant radiation, the use of high tangents or the addition of an axillary field during whole breast radiotherapy could readily be applied to avoid axillary recurrence and ALND (63, 64).

That the occurrence of significantly higher axillary recurrence in patients with the axilla left untreated after omitting ALND, the presence of no significant difference in axillary recurrence and survival or DFS in patients without undissected axilla but received axillary radiotherapy compared with ALND prove the evidence that ALND could be omitted should the axilla be treated with radiotherapy in SLNB-positive breast cancer patients undergoing BCT or mastectomy. Lack of significant difference in axillary recurrence and survival or DFS in cT1-2 patients with 1, 2 metastases on SLNB and without ENE who undergo BCS without ALND and receive whole breast radiotherapy compared with those undergoing ALND is attributed to the tangential radiotherapy for axillary region during whole breast radiotherapy. Thus omitting of ALND in those pa-

Table 2. Outcomes in observational studies with SLNB negative patients and in studies which compared SLNB with ALND in SLNB negative patients in clinical axillary negative patients

Prospective studies Follow-up	Number SLNB, ALND	Axillary recurrence % SLNB vs ALND	Survival % SLNB vs ALND	Arm morbidity % SLNB vs ALND	Quality of life SLNB vs ALND
ALMANAC trial (2006) Mansel et al. 18 months	515, 516	NR	NR	At 12 months Lymphedema: 5 vs 13 Arm function: Favours SLNB (p<0.01)	Favours SLNB p<0.01
Chen et al. (2009) 6/12 months	140, 81	NR	NR	Lymphedema: Favours SLNB (p=0.04) Arm movement: Favours SLNB (p<0.001-0.038)	Favours SLNB p=0.037
NSABP 32 (2010) 8 years	2011, 1975 All SLNB (-)	0.4 vs 0.1 NS	90.3 vs 91.8 NS	At 36 months Lymphedema: 8 vs 14 and Arm functions favour SLNB (p< 0.001)	Favours SLNB p<0.002
Veronesi et al. (2010) 10 years	259, 257 All SLNB (-)	0.8 vs 0 NS	93.5 vs 89.7 NS	At 24 months Any lymphedema: 7 vs 75 Arm mobility: 0 vs 21 Favour SLNB (p<0.01)	NR
Sentinella/GIVOM (2008) 56 months	336, 341	NR	DFS 88 vs 90 NS	At 6 months, lymphedema and movement restriction favour SLNB (p<0.01, 0.016)	PGWBI: Favours SLNB Significantly p=0.015
Purusthotham (2005) 12 months	86, 155	NR	NR	Lymphedema 20 vs 60 (p=0.007) Arm restriction favours SLNB	Psychological morbidity: Significantly less in SLNB
Kootstra et al. (2008) 24 months	61, 134	NR	NR	NR	NS
Dabakuyo et al. (2009) 12 months	222, 296	NR	NR	Arm symptoms scale favours SLND (p=0.013)	GHS favours SLND, p=0.018
Hunt et al. (2012) ACOSOG z0010. 8.4 years	3904 SLNB All SLNB (-)	0.5	Sur.: 93	NR	NR
Kell et al. (2010) 5 RT 6 months	Arm swelling: 1997, 1967 Paraesthesia: 1596, 1613	NR	NR	Arm swelling and Paraesthesia: Favours SLNB (p=0.0028, 0.0018)	NR
Pepels et al. (2011)	6,664, 1878	0.4 vs 0.3	NR	NR	NR
47 months	All SLNB (-)	NS			
Pepels et al. (2011) 50 studies, 36 months	26,000, SLNB All SLNB (-)	0.6	NR	NR	NR
Petrelli et al. (2012) 4 RT, 5-10 years	2699, 2725 All SLNB (-)	NS	NS	NR	NR
Galimberti et al. (2014) 7 years	5,262, SLNB All SLNB (-)	1.7	10 years Surv.: 91	NR	NR
Matsen et al. (2016) 10.4 years	1529 SLNB All SLNB (-)	0.9	Surv.: 84	NR	NR
Houvenaeghel et al. (2016) 55 months	8386, 945 All SLNB (-)	0.4 vs 0.5 NS	NS in MVA	NR	NR
De Boniface et al. (2017). 10.5 years	2216 SLNB All SLNB (-)	1.6	Surv.: 94	NR	NR

SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; LRR: locoregional recurrence; Surv.: survival; Neg.: negative; RT.: randomised trials; PGWBI: Psychologic General Well Being Index; GHS: general health status, NR: not reported; NS: not significant; MVA: multivariate analysis

Table 3. Characteristics and outcomes of studies that compared SLNB with or without axillary RT versus ALND for patients with SLN metastasis

Prospective studies (Follow-up)	Year/ Number (SLNB, ALND)	Outcome of SLNB	Axillary treatment	Micr. %	Axillary recurrence % SLNB vs ALND	Survival or DFS %	Arm morbidity %
ACOSOG Z0011 (9 years)	2011/420, 436	SLN 1-2 (+) SLN >2 (+) or ENE (+)	SLNB vs ALND	35	1.5 vs 0.5 NS	Similar NS	25 vs 70 p< 0.01
AMAROS (6.1 years)	2014/681, 744	SLN (+)	SLNB+ART vs ALND	40	1.7 vs 2 NS	Similar NS	5 vs 13 p< 0.01
OTOASOR 8 years	2017/230, 244	SLN (+)	SLNB+ART vs ALND	40	1.2 vs 0.43 NS	Similar NS	5 vs 15 p< 0.01
IBCSG 23-01 (10 years)	2018/469, 465	SLN 1-2 (+) SLN >2 (+) or ENE (+)	SLNB vs ALND	100	0.8 vs 0.2 NS	DFS Similar NS	18 vs 39 p< 0.01
AATRM (5 years)	2013/121, 112	SLN (+) 93.3% BCS	SLNB vs ALND	100	0.8 vs 0.9 NS	Similar NS	NR
Meta-analyses							
Bilimoria et al. NCDB (5 years)	2009/1988, 20,290	SLN (+)	SLNB vs ALND	18 vs 8.5	Mic.: 0.6 vs 0.2 NS, Mac.: 1.2 vs 1, NS	Similar NS	NR
Yi et al. SEER database (50 months)	2010/4425, 22,561	SLN (+)	SLNB vs ALND	51 vs 20	Mic.: 0.13 vs 0.09, NS Mac..: 0.2 vs 0.08 (p<0.002)	Similar NS	NR
Pepels et al. 30 months	2011/962, 15 studies	SLN (+)	SLNB±ART	Mic.: 61 Itc.: 25 Mac.:14	1.7	NR	NR
Retrospective studies							
Naik et al. (31 months)	2004/210, 1132	SLN (+)	SLNB vs ALND	NR	1.4 vs 0.35 p=0.08	NR	NR
Houvenaeghel et al. (55 months)	2016/282, 2923	SLN (+)	SLNB vs ALND	66 vs 40	Mic.: 1.6 vs 0.4, p=.05, Mac.: 0 vs 0.9 (NS)	NR	NR
Takei et al. (34 months)	2007/120, 402	SLN (+)	SLNB vs ALND	NR	0 vs 1 NS	NR	NR
Zakaria et al. (30 months)	2007/86, 421	SLN 1-3 (+) SLN (+)	SLNB±ART vs ALND	80 vs 24	0 in SLNB	NR	NR
Hwang et al. (30 months)	2007/196	SLN (+)	SLNB±ART	85	0 in SLNB	NR	NR
Park et al. (26 months)	2007/287, 1673	SLN (+)	SLNB vs ALND	NR	2 vs 0.4 p=0.004	NR	NR
Tjan-Heijnen et al. (60 months) MIRROR	2009/235, 793	SLN (+)	SLNB vs SLNB+ART ALND	100	5.6,0, 1.1 (p<0.01)	NR	NR
Spiguel et al. (95 months)	2011/123	SLN (+)	SLNB	67	0.8	DFS: 85	NR
Morrow et al. (37 months)	2017/484	SLN 1-2 (+) All BCT	SLNB	NR	0.2	DFS: 93	NR
Kuru et al. (37 months)	2019/81, 28	SLN 1-2 (+) SLN >2 (+) or ENE (+)	SLNB+ART vs ALND	0	0 vs 1 NS	Similar NS	6.2 vs 17.8 p< 0.01

BCT: breast conserving therapy; OS: overall survival; DFS: disease-free survival; Mic.: micrometastasis; Mac.: macrometastasis; Itc.: isolated tumor cells; SLN: sentinel lymph node; SLNB: SLN biopsy; ART: Axillary radiotherapy; NS: not significant. NR: not reported

tients does not create any unfavourable status in respect to axillary recurrence, survival or DFS.

These retrospective studies are crippled with the selection bias, because as in the study by Pepels et al. (34), 25% of patients had isolated tumor cells on SLNB which was accepted as pN0 in the current Guidelines. In three other studies patients with low risk of non-sentinel node metastasis by various nomograms was selected to omit ALND (53, 57, 58). In the two largest series with SLNB positive/no ALND from MSKCC and MD Anderson cancer center, the patients were at low risk for having additional positive non-SLNs and probably low probability of developing axillary recurrence with a median risk of <10% for non-SLN metastasis based on MSKCC nomogram (53, 57). Two meta-analyses reported that patients with older age and smaller size of breast tumor were more likely to undergo SLNB alone (63, 64). Many randomised trials have been conducted to overcome the selection bias by retrospective studies (65-70).

The American College of Surgeons (ACOSOG) Z0011 trial was carried out to assess whether omitting ALND would decrease the high arm morbidity following ALND in patients with 1–2 metastases on SLNB who underwent breast-conserving therapy (BCT) (65, 66). This trial showed that in women with clinically node-negative axilla who underwent BCT, the omission of ALND in T1-2 breast cancer patients with 1, 2 metastases on SLNB and without extra nodal extension (ENE) did not decrease survival, not increased axillary recurrence, and reduced arm morbidity compared with ALND. The ACOSOG Z0011 study changed the practice of axillary treatment and breast surgeons in some main breast centers began to omit the ALND in patients with T1-2 tumor and with 1, 2 metastases on SLNB and without ENE who underwent BCT (71-73). The National Comprehensive Cancer Network (NCCN) recommends the consideration of not performing ALND following SLNB in patients who match the ACOSOG Z0011 eligibility criteria (74).

The American Society of Clinical Oncology also does not recommend routine ALND, based on the ACOSOG Z0011 study (75). However, the Z0011 study had been criticized for its design and for its very favourable and low risk patient and tumor characteristics (76). The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) study compared ALND with SLNB plus axillary and supraclavicular radiotherapy in T1-2 early breast cancer patients with positive SLNB (67). The finding of this study revealed that the five-year axillary recurrence rate was not significantly different for the regional radiotherapy following SLNB without ALND compared with ALND following SLNB (1.2% vs 0.43%). However, the lymphoedema rate at five years was significantly lower in the radiotherapy group (13% vs 6%, p=0.0009) (67). The IBCSG 23-01 trial also showed that the DFS and axillary recurrence rate were not significantly different between the SLNB-only group and the ALND group in T1-2 patients with 1, 2 micrometastases on the SLNB who underwent BCT (68). In the OTOASOR (The Optimal Treatment of the Axilla - Surgery or Radiotherapy) study, 474 patients had positive SLNB. Two hundred and forty four patients with positive SLNB underwent completion ALND and 230 received axillary radiotherapy (69). There was no significant difference in axillary recurrence (2% in the ALND arm and 1.7% in the radiotherapy arm), and overall survival between the arms at the mean follow-up of 97 months. The arm morbidity was higher in the ALND group (15.3%) than in the radiotherapy (axillary levels, and supraclavicular, and ± internal mammary nodes) group at one year (4.7%). Considering that arm morbidity is important after surgery for breast cancer, and the prevention of arm morbidity, together with a low axillary recurrence rate are among the major objectives of breast cancer treatment without worsening the oncologic outcome, the findings from these 4 randomised trials seemed to achieve these aims.

In the study by Kuru et al. (54), patients with 1–2 metastases on SLNB without ENE were assigned to the SLNB-only plus radiotherapy for the axillary levels I-III and to supraclavicular fossa or ALND groups (plus radiotherapy for undissected axillary level III and to the supraclavicular fossa). However, contrary to the randomised trials micrometastases were not included in this study, and all patients had macrometastases on the SLNB (66-69).This study also showed that lymphoedema and arm morbidity were significantly lower in SLNB-only arm compared with the ALND arm (54).

In patients with metastasis on SLNB, residual non-sentinel node metastases could be left in the axilla inmany patients, and this is expected to be higher in patients with macrometastases on the SLNB than in micrometastasis on SLNB (77, 78). That residual disease left in the axilla could be responsible for axillary recurrence is the main argument for performing ALND or axillary radiotherapy in SLNB-positive patients, especially in patients with macrometastases on SLNB. As in systemic therapy adjuvant radiotherapy can be regarded as a treatment modality for any remaining axillary lymph node metastases. Radiotherapy for the breast as part of BCT includes the lowest portion of the axilla. In several studies it has been confirmed that the clip marking the SLN fell within the standard tangential fields of the whole breast radiotherapy in 78–94 % of the patients (79, 80). Veronesi et al. (81) reported that radiotherapy for the breast is one of the possible explanations for the lower than expected numbers of axillary metastases in the no axillary radiotherapy arm of their randomised trial that assessed the role of axillary radiotherapy. Axillary radiotherapy, tangentially or directly, is associated with low axillary recurrences (65, 67, 82, 83). What is important is the associated arm morbidity of the radiotherapy for the axilla levels.

As demonstrated in the AMAROS, OTOASOR studies, and the study by Kuru et al. (64, 67, 69) radiotherapy for three axillary levels resulted in significantly lower or no axillary recurrence in SLNB-only arm compared with ALND. These studies supported that the addition of radiotherapy for breast or chest wall was associated with a significantly higher risk of lymphoedema in patients who underwent ALND, but there was no association with lymphoedema in patients treated with SLNB plus radiotherapy (84). Sanuki et al. (85) reported that in 104 cT1-T2N0M0 breast cancer patients with positive SLNB who underwent BCT without ALND; the five-year axillary recurrence and lymphedema were 0%. In that study, macrometastasis was found in 33% of patients. In one of the two studies which looked like the design of the ACOSOG Z0011 study, Dengel et al. (71) reported that there was no axillary recurrence after omitting ALND for T1-2 invasive breast cancer patients with 1, 2 metastases on SLNB with a median follow-up of 13 months. However, 27% of patients had micrometastases, and the median tumor size was under 2 cm (71).

Briefly, in all of the above randomised studies, survival, DFS or axillary recurrence were not significantly different; and the arm morbidity rates were significantly lower in SLNB-positive patients treated with breast surgery and radiotherapy for three axillary levels and/or to the whole breast. Axillary dissection could safely be omitted in patients with 1, 2 metastatic SLNB and without ENE who undergo BCS or in patients with metastatic SLN who undergo BCS or mastectomy and have ad-

juvant radiotherapy for the all three axillary levels, the supraclavicular fossa, and ±mammaria interna and/or the whole breast or chest wall.

Axillary treatment after neoadjuvant chemotherapy in clinically axillary negative patients

Sentinel lymph node biopsy after neoadjuvant chemotherapy (NAC) in clinically axillary negative patients is recommended by current guidelines (74, 75). While ALND is recommended in patients with metastasis on SLNB, omitting ALND in patients with negative SLNB is increasingly being used after NAC (86). The identification and false negative rates of SLNB after neoadjuvant therapy in clinically axillary negative patients are over 90% and under 10%, respectively (Table 1). These figures justify the use of SLNB in this setting. Many studies and meta-analyses including NSABP B-27 showed that the identification and false negative rates of SLNB were similar to the rates of upfront surgery (29, 87-93) (Table 1).

Four hundred and nineteen patients who had cT1-3 and clinically and radiologically axilla negative breast cancer proved with fine needle aspiration biopsy (FNAB) and had negative SLNB after NAC had been treated with SLNB alone in GANEA 2 study (90). Only one axillary recurrence occurred during a median follow-up of 36 months and 3-year overall survival was 97.2% (90). In the MD Anderson study, among 3,746 clinically axillary negative cT1-3 patients, 3,171 patients underwent surgery first and 575 patients underwent SLNB after NAC (29). SLNB identification rates before and after NAC were 98.7% and 97.4%, respectively. False negative rate of SLNB before and after NAC were also similar as 4.1% and 5.9%, respectively. Of the 444 patients with negative SLNB after NAC, 409 did not undergo ALND. Regional recurrence rates for patients treated with and without NAC were1.2% and 0.9% with a median 47 months of follow-up, respectively, and not significantly different (29). This study also demonstrated that in patients with clinically axillary node negative T2-3 tumours treated with NAC, the axillary disease could be reduced and could lead to decreased ALND without impairment in locoregional control. These findings showed that NAC could eradicate non-palpable axillary nodal disease (94). Outcomes in two studies including patients with clinically node negative who received NAC showed that axillary/regional recurrence rate was 0% and 1.2% with a follow up time of between 47 and 51 months, respectively in SLNB negative patients who underwent SLNB only (29, 95). Axillary recurrence rate, DFS or survival was not significantly different in patients with SLNB alone compared with patients with ALND (96, 97) (Table 4).

Considering all, these data show that SLNB after NAC is accurate and feasible in clinically axillary node negative breast cancer and NAC could spare patients the morbidity of ALND and adjuvant treatment suggestions without impairing locoregional control by decreasing the number of patients with a positive SLNB (29). These findings also led to the questioning of the current recommendations that all axillary suspicious lymph nodes on axillary ultrasound in patients undergoing NAC should be biopsied (98). All data show that SLNB could be performed with more or less similar identification rate and similar FNR compared with upfront surgery (99).

Nguyen et al. (86) from Mayo clinic reported that overall, the proportion of patients undergoing ALND (±SLNB) in node positive patients treated with NAC decreased from 100% in 2009 to 38% in 2017 ($p<0.001$), and the use of axillary surgery limited to SLNB only increased from 0 to 62% over this time period (86). Further stratified, the use of ALND only without SLNB dropped from 72% to 14%, while SLNB without ALND for negative sentinel node (s), increased significantly over 50%.

Axillary treatment after neoadjuvant chemotherapy in clinically axillary positive patients

Sentinel lymph node biopsy after NAC for cN (+) axilla at presentation was in the past contentious and not recommended by guidelines even if axilla was converted to negative axilla either by clinical examination or imaging (21). The rationale for this was that the FNR of SLNB may be unacceptably high ranging from 10% to 30% (100-106) (Table 5). However, 3 randomised clinical trials (107-109) (Table 5) and other studies conducted in patients with biopsy proven positive axilla or clinically positive axilla that converted to clinically negative axilla showed that FNR rate was under 10% or could be decreased below 10% if 3 or more SLN removed, using dual mapping technique of SLNB or targeted SLNB methods by clipping of positive nodes before NAC (90, 107-113) (Table 5). These studies led to the conclusion that ALND was not required in all patients with clinically positive axilla that converted to clinically negative axilla, and SLNB without completion ALND is accurate and feasible if three or more negative SLN is removed or at least one negative SLN is removed by dual mapping technique with blue dye and radioisotope is used (107-109, 114).

Therefore, in patients with cN1-2, NAC may achieve complete axillary response (cN0) detected by clinical examination and imaging studies and may achieve pathological complete response (pCR). In fact in one forth or more or up to 83% of node-positive patients, axilla become cN0 after NAC (101, 107, 108, 115, 116) and in HER2 and triple negative tumors up to three forth of axillary metastasis can completely be cleared pathologically (pCR) (114, 116). Thus ALND and the associated morbidity could be avoided. The extent of disease at presentation, and tumor biologic subtype should also be considered in the selection of axillary approach (86). HER2 and triple negative tumors have been shown to respond to NAC more successfully with pCR rates that could exceed 50% (86, 117).

Current NCCN guidelines have incorporated SLNB after NAC as an accepted part of management and state that SLNB can be performed on selected patients with clinically N1 breast cancer who have clinically negative axilla after NAC, and that the SLNB false-negative rate can be improved by removing more than two lymph nodes, using dual tracers or marking biopsied lymph nodes to document their removal (74). The proportion of patients with positive SLNB who did not undergo ALND after NAC increased from %0 in 2009 to 10% 2017 (86).

Outcomes in many studies with clinically or biopsy proven node positive patients who converted to clinically negative after NAC showed that in SLNB negative patients, axillary recurrence rate, DFS or survival were not significantly different in patients with SLNB alone compared with patients with ALND (26, 86, 118, 119) (Table 4). Axillary recurrence rates were between 0% and 3.3% with a follow up time of between 9 and 51 months (Table 4).

Axillary treatment in pathological node positive patients after neoadjuvant chemotherapy

In locally advanced and axilla positive breast cancers (cT ≥4 cm N1-2M0), DFS was 51% versus 87%, respectively in patients who have residual disease with metastasis on SLNB following NAC compared with those who had negative SLNB ($p<0.001$) (116). In patients who have not received NAC, the size of the SLN metastasis is associated

Table 4. Outcomes in studies with clinical node negative and with clinical or biopsy proven node positive patients who converted to clinical negative after neoadjuvant chemotherapy

Studies Follow-up	Number/ Characteristics	SLNB and Groups	Axillary surgery SLNB vs ALND	Axillary recurrence % SLNB vs ALND	Survival or DFS% SLNB vs ALND
Hunt et al. (2009) 47 months	575 cT1-3cN0	409 neg.	SLNB	Regional recurrence: 1.2	NS compared with ALND
Galimberti et al. (2016) 61 months	396 cT1-4cN0-2 All ycN0 after NAC 260 Quart 136 mast.20% RT	1. 227 neg. 2. 169 pos.	1. SLNB 2. ALND	0.4 vs 0.6 NS	5-year survival cN0: 93.3 cN1-2: 86.3 NS
Nogi et al. (2017) 51 months	147 cN0	147 neg.	SLNB	0	5-year DFS 96%
Martelli et al. (2017) 72 months	216 cT2cN0-1	1. 77 neg. 2. 99 pos.	SLNB ALND	0	DFS NS
Choi et al. (2018) 51 months	213 cT1-4 pN1 (biopsy proven) All ycN0 after NAC	Groups 1.85 neg. 2. 49 pos.	1. SLNB 2. ALND 3. 79 ypN0 with ALND no SLNB	(Group 1 vs 3) 2.6 vs 1.3, NS	NS
Kim et al. (2015) 20 months	199 pN1 (biopsy proven)	Groups 1. 31 neg. 2. 20 neg. 3. 69 pos. or UD SLNB	1. SLNB 2. ALND 3. ALND 4. 79 ypN0 with ALND no SLNB	3.3 vs 5 vs 1.3 (Group 1 vs 2 vs 4) NS	Survival NS (Group 1 vs 2 vs 4)
Kang et al. (2017) 48 months	1247 cN1 (58% biopsy proven)	Groups 1a. 165 neg. 1b. 263 pos.	1a. SLNB 1b. ALND 2. 819 ALND no SLNB	1.2 vs 1 (Group 1a+1b vs 2) NS	DRFS 98 vs 99 NS for Group 1 vs 2
Nguyen et al. (2017) 9 months	430 cN1 (246 ALND 184 SLNB)	1. 82 neg. 2. 18 neg. 3. 73 pos. 4. 11 pos.	1.SLNB 2.ALND 3.ALND 4.SLNB+ART	0 vs 3.3 NS	NR
Kuru et al. (2019) 20 months Unpublished data	124 cN0-1 (99 SLNB 25 ALND)	1. 55 neg. 2. 25 pos. 3. 19 pos.	1. SLNB 2.SLNB+ART 3. ALND+ART	0, 0, 0 NS (Group 1 vs 2 vs 3)	NS

SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; LRR: locoregional recurrence; Surv.: survival; UD: undetected; DRFS: Distant recurrence-free survival; Neg.: negative; Rand.: randomised; PGWBI: Psychologic General Well Being Index; GHS: general health status, NR: not reported; NS: not significant; MV: multivariate; RT: radiotherapy; ART: Axillary RT.

with the probability of the non-sentinel nodal metastasis, and low-volume SLN disease (that is, isolated tumour cells [ypN0i+, <0.2 mm], and micrometastasis [ypN1mi, 0.2-2.0 mm]) does not always require completion ALND (32, 66). However, the potentially chemoresistant disease that persists in the axilla after NAC could not have the same outcomes as in the ACOSOG Z0011, AMAROS, OTOASOR and IBCSG 23-01 trials of upfront surgery (66-69). Thus ALND remains as a standard procedure in patients with low-volume disease and macrometastasis on SLNB who received NAC.

The status of residual disease after NAC is also important for the decision of adjuvant radiotherapy. An updated analysis of NSABP B-18 and B-27 trials demonstrated that 10-year rate of locoregional recurrence (LRR) in patients with clinically axillary positive who remained pathological node positive after NAC was high as between 15% and 22% following ALND and lumpectomy and radiotherapy for breast or mastectomy (120). This finding showed that adjuvant regional radiotherapy in addition to whole breast radiotherapy after lumpectomy and adjuvant radiotherapy for the chest wall and regional radiotherapy after mastectomy should be considered in these patients (120). Whether ALND could be omitted in favour of axillary radiotherapy in patients with positive SLNB after NAC is currently being investigated in ongoing phase III A011202 Alliance trial (121). In contrast, 10-year LRR in NSABP trials has been found 0% in clinically node positive patients who had pCR after mastectomy and had pathological negative node after NAC (ypT0N0) (120). This excellent LRR suggest that the response to NAC could be used in selection of patients for postmastectomy radiotherapy (120). This concept is currently being researched in NSABP B-51/Radiation Treatment Oncology Group (RTOG) 1304 (NRG 9353) phase III randomised trial (122). In this trial, the indication of radiotherapy for axillary or supraclavicular region in addition to whole breast or chest wall in patients with clinically axillary node positive who converted to pathological axillary lymph node negative and had negative SLNB after NAC is being investigated (122).

Axillary treatment is controversial in patients with positive axillary node either by physical examination, axillary ultrasound or fine needle aspiration biopsy. In French GANEA 2 trial, 307 patients from 19

Table 5. False negative rates of SLN biopsy in clinical and biopsy proven node positive patients who converted to clinical negative after neoadjuvant chemotherapy

Prospective studies (Number)	SLN identification rate %	False negative rate %	SLN number and false negative rate % 1	2	≥3	SLN technique and false negative rate %	Single agent Dual agent
SENTINA (592)	80.1	14.2	24.3	18.5	7.3	16	8.6
ACOSOG Z1071 (649)	92.9	12.6	31.5	21	9.1	20.3 6.8 (107 clipped nodes removed as SLN)	10.8
SN FNAC (153)	87.6	8.4	18.2	4.9 *	NR	16	5.2
GANEA2 (307)	80	11.9	19.3	7.8 *	NR		< 10
Enokido et al. (143)	90.9	16					
Donker et al. (100)							
MARI procedure	97	7					
Retrospective studies							
Cabioglu et al. (98)	88	16.7				4.2 (clipped nodes removed as SLN)	
Caudle et al. (208)	NR	10.1				2.4 (with addition of clipped nodes removed as SLN)	
Alvarado et al. (150)	93	20.8	FNR associated with <2 SLN number				
Park et al. (121)	96.7	7.8	NS	22.2	6.1		
Takahashi et al. (46) cN1 converted to cN0	87	27.3					
Shen et al. (64)	93	25					
Meta-analyses							
Fu et al. (2,471) 15 studies	89	14				with IHC 8.7	without IHC 16
El Hage (3,398) Chehade et al. 19 studies	91	13					
Tee et al. (1921) 13 studies	90	14	20	12	4	Single agent 19	Dual agent 11

*Reported as ≥2
NR: not reported; SLN: sentinel lymph node; N: not significant

centers with T2-3 breast cancer who had axillary node positive proved by axillary ultrasound and FNAB and converted to axillary node negative, the SLN detection rate after NAC was 80%, false negative rate (FNR) was 19.3% for 1 SLN and <10% for combined technique or for 2 SLNs (90) (Table 5).

In the three meta-analyses, 2,471, 3,398, and 1,921 patients with metastatic axillary nodes by clinical examination or FNAB who converted to clinically node negative axilla and underwent ALND following SLNB after NAC, the SLNB detection rates were 89%, 91% and 90%, and FNR rates were 14%, 13%, and 14% respectively (104-106) (Table 5). FNR rate dropped under 10% with dual agent or with ≥3 SLN or with IHC (104, 106). The authors reported that SLNB was a viable alternative to ALND (104-106) (Table 5). In the study from Korea which included the data of 5 hospitals, 1,247 patients with positive axillary node by clinically or FNAB who converted to axillary node negative by clinically or ultrasound imaging underwent SLNB or ALND. Of the 428 patients, 263 with positive SLNB underwent ALND, 165 with negative SLNB did not undergo ALND, and 819 patients underwent ALND without SLNB. Comparison of patients with or without SLNB revealed no significant difference in regard to axillary recurrence and distant metastasis-free survival. The findings of this study also demonstrated that SLNB is valid for patients with positive axillary nodes before NAC (119) (Table 4). So far, only one published study by Nguyen et al. (123) reported that axillary recurrence was 0 with a median 9 months of follow-up for 11 patients with metastatic SLNB after NAC who did not undergo ALND and received axillary radiotherapy. In the unpublished study by Kuru et al., there was no axillary recurrence with a median 20 months of follow-up in 19

patients with positive axillary nodes on SLNB after NAC who did not undergo ALND but received axillary radiotherapy (Table 4).

The approaches of SLNB application after NAC according to the current Guidelines are as follows: ASCO early stage breast cancer SLNB Guidelines recommend SLNB in T1/2 tumours, and do not recommend SLNB in T3/T4 patients after NAC (15). NCCN Guidelines recommend SLNB in clinical axillary node negative patients or in patients with clinically axillary node positive before NAC who converted to clinically node negative (74). According to NCCN, SLNB is not feasible for clinical axillary node positive patients after upfront surgery or after NAC. 15. St Gallen Breast Cancer Conference reported the conditions that SLNB is feasible in patients treated with NAC; clinically axillary node negative at initial diagnosis or after NAC and if 2 or more sentinel nodes removed at SLNB in patients with clinically axillary node negative (124). The conclusions from Guidelines are that SLNB is feasible in patients with clinically axillary node negative or in patients with clinically or histologically node positive before NAC who are clinically (by physical examination or radiological imaging) node negative after NAC.

Ongoing trials

Sentinel Node Vs Observation After Axillary Ultra-souND (SOUND) trial at the European Institute of Oncology was designed to investigate whether ultrasound staging of the axilla could replace with SLNB to improve patients' quality of life. Breast cancer patients with clinically node negative axilla by axillary ultrasound or axillary FNAB (cT1N0) were randomised to SLNB ± ALND or axillary observation without axillary staging. Patients with negative SLNB or micrometastasis will not undergo ALND, whereas patients with macrometastasis on SLNB will undergo ALND (125). The POSNOC randomised trial aimed in women with early stage breast cancer with 1 or 2 sentinel node macrometastases, to assess whether adjuvant therapy alone is no worse than adjuvant therapy plus axillary treatment, in terms of axillary recurrence within 5 years. The study will compare adjuvant therapy alone with adjuvant therapy plus axillary treatment (axillary node clearance or axillary radiotherapy) (126).

In patients treated with NAC, two randomised studies began to investigate the role of SLNB and radiotherapy. The AMAROS trial demonstrated that radiotherapy for axilla had similar efficiency as with ALND in the treatment of patients with positive SLNB. The ongoing A011202 Alliance trial is addressing the same question in T1-3 breast cancer patients with biopsy proven axillary node positive who converted to clinically negative after NAC. Patients who had positive SLNB after NAC were randomised to axillary radiotherapy or ALND. This trial investigates whether axillary radiotherapy could replace with ALND in patients with positive SLNB after NAC (121). In NSABP B-51/Radiation Treatment Oncology Group (RTOG) 1304 (NRG 9353) phase III randomised trial, patients with biopsy proven positive axillary node who converted to clinically axillary node negative after NAC underwent SLNB and patients with negative nodes on SLNB were randomised to observation or regional radiotherapy (axillary and supraclavicular). Whether axillary or supraclavicular radiotherapy in addition to breast or chest wall after lumpectomy or mastectomy is required in patents with negative SLNB is being investigated in this trial (122).

In SENOMAC trial, T1-3N0M0 breast cancer patients who underwent upfront surgery or surgery after NAC and had 1, 2 macrometastatic lymph nodes on SLNB were randomised to observation or ALND. The effects of omitting ALND on survival, LRR and morbidity in patients with positive SLNB are being investigated (127). In the study which is being conducted by Kuru et al., whether axillary dissection could safely be omitted in cT1-3N0-1M0 invasive breast cancer patients who had clinically negative axilla (ycN0) and metastatic nodes on SLNB after NAC and received adjuvant radiotherapy for the whole breast or the chest wall, to three axillary levels and the supraclavicular region is investigated (Table 4).

Conclusions

Sentinel lymph node biopsy is the standard procedure for early-stage breast cancer with cT1-2 clinically axillary negative patients. Women without SLNB metastases should not receive ALND. In patients with micro- or macrometastasis on SLNB, axillary radiotherapy successfully replaces the ALND.The arm morbidity rate was significantly lower in patients with positive SLNB treated with breast surgery and radiotherapy for three axillary levels and/or to the whole breast. Axillary dissection could safely be omitted in patients with 1, 2 metastatic nodes on SLNB and without extranodal extension who undergo BCS and whole breast radiotherapy or in patients with metastatic nodes on SLNB who underwent BCS or mastectomy and have adjuvant radiotherapy for the all three axillary levels, the supraclavicular fossa, and ± mammaria interna and/or the whole breast or chest wall. Treatment of breast cancer patients with NAC reduces the need for ALND and surgical morbidity without increasing the risk of LRR. Neoadjuvant chemotherapy often downstages the axillary disease in patients with clinically axillary node negative or positive at initial diagnosis. SLNB after NAC accurately represent the status of axillary lymph node and therefore, could guide the indication of ALND and this approach is associated with a low risk of LRR. In patients with clinically axillary node positive who converted to clinically axillary node negative, SLNB is feasible if more than 2 SLNs are removed or performed with dual tracer, but long term results from patients treated with SLNB alone in this setting are missing. While ALND could be avoided in clinically axillary node negative or in clinical or biopsy proven axillary positive patients who converted to clinical node negative and had at least three negative SLNs or had any negative sentinel node if SLNB is performed with dual tracer after NAC, ALND is the standard treatment for patients with positive SLNB after NAC. In patients with positive SLNB after NAC, axillary radiotherapy instead of ALND according to the ongoing trials could lead to conservation of the axilla and thus could avoid the probable morbidities of ALND.

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