CHAPTER

15

TIMING OF THE SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER PATIENTS RECEIVING NEOADJUVANT THERAPY – RECOMMENDATIONS FOR CLINICAL GUIDANCE

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European Journal of Cancer, 2013

ABSTRACT

Neoadjuvant chemotherapy (NCT) is an increasingly important component in the treatment of both locally advanced and early-stage breast cancer. With this, a debate on the timing of the sentinel lymph node biopsy (SLNB) has emerged. At the end of the last century, the SLNB was introduced as an axillary staging modality, and this paper aims to further elucidate this issue in the context of NCT. We compiled available data on the SLNB after NCT and provide clinical guidance for the timing of the SLNB in this context. On the basis of our findings, we recommend that the SLNB can be performed after NCT in all cases. In patients with a clinically node-negative (cN0) status prior to NCT, the SLNB should be performed after NCT, and in case of a histologically confirmed negative SLNB, a completion axillary lymph node dissection (ALND) has no added value and can be omitted. In patients with clinically positive nodal involvement (cN+) prior to NCT, all axillary surgery can also be performed after NCT.

INTRODUCTION

Nodal status is one of the most important determinants of breast cancer prognosis.[1, 2] Axillary staging is successfully achieved by sentinel lymph node biopsy (SLNB), [3, 4] followed by a completion axillary lymph node dissection (ALND) in patients with proven sentinel node metastases. Needless to say, the SLNB is a means of staging and not a treatment modality. Earlier, some have questioned the need for completion ALND in patients with sentinel lymph node (SLN) involvement[5, 6]; about half of the patients with a positive SLN are known to have additional axillary nodal involvement[7-9], and even in case of omitting an ALND, the risk of developing an axillary recurrence in the presence of a positive SLN is less than one per cent.[10]

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was initiated to investigate whether there were differences in axillary recurrences and survival in patients who underwent a completion ALND versus a SLNB alone.[11] In 2009 Bilimoria and colleagues investigated differences in axillary recurrences and survival in women with histologically confirmed node-positive breast cancer who underwent a SLNB with or without ALND.[5] All had clinically node-negative (cN0) disease. After a median follow-up of 63 months, there were no differences in axillary recurrence and survival for SLNB alone versus ALND. Even when assessing micrometastases and macrometastases separately, no differences were found in axillary recurrence and overall survival.[5] Despite evidence pointing towards equally good outcomes in terms of recurrence and survival when the ALND is withheld, we still largely perform a completion ALND in patients with a positive SLNB.

In the context of neoadjuvant chemotherapy (NCT), a similar debate has emerged on the subject of the appropriate use and optimal timing of the SLNB. Multiple studies confirm downstaging of the tumor and the axilla during NCT, increasing the likelihood of less extensive surgery.[12, 13] At present, one school of thought advocates performing a SLNB before commencing NCT, while the latter proclaim that the SLNB can be safely performed after completion of the NCT regimen. With the increasing use of NCT, clinicians are currently short of sound clinical guidelines for the management of the SLN in the context of NCT. The objective of this study was to aggregate available data on the SLNB after NCT and to provide clinical guidance for timing of the SLNB in the context of NCT.

METHODS

Search strategy

The databases Pubmed and Medline were searched until May 1st 2012 using free text and MeSH (Medical Subject Headings) terms for “breast cancer”, “Neoadjuvant chemotherapy” and “sentinel lymph node biopsy”. Only papers written in English were eligible. Included, were original studies in which accuracy or feasibility of the SLNB after NCT in invasive breast cancer was evaluated. There were no restrictions with regard to clinical nodal stage or tumor size. Completion of an ALND after a SLNB was mandatory for inclusion. Additionally, references of the included papers, and of three meta-analyses[14-16] and a systematic

review were checked.[17] Abstracts and data solely presented at conferences were excluded. In case of an update of previously published data, the most recent publication was chosen to be included.

Data extraction

For all included studies we recorded year of publication, number of patients, inclusion period, inclusion criteria, clinical nodal status, type of NCT, and conclusions made by the authors. For reason of comparison, accuracy parameters were calculated using a standard definition, and comprised 1) sentinel node identification rate (IR), 2) false negative rate (FNR), and 3) overall accuracy. IR was calculated as the number of patients with a successful SLNB divided by the total number of patients in whom a SLNB was attempted. True positive SLNB was defined as the number of patients with a positive SLNB, with or without additional positive lymph nodes at ALND. True negative SLNB was defined as the number of patients with a negative SLNB which was confirmed by a negative ALND. A false negative SLNB was defined as the number of negative SLNBs with a positive ALND. FNR was calculated as false negative / (true positive + false negative). Accuracy was calculated as (true positive + true negative) / number of patients with a successful SLNB. Whenever possible, these numbers were also calculated for subgroups based on nodal status. Weighted means were calculated based on the number of patients in each study.

RESULTS

A total of 40 original studies were retrieved for analyses, including 3328 patients. The studies were published between 2000 and 2011, and patients were included between 1994 and 2009. As some studies published data on various subgroups of patients along with overall accuracy data, these studies were included more than once. Results are shown by clinical nodal status before and after NCT.

Node-negative before NCT

An overview of the 17 studies including 1738 patients who were clinically node-negative (cN0) prior to NCT (pre-NCT) is shown in Table 1. The studies were published between 2001 and 2009, patients were included between 2001 and 2007. Mean sentinel lymph node IR was 95.0% (range 83.3%-100%); mean FNR was 11.4% (range 0%-28%); mean overall accuracy was 95.6% (range 80.6%-100%).

In patients who were cN0 prior to NCT, performing a SLNB after NCT was determined to be accurate in 14 out of 17 studies (Table 1). Three studies concluded otherwise.[18-20] The study by Papa and colleagues prospectively investigated performing a SLNB before NCT versus after NCT and found a significantly lower IR (87% versus 100%, $p<0.05$) and higher FNR (15.8% versus 0%, $p=0.04$) in patients who underwent a SLNB after— versus before NCT.[19] The other two studies found comparable higher FNRs.[18,20]

Table 1. **Overview of the results and conclusions of the included studies, cN0 preNCT**

cN0 preNCT Author	Year	n	SLN identification method	IR	FNR	Accuracy	Conclusion*
Cheung[48]	2009	78	Periaureolar Tc99; and periaureolar blue dye (patent blue, 2mL).	83.3%	16.7%	87.7%	Accurate
Hunt[37]	2009	575	At the discretion of the surgeon. Tc99 (0.5-2.5mCi) alone; or blue dye alone (isosulfan 3-5mL); or a combination of both.	97.4%	6.0%	97.0%	Accurate
Tausch[49]	2008	121	At the discretion of the surgeon. Blue dye alone; or radioactive colloid alone; or a combination of both.	-	5.9%	-	Accurate
Gimbergues[50]	2008	82	Periaureolar (at the site of tumor localization) Tc99 (1.6mCi).	93.9%	0.0%	100.0%	Accurate
Classe[51]	2008	130	Peritumoral or periaureolar 99Tc, and peritumoral and periaureolar blue dye (patent blue, 2mL).	94.6%	7.5%	97.6%	Accurate
Yu[34]	2007	127	Peritumoral and periaureolar blue dye (5mL).	91.3%	7.2%	95.7%	Accurate
Kinoshita[38]	2007	54	Peritumoral Tc99 (30-80mBq); and periaureolar blue dye (patent blue, 3mL).	96.3%	14.3%	92.6%	Accurate
Tanaka[23]	2006	17	Peritumoral blue dye (indigocarmine, 4mL).	100.0%	0.0%	100.0%	Accurate
Mamounas[52]	2005	326	Radioactive colloid alone; or blue dye alone (isosulfan); or a combination of both.	-	12.4%	-	Accurate
Shimazu[53]	2004	25	Periaureolar Tc99 (30-80mBq); and blue dye (isosulfan, 2mL).	96.0%	7.1%	95.8%	Accurate
Lang[54]	2004	30	Peritumoral Tc99 (0.5-1mCi) (1997-2003); and blue dye (isosulfan, 1997-2002).	96.7%	0.0%	100.0%	Accurate
Reitsamer[55]	2003	17	Peritumoral Tc99 (30-60mBq); and periaureolar blue dye (patent blue).	100.0%	-	-	Accurate
Piato[56]	2003	42	Peritumoral Tc99 (15mBq).	97.6%	16.7%	92.7%	Accurate
Tafra[57]	2001	29	Peritumoral Tc99 (37mBq, 1 mCi); and peritumoral blue dye (isosulfan, 2-5mL).	93.1%	0.0%	100.0%	Accurate
Papa[19]	2008	31	Tc99; and periaureolar blue dye (isosulfan).	87.1%	15.8%	88.9%	Inaccurate
Jones[18]	2005	17	At the discretion of the surgeon.	94.1%	10.0%	94.1%	Inaccurate
Vigario[20]	2003	37	Peritumoral Tc99 (14.8mBq).	97.3%	28.0%	80.6%	Inaccurate
Overall		**1738**		**95.0%**	**11.4%**	**95.6%**	

* Conclusion according to the authors of the original paper.

Node-positive before NCT

Fifteen studies in which 839 patients who were clinically node-positive (cN+) prior to chemotherapy were included, is shown in Table 2. The studies were published between 2003 and 2011, patients were included between 1994 and 2009. Mean SLN IR was 86.5% (range 68.4%-100%); mean FNR was 10.3% (range 5.1%-29.6%); mean overall accuracy was 92.8% (range 81.8%-96.7%).

Performing a SLNB after NCT was concluded to be accurate in 11 out of 15 studies (Table 2). Four studies concluded otherwise.[18, 21-23] Various reasons exist for the studies with negative conclusions. Reasons were lower IR [18] and higher FNR [21, 22] than when performing a SLNB before NCT. Controversy still exists on this issue, as some negative studies reported lower IR but satisfactory FNR after NCT [18] while others reported that the latter was unsatisfactory with a similarly high IR.[21, 22] Therefore, there is still no exact reason for the different negative studies. Another study did not state conclusions, because this was not the main research question of the study.[24]

Node-negative and node-positive before NCT

Some studies included both patients who were cN0 or cN+ prior to NCT, and only provided data for the whole study population. Results of these 11 studies comprising 480 patients are shown in Table 3. The studies were published between 2000 and 2010, patients were included between 1994 and 2007. Mean sentinel lymph node IR was 83.6% (range 70.9%-100%); mean FNR was 9.5% (range 0%-20%); mean overall accuracy was 97.4% (range 87.5%-100%).

Performing a SLNB after NCT (post-NCT) was concluded to be accurate in 9 out of 11 studies. Two studies concluded otherwise.[25, 26] Reasons were lower IR and high FNR (18.2%26 and 20%25 respectively).

Node-negative after NCT

An overview of the 8 studies including 348 patients who were cN0 after NCT, and whom, before NCT, were either cN0 or cN+ is shown in Table 4. The studies were published between 2000 and 2010, patients were included between 1996 and 2008. Mean SLN IR was 92.0% (range 85%-100%); mean FNR was 8.5% (range 0%-33.3%); mean overall accuracy was 94.6% (range 76.9%-100%).

Performing a SLNB after NCT was considered accurate in 7 out of 8 studies. One study concluded otherwise.[27] Nason and colleagues investigated 82 patients with a clinically negative axilla and who underwent a SLNB followed by an ALND, of which only 15 patients underwent NCT. This study found an IR of 80% and an increased FNR (33%); out of 9 patients with histologically confirmed positive axillary lymph nodes, three patients had a false-negative SLN.

DISCUSSION

We performed an in-depth investigation of the different studies performed to date. Studies included either cN+ or cN0 patients only, or both (pre-NCT). We assessed a selection of studies that combined cN0 and cN+ patients before NCT and, on the basis of these results it was concluded that overall, performing a SLNB after NCT is accurate. In the majority of the studies, it was concluded that the SLNB can be performed after NCT in patients with a clinically node-negative (cN0) disease before NCT. In case of a histologically confirmed negative SLNB, a completion axillary lymph node dissection (ALND) has no added value. Similarly, in patients with clinically positive nodal involvement (cN+) before NCT, all axillary surgery can be performed after NCT.

Staging procedure

Historically, the SLNB was introduced in order to indicate disease stage and prognosis more accurately and to add value to treatment decisions based on prognostic indicators. The SLNB was not intended as a therapeutic procedure. Consequently, staging accuracy is not an endpoint in itself.[28] Although a false-

Table 2. **Overview of the results and conclusions of the included studies, cN+ preNCT**

cN+ preNCT Author	Year	n	SLN identification method	IR	FNR	Accuracy	Conclusion*
Canavese[58]	2011	64	Peritumoral Tc99 (0.2mCi).	93.8%	5.1%	96.7%	Accurate
Tausch[69]	2008	46	At the discretion of the surgeon. Radioactive colloid alone; or blue dye alone; or a combination of both.	-	-	-	Accurate
Gimbergues[50]	2008	47	Periaureolar (at the site of tumor localization) Tc99 (1.6mCi).	93.6%	29.6%	81.8%	Accurate
Classe[51]	2008	65	Peritumoral or periaureolar 99Tc; and peritumoral and periaureolar blue dye (patent blue, 2mL).	81.5%	12.0%	94.3%	Accurate
Newman[59]	2007	54	Tc99; and blue dye (isosulfan).	98.1%	7.7%	94.3%	Accurate
Lee[39]	2007	219	Tc99 alone; or peritumoral blue dye alone (isosulfan, indigocarmine); or a combination of both.	77.6%	5.6%	95.9%	Accurate
Kinoshita[38]	2007	50	Peritumoral Tc99 (30-80mBq; and periaureolar blue dye (patent blue, 3mL).	90.0%	7.7%	95.6%	Accurate
Khan[24]	2005	20	Periaureolar Tc99; and blue dye (isosulfan).	100.0%	7.1%	95.0%	Accurate
Mamounas[52]	2005	102	Radioactive colloid alone; or blue dye alone (isosulfan); or a combination of both.	-	7.0%	-	Accurate
Lang[54]	2004	23	Peritumoral Tc99 (0.5-1mCi) (1997-2003); and blue dye (isosulfan, 1997-2002).	91.3%	9.1%	95.2%	Accurate
Reitsamer[55]	2003	13	Peritumoral Tc99 (30-60mBq); and periaureolar blue dye (patent blue).	69.2%	-	-	Accurate
Shen[21]	2007	69	Peritumoral Tc99 alone; or peritumoral blue dye alone (isosulfan); or a combination of both.	92.8%	25.0%	82.1%	Inaccurate
Jones[18]	2005	19	At the discretion of the surgeon.	68.4%	12.5%	92.3%	Inaccurate
Tanaka[23]	2006	26	Peritumoral blue dye (indigocarmine, 4mL).	100.0%	6.3%	96.2%	Inaccurate
Shimazu[53]	2004	22	Periaureolar Tc99 (30-80mBq); and blue dye (isosulfan, 2mL).	90.9%	15.8%	85.0%	Inaccurate
Overall		**839**		**86.5%**	**10.3%**	**92.8%**	

* Conclusion according to the authors of the original paper.

Table 3. **Overview of the results and conclusions of the included studies, cN0, cN+ preNCT**

cN0, cN+ preNCT Author	Year	n	SLN identification method	IR	FNR	Accuracy	Conclusion*
Reitsamer[33]	2010	143	Peritumoral 99Tc (30mBq); and periaureolar blue dye (patent blue, 2mL).	81.1%	8.3%	95.7%	Accurate
Hino[60]	2008	55	Peritumoral 99Tc (1mL).	70.9%	0.0%	100.0%	Accurate
Yamamoto[61]	2007	20	Radioactive colloid; and blue dye (isosulfan).	100.0%	14.3%	95.0%	Accurate
Balch[62]	2003	32	Peritumoral 99Tc (0.45mCi); and peritumoral blue dye (isosulfan 5mL).	96.9%	5.3%	96.8%	Accurate
Stearns[63]	2002	34	Peritumoral blue dye (isosulfan 3-5mL).	85.3%	14.3%	89.7%	Accurate
Brady[64]	2002	14	Peritumoral blue dye (isosulfan 1mL).	92.9%	0.0%	100.0%	Accurate
Haid[65]	2001	33	Peritumoral 99Tc (0.3-1.2mCi); and peritumoral blue dye (patent blue 4mL).	87.9%	0.0%	100.0%	Accurate
Cohen[66]	2000	38	Peritumoral blue dye alone (isosulfan); or in combination with Tc99.	81.6%	16.7%	90.0%	Accurate
Breslin[67]	2000	51	Peritumoral Tc99; and blue dye; or blue dye alone.	77.4%	12.0%	93.0%	Accurate
Hidar[26]	2009	20	Peritumoral or periaureolar blue dye (patent blue, 2 mL).	80.0%	18.2%	87.5%	Inaccurate
Fernandez[25]	2001	40	Peritumoral 99Tc (111mBq).	94.4%	20.0%	88.2%	Inaccurate
Overall		**480**		**83.6%**	**9.5%**	**97.4%**	

*Conclusion according to the authors of the original paper.

Table 4. **Overview of the results and conclusions of the included studies, cN0 postNCT**

cN0 postNCT							
Author	**Year**	**N**	**SLN identification method**	**IR**	**FNR**	**Accuracy**	**Conclusion***
Ozmen[68]	2010	77	Tc99; and blue dye (isosulfan, 5mL).	92.2%	13.7%	90.1%	Accurate
Kinoshita[38]	2007	104	Peritumoral Tc99 (30-80mBq); and periaureolar blue dye (patent blue, 3mL).	93.3%	10.0%	95.9%	Accurate
Aihara[69]	2004	20	Peritumoral blue dye (indigocarmine, 5ml).	85.0%	8.3%	92.9%	Accurate
Patel[70]	2004	42	Peritumoral Tc99 (1mCi) alone; or peritumoral blue dye alone (isosulfan 5mL); or a combination of both.	95.2%	0.0%	100.0%	Accurate
Schwartz[71]	2003	21	Peritumoral blue dye (isosulfan, 1mL).	100.0%	9.1%	95.2%	Accurate
Miller[72]	2002	35	Peritumoral Tc99 (1mCi); and peritumoral blue dye (isosulfan 3-5mL).	85.7%	0.0%	96.7%	Accurate
Julian[73]	2002	34	Peritumoral Tc99 alone; or peritumoral blue dye alone (isosulfan 5mL); or a combination of both.	91.2%	0.0%	100.0%	Accurate
Nason[27]	2000	15	Peritumoral Tc99 (1mCi); and peritumoral blue dye (isosulfan, 5mL).	86.7%	33.3%	76.9%	Inaccurate
Overall		**348**		**92.0%**	**8.5%**	**94.6%**	

* Conclusion according to the authors of the original paper.

negative result, i.e. a negative SLN in the presence of positive axillary lymph nodes, may lead to incorrect nodal staging and thus to potential undertreatment with regard to adjuvant therapy, the clinical implications of false-negative results in the neoadjuvant setting are not as critical. The decision to administer systemic therapy has already been made, and undertreatment is unlikely.[22] We must bear in mind that current adjuvant treatment also incorporates breast and axillary irradiation to further reduce the probability of axillary recurrences.[29, 30] Surgical overtreatment, however, is conceivable, and the impact of additional comorbidity following more extensive surgery where it could be prevented cannot be ignored.[31] Furthermore, the risk of developing an axillary recurrence at 5 years when an ALND has been omitted in the presence of a positive SLN remains low.[10, 32]

Axillary Downstaging

One of the major advantages of axillary surgery after neoadjuvant therapy is the potential for less extensive surgery as well as reducing surgery to a single procedure. Overall, 20-44% of node-positive patients achieves a complete pathological response in the axilla with NCT[12, 13] and may thereby be spared an ALND, with its well-known comorbidities.[31] Moreover, patients who are clinically node-negative before NCT may also be spared a second surgical procedure when the SLNB is performed after NCT.[33]

Axillary response to NCT

One of the arguments restraining the progression of clinical guidelines is the potentially selective complete response following NCT in the SLN, but not in the axillary lymph nodes.[34] Dixon and colleagues correctly state in an earlier editorial that the areas of concern for surgeons as well as other physicians dealing with breast cancer patients include the alteration in lymphatic drainage leading to potentially lower IR and higher FNR.[28] Excessive fibrosis of the tumor involved lymphatics after neoadjuvant chemotherapy and the potential obstruction of lymphatic channels with cellular debris or tumor emboli may lead to inaccurate lymphatic

mapping[35], although the latter has never been proven.[28, 33] Alteration in lymphatic drainage is a heterogeneous process, and multiple studies have found that NCT does not influence mapping success.[27, 36] Fringuelli evaluated the influence of NCT on lymphatic drainage using lymphoscintigraphy before and after NCT in 129 patients; in 123 patients (95.3%), no change in drainage pattern between before and after NCT was observed.[36]

Several studies observed a uniform axillary response to NCT.[16] The SLN was shown to accurately predict axillary status, also after NCT.[37-39] We must also acknowledge that only 40-60% of patients with a positive SLN have additional axillary nodal involvement.[7] Moreover, it is important to bear in mind that there will always be a risk of axillary lymph node involvement, also in the absence of a positive SLN, and that the introduction of breast and axillary irradiation has further reduced axillary recurrences. Therefore, in patients with a histologically confirmed negative SLNB, an ALND has little added value.

Accuracy and Safety

In light of the results of previous practice-changing studies that lead to the introduction of the standard staging procedure using the SLNB, accuracy rates in terms of IR and FNR were similar to the current findings in the neoadjuvant setting. Some have commented that because these were early studies, rates are no longer acceptable in current clinical practice.[18] However, several studies have also found that IR improves with augmenting experience.[38-40] Furthermore, several direct comparisons of the accuracy of the SLNB with- versus without NCT have been conducted recently, and all have observed a similar accuracy for both strategies.[39,41] Of note, patients included in these studies were cN0 prior to NCT.

Although results are comparable across studies, some consider it safe and accurate to perform a SLNB after NCT, whereas others do not recommend the procedure. The false-negative rate is a probability of axillary nodal involvement when the SLN is negative. Currently, no FNR standard has been set, but an FNR of 5% has been deemed reasonable by several investigators.[23,43,44]

The current SENTINA trial, a substudy of the German Geparquinto neoadjuvant trial, is a four-arm trial in which the role of the sentinel lymph node (cN0 and cN+) is being investigated in patients undergoing NCT.[40,42] Recent results from the San Antonio Breast Cancer Symposium (SABCS) in 2012 showed that FNR is less favorable in patients who underwent SLNB after NCT than when the SLNB is performed before NCT.[40] The other trial is the ACOSOG Z1071 trial, a phase II study in which a SLNB + ALND after NCT is performed in T0-4, N1-2, M0 patients.[41] The primary objective is to determine FNR for sentinel lymph node surgery in women with node-positive breast cancer at initial diagnosis. To the author's knowledge, the latter has currently been suspended, however, results presented at SABCS 2012 revealed that NCT results in conversion to node-negative disease in 40% of node-positive cases, with a FNR of 12.8%.[41]

Some argue that the FNR may not be the best endpoint to use in the neoadjuvant setting and that its value is slightly overrated. Instead, looking at the risk of locoregional recurrences when an ALND is withheld may be a better approach to determining the future of the management of the axilla. Adjuvant locoregional

and systemic treatment has had a tremendous impact on improving locoregional control in recent years. In the 1980s, several studies reported on the effectiveness of radiotherapy following breast conserving therapy in patients with a positive and/or negative SLN. The majority of studies reported axillary recurrence rates below 4%, with the exception of one study reporting a 16% axillary recurrence rate.[42] A later study investigated the effect of axillary radiotherapy on locoregional recurrences in patients with a positive SLN who did not undergo an ALND.[43] Out of 73 patients, only one developed an axillary recurrence (median follow-up 32 months). All patients received adjuvant systemic treatment. In the context of NCT, all patients will already have been systemically treated, therefore axillary radiotherapy may be a suitable alternative to axillary surgery in these patients. Furthermore, the majority of hormone receptor-positive patients will also receive adjuvant endocrine therapy for a period of five years or longer to further reduce recurrence rates.

Based on comparable results, some consider it safe and accurate to perform a SLNB after NCT, whereas others do not recommend the procedure. The discrepant conclusions extend beyond individual studies. To date, three meta-analyses[15-17], and one systematic review[18] were completed. Although there is considerable overlap in the studies included, conclusions vary. Several contained studies with cN0 and cN+ patients prior to neoadjuvant therapy.[15, 17, 18] and one restricted inclusion to studies consisting of patients with cN0 after NCT only.[16] As different studies have investigated groups of patients that are all at different risks of presenting with involved lymph nodes, there is a great variability in FNR. Unfortunately, small sample sizes may also obscure statistical analyses and outcomes. No evident publication bias was shown in previous reports.[16, 17]

SLN identification method

In the reviewed studies, we summarize the identification rates based on different detection methods. (Supplementary Table 1) Several methods of SLN identification were utilized, and a majority of studies applied a combination of blue dye and radioactive colloid (usually Technetium-99m (Tc99)). Studies also varied with respect to injection location. It is difficult to draw conclusions based on these results, as they vary across studies with respect to the different clinical presentations and procedures. Zhang et al. attempted to compare SLN identification techniques in different studies and found that a combined technique resulted in a higher IR than either dye or isotope alone.[44]

CONCLUSION

In the context of NCT, clinicians are still at a loss, given the discrepancies demonstrated in conflicting guideline recommendations. The ASCO guidelines dating from 2005[45] state that performing a SLNB after NCT is not recommended. Contrary, the more recent St. Gallen expert consensus meeting in 2009 concluded that 'results of sentinel node biopsy after NCT are reliable, as described in a meta-analysis and supported by experience at a single institution'.[46] As stated earlier, NCT is an essential element in the

treatment of breast cancer in patients with large operable tumors with the potential of being downstaged and undergoing breast conserving therapy. NCT is equally effective as adjuvant chemotherapy when adequate local treatment ensues.[47] Similarly, adjuvant radiation therapy is of critical significance in reducing axillary recurrences. In this multidisciplinary approach, surgical intervention is but one of the components of the entire treatment regimen. It is therefore unjustified not to adjust surgical treatment if downstaging of the tumor and axilla occurs through valid treatment. This would certainly undermine the true potential of NCT, especially if neglecting to do so brings additional comorbidity to patients already burdened by multiple demanding treatments.

Supplementary Table 1. **Identification rate by detection method***

	Studies *N*	Patients *N*	Identification Rate
cN0 preNCT			
Combination blue dye and radioactive colloid	8	394	92%
Either blue dye or radioactive colloid	5	305	94%
cN+ preNCT			
Combination blue dye and radioactive colloid	7	247	89%
Either blue dye or radioactive colloid	3	137	95%
cN0, cN+ preNCT			
Combination blue dye and radioactive colloid	4	228	86%
Either blue dye or radioactive colloid	5	163	85%
cN0 postNCT			
Combination blue dye and radioactive colloid	4	231	91%
Either blue dye or radioactive colloid	2	41	93%

*Studies not reporting on IR or where IR was at the discretion of the surgeon were excluded from this table.

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