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RESEARCH ARTICLE

Multi-tracer sentinel node biopsy for patients with breast cancer after neoadjuvant chemotherapy

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ABSTRACT

Background: For post-neoadjuvant chemotherapy patients with breast cancer, sentinel lymph node biopsy (SLNB) was recommended using the dual-tracer mapping technique (radioisotope plus blue dye) or placing a biopsy clip into the positive node at diagnosis and identifying it at the time of surgery due to SLN identification rates were lower and false negative rates were greater for patients with local advanced BC than those of patients with early-stage BC in the absence of NAC. Our previous clinical trial has indicated that the real-time ICG fluorescence (RT-ICG) imaging technique could improve the diagnostic sensitivity and detection accuracy for SLNB.

Methods: The SLNs was detected by conventional procedures of blue-dye (Indigo carmine) plus 99mTc radioisotope (dual-tracer) and combined with concurrent RT-ICG technique. The positivity of each single SN by each single tracer (blue dye, ICG, or radioisotope alone) was counted and identified, respectively. 51 enrolled cN1patients after NAC are required to undergo SNB followed by completion axillary lymph node dissection (CND). The identification rate and false negative rate of each single tracer and their summation (triple tracer) were calculated by comparing the results of the SLNB and the histopathology of the resection specimens of CND.

Results: post-neoadjuvant patients, the identification rate and false negative rate of each single procedure for SLNB was 84.3% and 5.9% when used Indigo Carmine blue, 94.1% and 0 when used ICG fluorescence, 92.2% and 3.9% when used RI, respectively. In contrast, the total calculation of triple tracer showed that identification rate reached to 96.1% and false negative rate was 0, respectively.

Conclusions: Our results suggested that the multitracer technique combining blue dye, ICG, and radioisotope is effective method for detection of SLNs in post-neoadjuvant cN+ BC pts. The identification rate and false negative rate of SLNB might be improved by this multiple tracer mapping technique, particularly for patients with ypN(+) after NAC. It is considered that the multi-tracer can complement each other for what was not able to be traced and detected by the single tracer with one mapping material, and that result in totally the improvement of identification rate of SLNB.

Keywords: breast cancer, neo-adjuvant chemotherapy (NAC), sentinel lymph node biopsy (SLNB)

Introduction

Despite the use of sentinel lymph node biopsy (SLNB) has been supported by current guidelines for node negative (cN0) patients either before or after neoadjuvant chemotherapy (NAC) setting, SLNB is not strongly recommended for patients with node-positive(cN+) operable breast cancer (BC) who become clinically node negative (ycN0)[1-3]. Although evidences showed that patients with initially cN1 become to ycN0 after NAC, who had identification of three or more SLNs and nodal pathologic complete response (pCR), could be able to avoid axillary lymph node dissection (ALND). The prospective clinical trials have reported that these patients tended to have lower SLN identification rate (IR), and higher false-negative rate (FNR). Several trials indicated that the accuracy of SLNB increased with the number of SLNs detected, and the FNRs were consistently less 10% when three or more SLNs were detected and removed by dual tracer mapping technique[4-7]. However, the role of SLNB in node positive patients and the optimal surgical approach in the axilla after NAC continues to be controversial for discussion[8,9]. The aim of this study is to discuss and report here the clinical evidence about the techniques of SLNB using multitracer and present our early experience regard of SLNB setting for patients with node positive (cN+) breast cancer after NAC using the procedure of blue-dye plus real-time Indocyanine green (ICG) fluorescence imaging combined with radioisotope.

Background:

The procedure of SLNB is a standard treatment as a de-escalation method of axillary surgery for node-negative patients with early-stage breast cancer. The meta-analyses in initially clinically node-negative (cN0) breast cancer patients after NAC have demonstrated the feasibility and accuracy of SLNB. Based on the current practice guidelines, SLNB after NAC is a reasonable surgical procedure for patients with cN0 before NAC for staging axillary status, and the clinical outcome could be comparable to cN0 patients who did not undergo NAC[1,3]. However, SLNB or fine needle aspiration cytology (FNAC) usually performed before NAC in initially cN0 patients for reducing the potential influence of NAC.

Since evidence from recent numerous clinical trials, the use of SLNB after NAC for initially node-positive patients (cN+) has gradually increased[10-14], but the accuracy and feasibility of SLNB after NAC remain be challenged including weather and how often axillary lymph node dissection (ALND) can be avoided for cN+ patients presenting ycN0, because of the tumor regression and/or the eradication of axillary metastatic SLN after NAC could possibly change lymphatic drainage pathway due to the fibrosis of lymphatic channels and lead to a decreased identification rate (IR) and an increased false negative rate (FNR) of SLNB in these cases[15,16]. Moreover, the data from most clinical trials for cN+ patients who received NAC indicated that the FNR of SNB were also greater than those identified when SLNB is performed before chemotherapy, and the combination of blue dye (BD) and radioisotope has been recommended for increasing the IR and accuracy of SLNs after NAC[17].

In patients with biopsy-proven node-positive (cN+) of the ACOSOGZ1071, there were found no SLN in 7% and only one SLN in 12% after NAC. The observed FNR was 31.5% when only one SLN was detected and 12.6% when two or more were tested[18,19]. And SENTINA [Sentinel Neoadjuvant] study also demonstrated an IR

of 80% and an FNR of 14.2% in cN+ patients who were found to have ycN0 after NAC, furthermore, the FNR was observed as high as 24.3% in those with only one SLN removed[20]. The meta-analysis of published studies for node positive breast cancer after NAC showed that IR ranged from 78% to 98% (overall, 89%), whereas the FNR ranged from 5% to 25% (overall, 14%)[21]. (Table 1) Therefore, the use of SLNB after NAC setting would be an important consideration supported by novel procedures with the higher IR and lower FNR. Beside of the clinical factors including the initial primary tumor size and axillary node status of the patients with breast cancer could impact SLN identification after NAC, the methods of lymphatic mapping could be an important factor affecting IR of SLN, most studies showed that the IR of SLNB after NAC was higher when lymphatic mapping was performed using radioisotope combined with BD (dual tracer) than with either radioisotope or BD alone (single tracer). Currently, SLNB mapping after NAC using dual tracers was usually associated with higher IR and lower FNR, whereas use of single-agent radioisotope or blue dye with inadequate IR and FNR. However, the overall IR and FNR of SLNB which were reported in three major prospective clinical trials after NAC by using the dual tracers were 87.8-93.8 % and 5.2-10.8 %, respectively[18,20,22]. (Table 1)

Table 1. Clinical studies of sentinel lymph node biopsy (SLNB) in patients with node positive breast cancer after neoadjuvant chemotherapy

Clinical trail	SN FNAC (2015)	ACOSOG (Alliance) (2013)	SENTINA (2013)
No. of patients	153	637	226 (Arm C)
Requirement of biopsy-proven SN metastasis	YES	YES	NO
No. of removed SLN after NAC (mean or median)	2.7 (mean)	1 (at least)	2 (median)
Overall IR (%)	87.6	92.9	80.1
IR using Single tracer (%) Blue dye Isotope	 NC# 31.1*	 78.6 91.4	 NC# 77.4
IR using Dual tracer (%)	69.9 *	93.8	87.8
Overall FNR (%)	8.4	12.6	14.2
FNR using Dual tracer (%)	5.2	10.8	8.6
FNR using Single tracer (%)	16	20.3	16
FNR by No. of SNs removed (%)			
1	18.2	29.3	24.3
2	9.5	21.1	38
≥ 3	2.5	9.1	7.3
pCR rate after NAC (%)	34.5	41.0	52.3
Year of publication	2015	2013	2013

* SN identification for positive metastatic node.

did not counted

Advances since early 2000 in the development of image guide SLNB using Indocyanine green (ICG) have resulted in significantly improved SLN identification comparing to use of BD or isotope alone as a new standard procedure for patients with early breast cancer [23-25]. But little information is available on the SLNB using ICG-guided technique as well as that combined with conventional BD or radioisotope after NAC in patients presenting with nodal metastases.

Based on these concepts, the technique of multi-tracer for SLNB after NAC may provide more options and increase probability for searching residual SLN declined by treatment prior to the surgery such as NAC. Moreover, the development of novel mapping techniques including use of multiple tracer system may be important for increasing IR and reducing the FNR. And we focus on the aspect for the detection of residual lymphatic vessels in patients with cN+ breast cancer receiving NAC and conduct the clinical study to exam the IR and FNR of SLNB after NAC by the multi-tracer technique using radioisotope combined with the mixture of BD (Indigo Carmine dye) and ICG (Indocyanine green).

Methodology:

Between April 2017 and May 2022, patients with early-stage BC were enrolled in this clinical observation study. Baseline demographic and clinical characteristics of the 51 participants with cN+ before receiving NAC are shown in Table 2, and this multi-tracer technique has been performed for SLNB mapping in 79 patients with early breast cancer (T1-2, N0) and in 51 with node-positive patients receiving NAC (T1-3, N1).

In this study, BD mixed with ICG solution and radioisotope ^{99m}Tc solution were injected into the sub-areolar region of the breast intraoperatively and in the day before operation, respectively. The surgical SLNB was guided by BD stained green and shiny ICG fluorescence using the real time color ICG imaging system (HyperEye Medical System, MIZUHO, Japan)[23]. The cN+ patients after NAC are required to undergo SLNB followed by completion node dissection. The SLN was defined as the BD staining node, the hottest node with highest count by gamma probe, or with counts of > 10% of those of the hottest node, and any shiny blue node detected by real time ICG imaging, or any palpable suspicious node.

Results:

We found that use of the multi-tracer technique was able to detected more SLNs after NAC than use of each single tracer of the BD, ICG or isotope alone. Each IR calculating for nodes with BD staining, shiny ICG imaging and radioisotope reactive were 97.4% (77/79 cases), 100% (79/79 cases) and 91.1% (72/79 cases) in patients with operable early breast cancer, respectively. The high IRs were accomplished for cN0 patients by each technique of single tracer similar to subsequent studies. In contrast, although the positive rate based on total detected number of SLNs were 54.5% (79/145 SLNs) by BD staining, 96.6% (140/145 SLNs) by ICG imaging and 80% (116/145 SLNs) by radioisotope reaction, and the total account of positive SLN rate reached to 97.2% (141/145 SLNs). On other hand, the IRs were 84.3% (43/51 cases) of BD staining, 94.1% (48/51 cases) of ICG imaging and 92.2% (47/51 cases) of radioisotope reaction in patients receiving NAC, respectively, the total account of IR reached to 96.1% calculated positively by any or all of the three tracers in patients receiving NAC as

well as in patients who did not undergo NAC. (Table 2.) Furthermore, the FNR of each single procedure for SLNB was 5.9% when used Indigo Carmine blue, 0 when used ICG fluorescence, 3.9% when used RI, respectively. In contrast, the total calculation of triple tracer showed that FNR was 0, respectively. (Table 2.)

Table 2. Patients Characteristics and SLN identification rate (IR) after neo-adjuvant chemotherapy (NAC)

Number of patients	51				
Median Age(years old)	55				
Stage I/IIA/IIB/III/IV	2	19	18	8	4
Subtypes					
HR(+) HER2(-)	18				
HR(+) HER2(+)	6				
HR(-) HER2(+)	8				
TNBC	19				
NAC regimen (cases)					
Anthracyclin	32				
Taxane	16				
Anthracyclin, Taxane +/- Trastuzumab and Pertuzumab	14				
Operation *					
Mastectomy (Bt)	25				
Partial mastectomy (Bp)	22				
Nipple-areola-sparing mastectomy (NSM)	2				
Bt+reconstructive surgery	2				
SLN identification rate (IR) after NAC	**Blue-dye staining**	**ICG imaging**	**Radioisotope reaction**	**Triple tracer**	
IR (%) based on positive numberof SLN /total number of SLN	54.5 (79/145)	96.6 (140/145)	80 (116/145)	97.2 (141/145)	
False negative rates (%)	50	0	31.2	6.3	
IR (%) based on positive number of patients/ total number of patients	84.3 (43/51)	94.1 (48/51)	92.2 (47/51)	96.1 (49/51)	
False negative rates (%)	5.9	0	3.9	0	

*: The cN+ patients after NAC are required to undergo SLNB followed by completion node dissection.

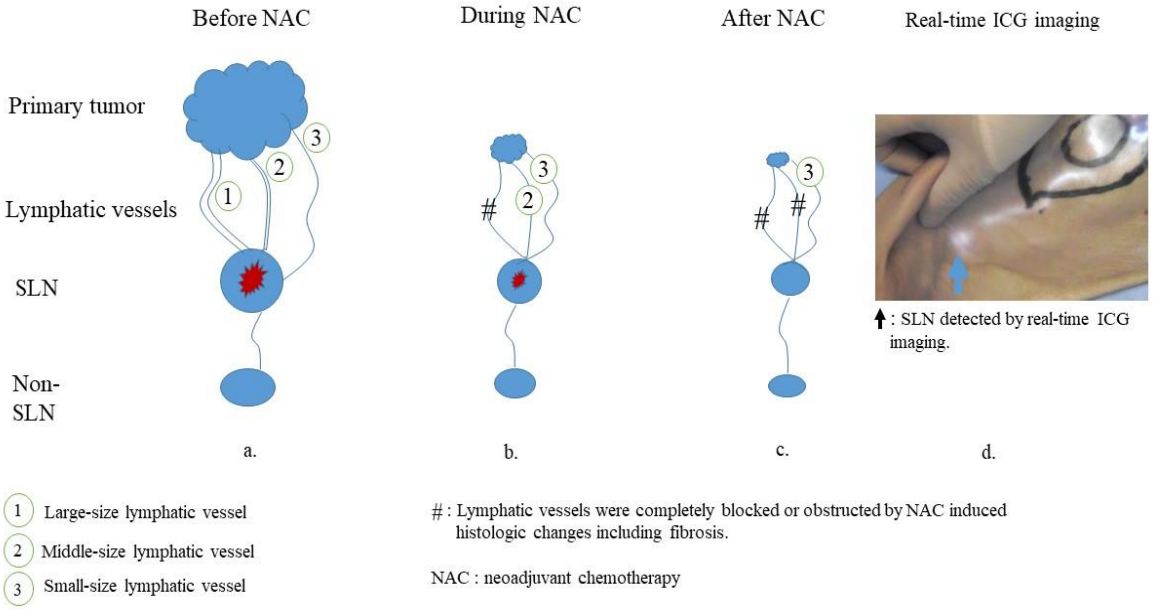
Discussion:

Because of NAC may induce theoretically histological changes at the sites of both the lymphatic drainage channels and the involved regional axillary lymph nodes in cN+ patients. The effect of cytotoxic chemotherapies for large and bulky breast cancer may induce fibrosis of lymphatic drainage channels and result in the shrinkage or constriction of lymphatic vessels that link to the involved regional ALNs, and these histological changes after NAC mostly accompanied by a foamy histiocytic infiltrate, calcifications, fat necrosis, and hemosiderin deposition were observed at the of both the primary tumor and the regional ALNs with partial or complete pathological response[26,27]. These pathological changes in the microenvironment surrounding tumor and the axilla could explain why the IR and FNR of SLNB remain inconsistent in patients after NAC, although these possibilities have not yet been fully identified[28].

Despite the treatment effects were observed in SLNs of most patients received NAC, whereas only in 3% of the patients without the NAC effect[29,30], there have been reported that SLN locations were not influenced by NAC in either cN+ or cN0 patients, even the lymphatic pathway could be changed by the damage due to NAC[31]. In spite of the lymphatic mapping materials after NAC may diverted from original lymphatic vessels to other non-sentinel lymph nodes in the axilla when lymphatic vessels were completely blocked or obstructed by NAC induced histologic fibrosis, but when these histologic changes by the chemotherapeutic toxicity were incompletely, and that only resulted in a partial obstruction of lymphatic pathways, or the large size lymphatic vessels could be narrowed, some tracer materials may be transported or bypassed to the SLN through residual pathways of damaged lymphatic vessels. (Figure 1) Otherwise several studies have demonstrated the rate of tracer materials transport through the lymphatic vessels is directly associated to their particle size. Small particles with a diameter in less than 4–5 nm have been reported to penetrate capillary membranes and may be difficult to migrate through the lymphatic vessels and larger particles do not pass easily through the lymph node site[32,33]. Therefore, the ideal tracer materials for SLNB of breast cancer should also comprise particles with an appropriate size for travelling through lymphatic vessels and achieving high retention in the subsequent lymph nodes including SLN. Although the BD such as Indigo carmine and Isosulfan blue or Patent blue containing a smaller molecular have been considered with more than 90% localization rate in the SLN of breast cancer[34,35], the efficiency of this material migrating through the lymphatic vessels damaged by NAC induced histological changes is unclear. However, ICG has previously been demonstrated to rapidly and completely bind to albumin in plasma as well as in lymph tissue, albumin is preferentially taken up into lymphatics and drained to regional lymph nodes after a dermal injection. Although the albumin binding affinity of ICG in the tissues could be a limiting factor in ICG uptake into lymphatic vessels, and histological fibrosis or fat deposition after NAC can change the flow of lymphatic vessels, without or less effect on the ability of ICG bound with albumin, which may relate to high passage rate for infiltrating lymphatic channels as well as to keep high localization of the lymph nodes even after NAC[36,37]. In contrast, the tracer particles

of radiocolloidal isotope (^{99m}Tc labled colloid) using for lymphatic mapping of SLNB generally have a size of between 31 to 180 nm, and the size of the radioactive sulfide colloidal particles in clinical practice has been reported with a high, wide range of molecular size, up to 1000 nm[32,38,39]. Further, as the colloidal particles are not uniformly sized with chemical heterogeneous, the concentrations of particles penetrating and travelling into environment surrounding the tumor and axilla will be unreliable and that may result in a variety in the sensitivity of SLN detection. The conditions for transporting tracer particles after NAC, which induce histological changes such as tissue fibrosis and inconsistent permeability of the vessel environment, may result an instability of IR and accuracy for SLNB in patients received NAC compare to who did not receive that. Presuming when the original large lymphatic vessels surrounding primary tumor are destroyed by NAC induced histological changes including tissue fibrosis, the tracer material with relative large particles such as radiocolloid isotope (^{99m}Tc labelled colloid) could be difficultly passed through the narrowing damaged lymphatic vessels to the SLN after NAC , but that may be possible for the small molecules such as ICG for passing though remained middle or small vessels surrounding the tumor or axilla and the multiple mapping materials may have more opportunity for the tracking and the detection of SLN by using multiple tracer techniques after NAC. (Figure 1-b, c)

Figure 1. The lymphatic vessels after neoadjuvant chemotherapy.



Therefore, with the definition of SLN after NAC as that which was BD stained, ICG fluorescence reactive and radioactive or all, the technique using the multiple tracers of BD combined with ICG in addition to radioisotope had extremely high identification of at least one or more SLNs in all patients either with cN0 or cN+ after NAC. A previous report from our hospital described the early experience using this multiple tracer technique for nine consecutive node-positive patients receiving NAC and indicated that use of the combination

of those tracers was able to detected in all 9 patients with median number of 3 SLNs (range: 1-8) after NAC than use of each single tracer of the BD, ICG or radioisotope alone [40].

It is considered that the multi-tracer can complement each other for what was not able to be traced and detected by the single tracer with one mapping material, and that result in totally the improvement of identification rate of SLNB.

Conclusions

Recent evidences have also demonstrated that the use of the dual tracer techniques with blue dye combined RI by conventional imaging of the axilla after NAC, removing more than 2 sentinel nodes, and marking the suspected positive node with a clip of marker or by tattooing before NAC and subsequent removal of the clipped node in addition to the SLNB lead to lower the FNR and improve accuracy[29,41]. Moreover, a similar marking technique for the suspicious axillary lymph node with radioactive iodine seeds (MARI procedure) has also been reported with low FNR, which allowed its removal as a marker of chemotherapy response in a similar procedure to SLNB[42-44]. Otherwise, the addition of immunohistochemistry to conventional histopathological evaluation has been indicated that a more completely histological analysis to examine isolated tumor cells and micrometastases may also improve the FNR[21,22]. However, the clinical study on mapping technique of SLNB using the multi-tracer to compare to that using dual tracers or single tracer for SLNB after NAC is still limited. Our ongoing study investigate whether the SLNB technique of the multiple tracers using radioisotope combined with the mixture of blue dye and ICG will be more optimized and refined method for improving the FNR and IR in cN+ patient population. The results of this study should be validated in future by the large-scale prospective studies and the clinical prognosis warrants a long-term follow-up.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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