Chapter 20

Internal Mammary Sentinel Lymph Node Biopsy

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Additional information is available at the end of the chapter

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Abstract

The conception of internal mammary sentinel lymph node biopsy (IM-SLNB) has been added to the 2009 American Joint Committee on Cancer breast cancer staging manual. However, there has still been slight variation in the surgical treatment model owing to the low visualization rate of internal mammary sentinel lymph nodes (IM-SLN) with the traditional radiotracer injection technique. According to the hypothesis of IM-SLN, a modified injection technique (periareolar intraparenchymal, high volume, and ultrasound guidance) was established, which could significantly improve the IM-SLN visualization rate, and make the IM-SLNB procedure possible in routine practice. IM-SLNB could provide minimally invasive staging, prognosis, and decision-making individually, especially for the patients with clinically positive axilla lymph nodes. Moreover, radiotherapy targeting on internal mammary lymph nodes (IMLN) should be tailored and balanced between the potential benefit and toxicity, and radiotherapy guided by IM-SLNB could achieve this goal. In the era of emphasizing the effective adjuvant therapy, within the changing therapy approach—more systemic treatment, less loco-regional treatment—oncologist should reconsider the application of regional IMLN therapy.

Keywords: breast cancer, internal mammary lymph node, internal mammary sentinel lymph node biopsy, radiotherapy, lymphatic drainage

1. Introduction

Surgical management of the axilla, however, has undergone a paradigm change since the concept of lymphatic mapping in breast was introduced at the John Wayne Cancer Institute in 1991, and sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) for axillary staging in clinically node-negative early breast cancer. There is a large body of evidence showing that SLNB is an accurate staging procedure in expert hands, and it is now the standard of care for staging clinically node-negative invasive breast cancer.

Furthermore, the results of the ACOSOG Z0011 trial indicated that the patients with a positive axillary sentinel lymph node (ASLN) that may avoid ALND include those with clinical T1–2, N0 breast cancer with one or two positive ASLN who plan to undergo lumpectomy with whole breast radiation and systemic therapy. However, the internal mammary sentinel lymph node biopsy (IM-SLNB) is far behind that of the axilla for the low visualization rate of internal mammary sentinel lymph node (IM-SLN) with the traditional radiotracer injection technique. Based on the hypothesis that the IM-SLN receives the lymphatic drainage from not only the primary tumor area, but also the entire breast organ. The Modified radiotracer injection technique significantly improved the IM-SLN visualization rate, making the routine IM-SLNB possible in daily practice, and further offer individual management for IMLN. In this article, the technical matter, indication and clinical significance of IM-SLNB were discussed, and we would like to identify the breast cancer patients who may benefit from this minimally invasive diagnostic technique.

2. The significant of internal mammary lymph node in breast cancer

In addition to the axillary lymph nodes (ALN), the internal mammary lymph nodes (IMLN) drainage is another first-echelon nodal drainage site in breast cancer [1]. The status of IMLN also provides important regional staging and treatment choice information for breast cancer patients [1, 2]. As reported in the previous studies of extended radical mastectomy, patients with no ALN/IMLN metastases had a 10-year overall survival (OS) rate of 82% compared with 54% for only ALN metastases patients, 38% for only IMLN metastases patients, and 17% for patients with involvement of both nodal, suggesting that regional disease in either nodal chain has the same prognostic relevance [3–5]. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend to strongly consider radiotherapy to IMLN for patients with positive ALN or tumor >5 cm (category 2B), noting "radiotherapy should be given to the IMLN that are clinically or pathologically positive; otherwise, the treatment to the IMLN is at the discretion of the treating radiation oncologist" on this topic.

The nodal status of axillary has been well-established with SLNB and/or ALND in breast cancer patients. However, regional staging and treatment choice could not be achieved just with the ALN status, which might cause under-stage and under-/over-treatment. Handley and Thackray reported that 33% patients had IMLN involvement during survey biopsy, and a back-up IMLN dissection was frequently added to the radical mastectomy starting in the 1950s [6–9]. However, this radical surgical procedure was abandoned due to its extra complications, longer operation time, and lack of survival benefit [10]. Imaging techniques, such as ultrasound, MRI, and PET/CT, could usually detect metastases lesions larger than 5 mm, but due to the deep anatomical location and small size of IMLN, the sensitivity of current imaging techniques cannot satisfy the clinical practice. Therefore, a minimally invasive method is still lacked to evaluate the status of IMLN, and individual IMLN radiotherapy could not be performed.

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3. Modified injection technique with high visualization rate

The IM-SLNB provided a less invasive method for assessing IMLN than surgical dissection (**Figure 1**) and may affect decision-making for regional and systemic therapy [11, 12]. Although the 2009 American Joint Committee on Cancer (AJCC) staging incorporated the IM-SLNB concept, there has been little change in surgical practice patterns due to the low visualization rate of IM-SLN with the traditional radiotracer injection technique [13, 14]. Several studies have discovered that superficial injection (intradermal, subdermal, periareolar, and subareolar) of radiotracer was hard to identify IM-SLN, while intraparenchymal injection (peritumoral, intratumoral, or subtumoral) was more reliable [15–18]. These results suggest that the dermal and subdermal lymphatic flow is rarely directed to the internal mammary region, while some intraparenchymal lymphatic flow is directed to the internal mammary region. Unfortunately, with the traditional intraparenchymal injection technique, the internal mammary hotspots were only seen in a small proportion of patients (average 13%, range 0–37%), which has restricted the clinical studies and daily practice of IM-SLNB to date (**Table 4**) [15–20].

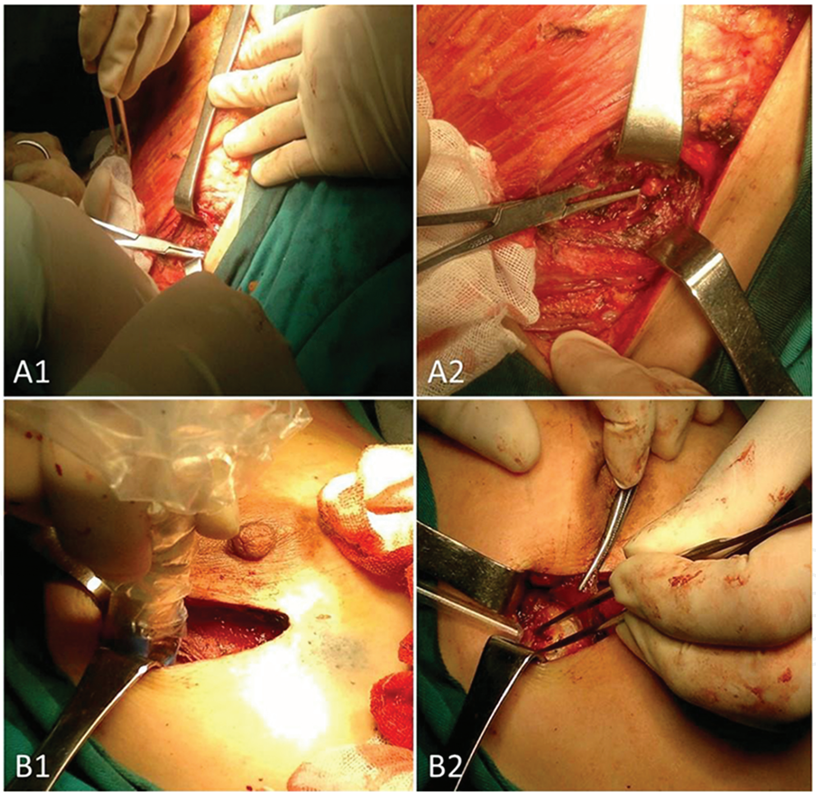

Figure 1. Internal mammary sentinel lymph node biopsy. (A1 & A2 is mastectomy, B1 & B2 is lumpectomy.)

Qiu et al. tried injecting radiotracer with a modified technique (periareolar intraparenchymal, high volume, and ultrasound guidance) and got a high lymphoscintigraphy visualization rate of IM-SLN (71.1%, 248/349) (**Figure 2**) [21, 22]. This might provide a technical feasibility of IM-SLNB, therefore, IM-SLNB could be performed routinely in clinical studies and daily practice and might potentially impact treatment decision-making. However, the basic problem in Qiu's study is the same as all the previous research, because a back up IMLN dissection have not been performed following the IM-SLNB, the accuracy of this minimally invasive technique have not been verified directly. During the IM-SLNB studies, the IM-SLN were concentrated in the 2nd and 3rd intercostal space, which were consistent with the sites of IMLN metastasis in the previous studies of IMLN dissection [6, 10]. These results indirectly confirmed accuracy of IM-SLNB. However, a backup IMLN dissection should be required to validate accuracy of IM-SLNB before its clinical application.

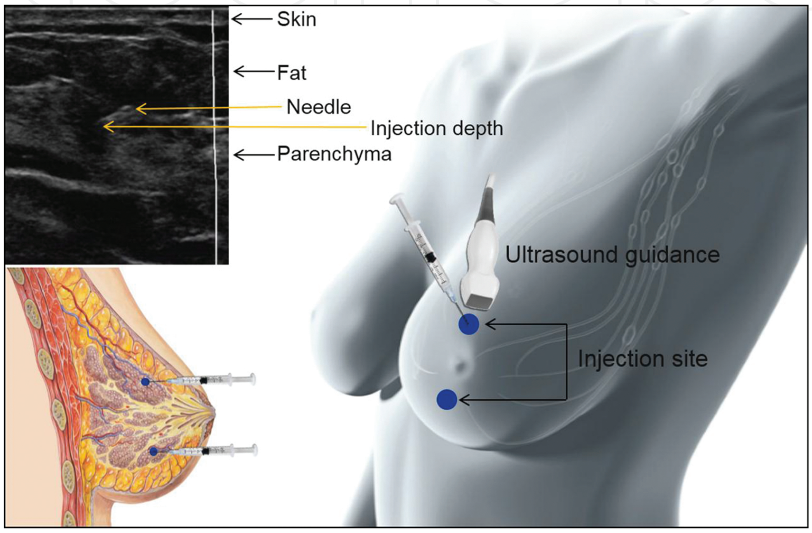

Figure 2. Schematic model of the modified injection techniques.

Additionally, the IM-SLNB is more difficult than axillary SLNB, with success rates of 70–100%. Pleural breach and internal mammary vessel bleeding are the most commonly reported complications from IM-SLNB, occurring in approximately 5% of patients, although pneumothorax and significant postoperative morbidity are rare. Several studies reported the change in clinical management caused by the additional information provided by IM-SLNB [23–28]. IM-SLNB leads to more complete regional staging.

4. Validation study for the hypothesis of internal mammary sentinel lymph node lymphatic drainage in breast cancer

It is generally known that the hypothesis of ASLN lymphatic drainage pattern was proved with subsequent ALND in the breast cancer [29–31]. However, the hypothesis of IM-SLN lymphatic drainage has not been confirmed. As the extended radical mastectomy (included complete internal mammary chain dissection) has been abandoned since 1960s [4, 32, 33], the hypothesis of IM-SLN lymphatic drainage pattern cannot be validated by this way. Now, another method was used to validate the IM-SLN lymphatic drainage hypothesis in our study. Two different tracers (fluorescence tracer [ICG] and radiotracer [^{99m}Tc-labeled sulfur colloid]) were injected in different sites of the intra-parenchyma to observe whether they could reach to the same IM-SLN in the breast cancer patient. In the clinical practice, the ICG fluorescence tracer is a safe and effective method for sentinel lymph node biopsy (SLNB) in the breast cancer with acceptable sensitivity and specificity comparable to conventional methods (blue dye and radioisotope) [34–36]. In our breast cancer center, it has been compared with the combined method (blue dye with radiotracer [^{99m}Tc-labeled sulfur colloid]) in identifying ASLN. The results showed that all ASLN identified by the combined method also were the ICG fluorescence positive and the non-sentinel lymph nodes were the ICG negative after ALND ($n = 69$, $P < 0.05$). The anatomy study of the lymphatics in the breast found that IMLN commonly receive less than 25% of the total lymphatic drainage from the breast [37]. Due to little volume of ICG tracer is difficult to detect by the fluorescence imaging system, it is hard to find IM-SLN by this tracer in the internal mammary lymph chain. But IM-SLN can be detected by radiotracer with the modified radiotracer injection technique and can be performed biopsy in the internal mammary lymph chain guided by this technique. In the validation study of the IM-SLN lymphatic drainage hypothesis, the ICG fluorescence tracer was injected intraparenchymally guided by breast ultrasound at the peritumoral, the radiotracer was injected intraparenchymally with the modified radiotracer injection technique. This method is used to identify different tracers injected in different sites that could reach to the same IM-SLN. The radioactive IM-SLNs were detected by preoperative lymphoscintigraphy (**Figure 3**) 30 min before the surgery and gamma probe during the surgery. IM-SLNB was performed for patients with the radioactive IM-SLNs. After IM-SLN removed, the status of IM-SLN was identified by intraoperative gamma probe and fluorescence imaging system (**Figure 4**). The correlations between the radiotracer and the fluorescence tracer in the same IM-SLN were calculated using the Spearman rank correlation coefficient. The criteria for judging the size of the correlation coefficient were applied: correlations <0.30 are considered minor, correlations between 0.3 and 0.49 are considered medium, and ≥0.5 are considered strong. Cohen's kappa statistic was used to determine inter-examiner agreement. According to Altman's guidelines, it is poor when kappa scores ≤0.20, fair when kappa between 0 and 0.40, moderate when kappa between 0.41 and 0.60, good when kappa 0.61–0.80, and very good when kappa ≥0.80. The results showed that 145 patients underwent IM-SLNB successfully and 127 cases of them identified the radiotracer and the fluorescence tracer reached to the same IM-SLN, 18 cases were detected only the radiotracer positive IM-SLN (**Table 1**). Accordingly, the radiotracer and the fluorescence tracer in the same IM-SLN showed a strong correlation coefficient at 0.836 (*Case-base*, $r_s > 0.5$, $P < 0.05$). The degree of agreement between the radiotracer and the fluorescence tracer was *Kappa* = 0.823 (very good), showing high degree of agreement between the two tracers (*Kappa* > 0.8, $P < 0.05$). The results showed that the lymphatic drainage from different location of the breast (the primary tumor, the subareolar plexus) reached to the same IM-SLN, which means that IM-SLN receives lymphatic drainage from not only the primary tumor area but also the entire breast parenchyma. By this method, the hypothesis of IM-SLN lymphatic drainage pattern was demonstrated [38].

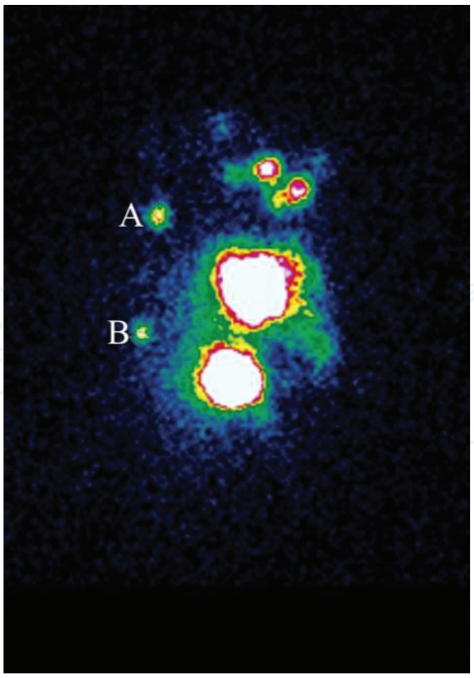

Figure 3. Preoperation lymphoscintigram with radiotracer. Hotspots are evidently shown in both the second intercostal space (A) and the fourth intercostal space (B) in patient with left-sided breast cancer.

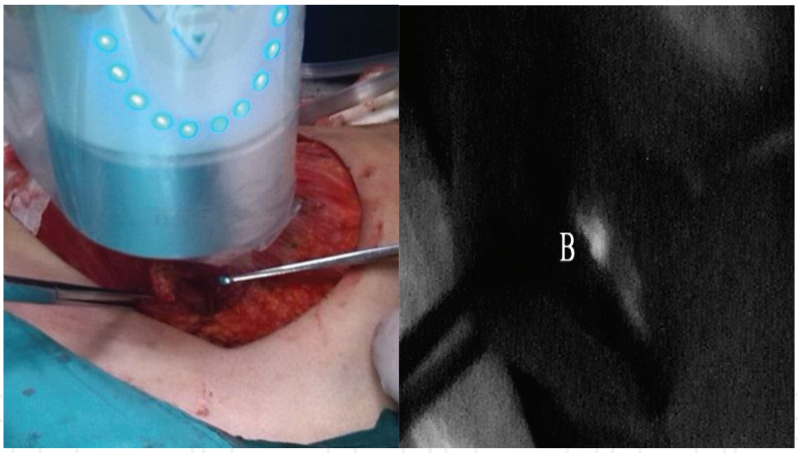

Figure 4. Intraoperative IM-SLNB identified the location of IM-SLN in the fourth intercostal space. The fluorescence imaging system showed the IM-SLN fluorescence tracer positive (B).

Tracers map	Radiotracer+	Radiotracer-	Total
Fluorescence tracer+	127	0	127
Fluorescence tracer-	18	71	89
Total	145	71	216

Table 1. Different tracers identified in IM-SLN.

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Furthermore, the radiotracer was not injected in peritumoral intra-parenchyma but in periareolar intra-parenchyma with the modified technique based on the hypothesis. The question arises as to whether all nodes detected by the modified technique should be considered as "true" IM-SLN or whether some of them are actually "second-tier" IMLN. The accuracy of the modified radiotracer injection technique has been confirmed by our team at the previous study [39]. The results showed that IM-SLN detected by the modified technique could reflect the real lymphatic drainage of the whole breast parenchyma. In other words, the modified technique can detect the "true" sentinel node in the internal mammary chain. Also, the results of the metastases site and the number of IM-SLNs were in accordance with the past study of extended radical mastectomy, which could reflect the accuracy of IM-SLNB indirectly [2, 40, 41]. There were no serious adverse events or reactions after the radiotracer injected guiding by the modified injection technique.

5. IM-SLNB should be performed in clinically ALN-positive patients

Several studies indicated that IM-SLNB have little clinical relevance because tumor-positive IM-SLN rarely influence adjuvant treatment strategy and did not affect overall survival [11, 13]. We agree with these results but it should be interpreted with caution for the limitation of their study population. The study population in all current research relate to SLNB (both axilla and internal mammary) was the patients with clinically negative ALN. Because the IMLN involvement is mostly found concomitantly with ALN involvement [10], more attention should be focused on the IM-SLNB in clinically positive ALN patients. Huang et al. [42] retrospectively analyzed 2269 Chinese patients who received extended radical mastectomy and showed that the probability of IMLN metastases was 4.4% for patients with negative ALN, 18.8% for 1–3 positive ALN, 28.1% for 4–6 positive ALN and 41.5% for more than 6 positive ALN. Veronesi et al. also indicated that the IMLN positive rate increased significantly from 9.1% in negative ALN to 29.1% in positive ALN patients [6]. Qiu reported that the IM-SLN positive rate was only 8.1% in clinically negative ALN patient, and adjuvant therapy was altered in a small proportion. However, the IM-SLN positive rate was 20.5% in clinically positive ALN, and individual radiotherapy strategy could be tailored with this IM-SLNB result [22]. To summarize, previous IM-SLNB research failed to assess the IMLN status who really were in need, we could found the evidence from the above results that the patients with clinically positive ALN could get more benefit from the IM-SLNB. Therefore, Qiu et al. suggested that the IM-SLNB research should be encouraged in the clinically positive ALN patients [43].

6. Internal mammary lymph node radiotherapy of breast cancer

For many patients, improvement of systemic therapy will decrease the risk of death due to distant metastasis, after which the importance of optimized local therapy—which will already be better after systemic treatment—will, relatively, contribute more to survival [44]. Radiotherapy could reduce local recurrence and improve survival after mastectomy and breast conserving surgery [45, 46].

The results of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that one breast cancer death being avoided in the first 15 years after radiotherapy for every four recurrences of any type (i.e., either loco-regional or distant) avoided in the 10 years after radiotherapy for patients with breast conserving surgery. And about one breast cancer death was avoided in the 20 years after radiotherapy for every 1.5 recurrences of any type (i.e., either loco-regional or distant) avoided during the first 10 years after radiotherapy for patients with positive lymph node [46].

The meta-analysis from EBCTCG involved 8135 patients and randomly assigned them to the chest wall and regional lymph nodes radiotherapy after mastectomy and axillary surgery versus the same surgery but no radiotherapy. For 1314 patients with 1–3 positive ALN after ALND, postmastectomy radiotherapy could reduce loco-regional recurrence (LRR), overall recurrence (OR, rate ratio [RR] 0.68, 95% confidence interval [CI] 0.57–50.82), and breast cancer mortality (BCM, RR 0.80, 95% CI 0.67–60.95, all $P < 0.05$). For patients with systemic therapy (86.2%, 1133/1314), postmastectomy radiotherapy also could reduce LRR, OR (RR 0.67, 95% CI 0.55–50.82), and BCM (RR 0.78, 95% CI 0.64–60·94, all $P < 0.05$). Furthermore, for 1772 patients with ≥4 positive ALN after ALND, radiotherapy also could reduce LRR, OR (RR 0.79, 95% CI 0.69–60.90), and BCM (RR 0.87, 95% CI 0.77–70.99, all $P < 0.05$). However, the benefit of postmastectomy radiotherapy might be greater for patients irradiated today because of radiotherapy planning changing substantially and patients receiving better coverage of target areas. Today, with the rapid development of the radiotherapy techniques, the doses to normal tissues would be lower, the risks of radiotherapy would be lower, and the benefits of post-mastectomy radiotherapy would be larger than in these trials. However, due to the improvement of detection and treatment in breast cancer, which makes the absolute risks lower in breast cancer recurrence and mortality, the absolute benefit of postmastectomy radiotherapy today would be smaller than in this study [47].

The MA.20 trial from National Cancer Institute Common Clinical Trials Group found that the addition of regional nodal radiotherapy (including IMLN) to whole-breast radiotherapy reduced the rate of breast cancer recurrence in patients with node-positive or high-risk node-negative breast cancer. A total of 1832 patients were assigned to the nodal-radiotherapy group or the control group (916 patients in each group) in this trial. At the 10-year follow-up, the rates of disease-free survival (DFS) in the nodal-radiotherapy group was better than that in the control group (82.0 vs. 77.0%; [HR] 0.76 [95% CI, 0.61–60.94], $P = 0.01$). But, there was no significant between group difference in OS, with a rate of 82.8% in the nodal-radiotherapy group and 81.8% in the control group (hazard ratio [HR], 0.91; 95% [CI], 0.72 to 1.13; $P = 0.38$) [48].

In the European Organization for Research and Treatment of Cancer (EORTC) 22922/10925 study, a total of 4004 patients were assigned randomly to the regional nodal radiotherapy (included IMLN) group or the control group. At a median follow-up of 10.9 years, the results showed that regional nodal radiotherapy did not change overall survival (OS) (82.3 vs. 80.7%, HR 0.87, 95% CI, 0.76–71.00, $P = 0.06$), but improved DFS (72.1 vs. 69.1%, HR, 0.89, 95% CI, 0.80–81.00, P = 0.04), the distant metastasis-free survival (DMFS) (78.0 vs. 75.0%, HR, 0.86, 95% CI, 0.76–70.98, P = 0.02), and reduced the breast cancer mortality (12.5 vs. 14.4%, HR, 0.82, 95% CI, 0.70–0.97, P = 0.02) [49].

In the French study, all patients received postoperative radiotherapy to the chest wall and supraclavicular nodes and were randomly assigned to receive IMLN radiotherapy or not. A total of 1334 patients were analyzed after a median follow-up of 11.3 years among the survivors. No benefit of IMLN radiotherapy on OS could be demonstrated: the 10-year OS was 59.3% in the IMLN non-irradiated group versus 62.6% in the IMLN irradiated group (P = 0.8). The overestimation of the risk of IMLN involvement (25%) probably decreased the power of the study [50].

Budach et al. did a meta-analysis of the MA. 20, EORTC22922/10925, French trials and the results showed that additional regional radiotherapy to IMLN statistically significantly improves DFS, DMFS, and OS in stage I–III breast cancer. The absolute benefits in 5-year OS were 1.6% in the MA.20 trial, 10-year OS were 1.6% in the EORTC trial, and 10-year OS were 3.3% in the French trial (HR 0.88 [95% CI 0.80–0.97], P = 0.012). Regional nodal (the medial supraclavicular lymph node and IMLN) irradiation (MA.20 and EORTC) was associated with a significant improvement of DFS (HR 0.85 [95% CI 0.77–0.94]) and DMFS (HR 0.82 [95% CI 0.73–0.92]) [51].

The 2016 NCCN Breast Cancer Clinical Practice Guidelines recommend radiotherapy to IMLN for patients with ≥4 positive ALN (category 1), and strongly consider radiotherapy to IMLN for patients with 1–3 positive axillary nodes (category 2A), both after mastectomy and lumpectomy [52].

The DBCG-IMN Study initiated by Danish Breast Cancer Cooperative Group, a prospective population-based cohort study, found that IMLN radiotherapy increased OS in patients with early-stage node-positive breast cancer. A total of 3089 patients were included in the study, 1492 of them received IMLN radiotherapy and others were no IMLN radiotherapy. With a median of 8.9 years of follow-up time, the 8-year OS rates of IMLN radiotherapy group was higher than that in the no radiotherapy group (75.9% [95% CI 73.6–78.0] vs. 72.2% [95% CI 69.9–74.4]; [HR] 0.82 [95% CI 0.72–70.94], P = 0.005). Breast cancer mortality in IMLN radiotherapy group was lower than that in the no radiotherapy group (20.9% [95% CI 18.8–23.0] vs. 23.4% [95% CI 21.3–25.5]; [HR] 0.85 [95% CI 0.73–70.98], P = 0.03) [53].

In sum, IMLN radiotherapy could reduce loco-regional and distant recurrence and improve survival in breast cancer.

7. Internal mammary lymph node radiotherapy guided by internal mammary sentinel lymph node biopsy

Although the 2016 NCCN Breast Cancer Clinical Practice Guidelines recommend radiotherapy to IMLN for patients with ≥4 positive ALN, and strongly consider radiotherapy to IMLN for patients with 1–3 positive axillary nodes, but according to the status of ALN to estimate the metastasis risk in IMLN, low-risk did not mean IMLN negative and high-risk did not mean IMLN metastases [54]. Studies of extended radical mastectomy reported that 38.3% (36.8–46.2%) patients with ≥4 positive ALN, 19.6% (18.8–26.7%) patients with 1–3 positive ALN identified IMLN metastases, and 9.2% (4.4–16.8%) with negative ALN identified IMLN metastases. It is obvious that negative IMLN was found in about 60% patients with ≥4 positive ALN and positive IMLN was found in about 9% patients with negative ALN [33, 42, 55]. Thus, these inclusion criteria of NCCN Guidelines might induce over- and under-treatment. We should use a more accurate technique to evaluate the pathology status of IMLN and to guide IMLN radiotherapy.

The study by Veronesi et al. found that radiotherapy to IMLN will improve the survival obviously after identifying the metastases by IMLN biopsy. In this clinical study of 68 (10.3%, 68/663) patients receiving radiotherapy to IMLN for histologically proven metastases, radiotherapy was highly effective yielded a 5-year OS of 95% [56].

Currently, IM-SLNB via intercostal space could make it possible—tailored IMLN radiotherapy and minimally invasive staging. Even though breast cancer staging has incorporated IM-SLNB concept since the 6th edition of AJCC, IM-SLNB has not been performed routinely [57]. The studies of IM-SLNB showed that the success rate of IM-SLNB has reached 60–100% with minimal or no changes in operative time, but the visualization rate of IM-SLN was low [12–14, 58], which has been the restriction for both clinical study and daily practice of IM-SLNB.

Now, the modified radiotracer injection technique could improve the IM-SLN detection rate from 15.5 to 71% ($P < 0.001$). Also, the visualization number of IM-SLN was no difference between the modified technique group and the traditional tracer injection technique (peritumoral intraparenchymal injection) group in our pilot study ($P = 0.692$). Up to now, 219 patients with breast cancer received IM-SLNB guided by the modified radiotracer injection technique. The clinically pathological characteristics of the 216 enrolled patients are presented in **Table 2**. The detection rate of ASLN was 98.6% (213/216). The overall visualization rate of IM-SLN detected by preoperative lymphoscintigraphy and gamma probe was 71.8% (155/216). 96.1% (149/155) of them received IM-SLNB. The success rate of IM-SLNB was 97.3% (145/149). The data on clinical outcome of the patients underwent IM-SLNB show in **Table 3**. In 12 patients underwent breast conserving surgery, 5 cases who were identified the location of primary tumor could not reach IM-SLNB had to be made an extra incision in the skin to reach IM-SLNB. In patients who performed IM-SLNB successfully, a total of 279 lymph nodes were removed, the median number of IM-SLNs was 2 (range 1–4 nodes). The IM-SLNs were located in the first (5.4%, 15/279), second (46.2%, 129/279), third (40.5%, 113/279) and forth (7.9%, 22/279) intercostal space. All positive IM-SLNs were in the second (61.1%, 11/18) and the third (38.9%, 7/18) intercostal space. 54.1% (151/279) of IM-SLN was found in the outside of the internal mammary vessels and 45.9% (128/279) was in the inside. Details of IM-SLN mapping and biopsy are shown in **Table 4**. The IM-SLN involvement rate was 8.1% (7/86) in patient with clinically axillary node negative patients and 18.6% (11/59) in positive patients, respectively. All patients with positive IM-SLN received regional nodal radiotherapy to IMLN. The clinical, pathological, and treatment details of these patients were shown in **Table 5**. In patients with ≥4 positive axillary lymph nodes, regional nodal radiotherapy to IMLN had been avoided in

50.0% cases (9/18) with negative IM-SLN. In patients with 1–3 positive axillary lymph nodes, regional nodal radiotherapy to IMLN might be avoided in 91.2% cases (52/57) with negative IM-SLN.

Characteristic	No.	%
Age (years)		
Median	50	
Range	27–79	
≤50	119	55.1
>50	97	44.9
BMI		
Median	24.1	
Range	17.2–33.5	
Tumor size		
Tis	16	7.4
T1	99	45.8
T2	79	36.6
T3	22	10.2
Tumor location		
UOQ	92	42.6
LOQ	25	11.6
UIQ	48	22.2
LIQ	5	2.3
Central	46	21.3
Tumor type		
Ductal	187	86.6
Lobular	8	3.7
Mixed	5	2.3
Other	16	7.4
Radiotracer intensity (MBq)		
Median	36	
Radiotracer volume (mL/point)		
Median	0.5	
Intervals from injection to SLNB (h)		
2–5	89	41.2
16–22	127	58.8

Abbreviations: BMI, body mass index: UOQ, upper outer quadrant; LOQ, lower outer quadrant: UIQ, upper inner quadrant; LIQ, lower inner quadrant.

Table 2. Descriptive characteristics of eligible patients (N = 216).

Characteristic	No.	%
T stage		
Tis	9	6.2
T1	70	48.3
T2	57	39.3
T3	9	6.2
N stage		
N0	70	48.3
N1	57	39.3
N2	7	4.8
N3	11	7.6
ER		
Positive	101	69.7
Negative	44	30.3
PR		
Positive	98	67.6
Negative	47	32.4
HER-2		
Positive	44	30.3
Negative	101	69.7
Type of surgery		
Lumpectomy + ASLNB	9	6.2
Lumpectomy + ALND	3	2.1
Mastectomy + ASLNB	93	64.1
Mastectomy + ALND	40	27.6
Radiotherapy		
WBI	7	4.8
WBI + RNI	5	3.5
PMRT + RNI	79	54.5
No	54	37.2
Chemotherapy		
Yes	121	83.4
No	24	16.6

Abbreviations: ER, estrogen receptor status; PR, progesterone receptor status; HER-2, human epidermal growth factor receptor-2; WBI, whole breast irradiation; RNI, regional node irradiation; PMRT, postmastectomy radiotherapy.

Table 3. Clinical outcome of patients who underwent IM-SLNB (N = 145).

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Characteristic	No.	%
IM-SLN map+	155	71.8 (155/216)
Pt. performed IM-SLNB	149	96.1 (149/155)
Success rate of IM-SLNB	145	97.3 (145/149)
Total no. of IM-SLN	279	
Median	2	
Range	1–4	
IM-SLN metastatic	18	12.4 (18/145)
IM-SLNB time (min)		
Median	10	
Range	3–55	
IM-SLN size (mm)		
Median	5	
Range	3–12	

Table 4. Details of IM-SLN mapping and biopsy.

No.	Tumor location	T stage	No. of positive ALN	N stage without IM-SLN	No. of positive IM-SLN	N stage with IM-SLN	Finally stage	Chemo-therapy	Radio-therapy
1	UOQ	T2	0	pN0	2	pN1b	IIA→IIB	Yes	No→Yes
2	UIQ	T2	2	pN1a	1	pN1c	IIB (no change)	Yes	? →Yes
3	Central	T2	14	pN3a	1	pN3b	IIIC (no change)	Yes	Yes
4	UOQ	T2	9	pN2a	1	pN3b	IIIA→IIIC	Yes	Yes
5	UIQ	T1c	2	pN1a	1	pN1c	IIA (no change)	Yes	? →Yes
6	UOQ	T2	1	pN1a	1	pN1c	IIB (no change)	Yes	? →Yes
7	UIQ	T1a	0	pN0	1	pN1b	IA→IIA	No→Yes	No→Yes
8	UOQ	T2	9	pN2a	2	pN3b	IIIA→IIIC	Yes	Yes
9	LIQ	T2	5	pN2a	1	pN3b	IIIA→IIIC	Yes	Yes
10	UOQ	T1a	3	pN1a	1	pN1c	IIA (no change)	Yes	? →Yes
11	UIQ	T2	0	pN0	1	pN1b	IIA→IIB	Yes	No→Yes
12	UOQ	T3	13	pN3a	1	pN3b	IIIC (no change)	Yes	Yes
13	Central	T1c	1	pN1a	1	pN1c	IIA (no change)	Yes	? →Yes
14	UOQ	T2	13	pN3a	1	pN3b	IIIC (no change)	Yes	Yes
15	Central	T2	11	pN3a	1	pN3b	IIIC (no change)	Yes	Yes
16	UOQ	T2	20	pN3a	1	pN3b	IIIC (no change)	Yes	Yes
17	UOQ	T2	5	pN2a	1	pN3b	IIIA→IIIC	Yes	Yes
18	UIQ	T1c	0	pN0	1	pN1b	IA→IIA	No→Yes	No→Yes

Abbreviations: UOQ, upper outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; ?, radiotherapy is controversy.

Table 5. The clinical, pathological, and treatment details of patients with positive IM-SLN.

8. Conclusion

Modified injection technique (two-quadrant, high volume, and ultrasound guidance) could significantly improve the detection rate of IM-SLN and would promote research on IM-SLNB. The hypothesis of IM-SLN lymphatic drainage pattern was demonstrated. As IMLN metastasis is mostly concomitant with ALN metastasis, IM-SLNB should be encouraged in clinically positive ALN patients. IM-SLNB should be performed routinely, for it could lead to accurate IMLN staging and provide IM-SLNB guided IMLN-RT.

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Abbreviations

ALN = axillary lymph nodes

IMLN = internal mammary lymph nodes

SLNB = sentinel lymph node biopsy

IM-SLNB = internal mammary sentinel lymph node biopsy

IM-SLN = internal mammary sentinel lymph nodes

SLN = sentinel lymph nodes

OS = overall survival

DFS = disease-free survival

DMFS = distant metastasis free survival

ALND = axillary lymph node dissection

NCCN = National Comprehensive Cancer Network

EBCTCG = Early Breast Cancer Trialists

Collaborative Group

EORTC = European Organization for Research and Treatment of Cancer

ASLN = axillary sentinel lymph node

ICG = indocyanine green

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