Sentinel Lymph Node Biopsy Following Neoadjuvant Chemotherapy: Review of the Literature and Recommendations for Use in Patient Management

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Breast cancer is a significant health problem worldwide and is one of the leading causes of cancer-related mortality in women. Preoperative chemotherapy has become the standard of care for patients with locally advanced disease and is being used more frequently in patients with early-stage breast cancer. Sentinel lymph node biopsy has shown great promise in the surgical management of breast cancer patients, but its use following preoperative chemotherapy is yet to be determined. Eleven studies have been published with respect to the accuracy of sentinel lymph node biopsy following neoadjuvant chemotherapy. Ten studies showed favourable results, with the ability to identify a sentinel lymph node in 84% to 98% of cases, and reported false negative rates ranging from 0% to 20%. The accuracy of sentinel lymph node biopsy following preoperative chemotherapy for breast cancer ranges from 88% to 100%, with higher rates when specific techniques and inclusion criteria are applied. The published literature supports the use of sentinel lymph node biopsy for assessment of the axilla in patients with clinically node-negative disease following preoperative chemotherapy. [*Asian J Surg* 2004;27(4):262–7]

Introduction

More than one million patients were diagnosed with invasive breast cancer worldwide in 2000.[1] In the current era of mammographic detection, most of these patients were diagnosed with early-stage disease.[2,3]

Preoperative chemotherapy, also called neoadjuvant, induction or primary chemotherapy, is recognized as standard therapy for patients with locally advanced breast cancer. More recent clinical trials have examined the potential benefits of preoperative chemotherapy in patients with early-stage breast cancer (stages I–IIB).[4,5] There are a number of potential advantages for administering preoperative chemotherapy to this patient population. First, several studies have demonstrated that it is possible to achieve a substantial reduction in the size of the primary tumour as well as nodal metastases in up to 80% of patients after only three to four cycles of chemotherapy.[6] With a decrease in the size of the primary tumour, there is a greater probability that breast-conserving surgery can be performed.[6–9] Another advantage of preoperative chemotherapy is that it permits the *in vivo* assessment of tumour response to a particular chemotherapy regimen.[10]

Sentinel lymph node biopsy can accurately determine tumour spread to the regional lymph nodes and is rapidly replacing traditional axillary lymph node dissection as the primary staging modality for patients with early-stage breast cancer.[11] The reported identification rates and false-negative rates with sentinel lymph node biopsy in patients who have not received preoperative chemotherapy range from 84–100% and 0–13%, respectively.[12,13]

The questions of whether sentinel lymph node biopsy is feasible and accurate after preoperative chemotherapy are

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critical since the sequencing of chemotherapy first followed by surgery has been proposed as the new paradigm in breast cancer treatment. Some clinicians have postulated that lymphatic mapping may not be successful after preoperative chemotherapy because of excessive fibrosis of the primary tumour and lymphatics and/or blockage of lymphatic channels with cellular material or tumour emboli.[10,14] The objective of this review was to identify and summarize the findings of published clinical studies that have examined the results of sentinel lymph node biopsy following preoperative chemotherapy and to provide recommendations for its use in clinical practice.

Published clinical studies

Relevant studies available for review as of June 2003 were identified through MEDLINE (1990 to June 2003) and Cancerlit (to October 2002). Subject headings used to perform the searches were "breast neoplasms", "sentinel lymph node biopsy" and "neoadjuvant therapy" including all subheadings. Studies examining the results of sentinel lymph node biopsy following preoperative chemotherapy in patients with operable breast cancer were included in the analysis. The accuracy of sentinel lymph node biopsy is measured primarily by examining the false-negative rate. This is determined by evaluating the histological results of the sentinel lymph node in conjunction with the histological results of axillary lymph node dissection (the gold standard). A false-negative event occurs when the sentinel lymph node is histologically negative for metastasis but one or more of the axillary lymph nodes is found to contain metastatic disease.

There are published data from 10 non-randomized studies[15–24] and one large randomized trial (National Surgical Adjuvant Breast and Bowel Project, NSABP, B-27 trial)[25] that have examined the accuracy of sentinel lymph node biopsy following preoperative chemotherapy in a total of 738 patients (Table 1). Most of the studies (82%) were conducted in single institutions,[15–18,20–24] two were based on a single surgeon's experience[22,23] and two were multicentre trials.[19,25] Three of the studies included data for comparison from groups of patients with breast cancer who did not receive preoperative chemotherapy;[16,17,19] three studies collected patient data prospectively.[19,20,25] Sample sizes for the preoperative chemotherapy groups ranged from 14 to 420 patients.

The methods of sentinel lymph node detection included combination radioactive isotope and blue dye, isotope alone and blue dye alone (Table 2). Clinical stage ranged from I to IIIB, but was not reported in all studies. Various chemotherapy combinations were used, with most patients receiving anthracycline-based regimens (Table 2). The reported clinical response rates (partial or complete) ranged from 57–

Table 1. Descriptions of 11 studies published from 2000–2003

Authors	Year	Study design	Study period	Setting	*N*	Treatment group	
						Preop chemo	No chemo
Breslin et al [15]	2000	Retrospective consecutive	1994–1999	Single institution	51	51	NA
Nason et al [16]	2000	Retrospective cohort with comparison	10/1996–06/1999	Single institution	82	15	67
Fernandez et al [17]	2001	Retrospective cohort with comparison	NA	Single institution	76	40	36
Haid et al [18]	2001	Retrospective consecutive	NA	Single institution	33	33	NA
Tafra et al [19]	2001	Retrospective cohort with comparison	02/1997–03/2001	Multicentre trial (private practice and academic centre)	968	29	939
Balch et al* [20]	2002	Consecutive data from prospective clinical trial	07/1997–08/2001	Single institution	26	26	NA
Mamounas et al* [25]	2002	Consecutive data from prospective clinical trial	01/1996–12/2000	Multicentre trial NSABP B-27	420	420	NA
Stearns et al [21]	2002	Retrospective consecutive	11/1997–07/2000	Single institution	34	34	NA
Brady [22]	2002	Retrospective consecutive	02/1998–07/2000	Single surgeon	14	14	NA
Julian et al [23]	2002	Retrospective consecutive	05/1997–03/2002	Single surgeon	34	34	NA
Piato et al [24]	2003	Retrospective consecutive	NA	Single institution	42	42	NA

*Abstract only. Preop chemo = preoperative chemotherapy; No chemo = no preoperative chemotherapy; NA = not available; NSABP B-27 = National Surgical Adjuvant Breast and Bowel Project B-27 trial.

Table 2. Influence factors

Authors	SNB method	Staging		Neoadjuvant therapy	Primary tumour response rate			
		T	Stage		Clinical			Pathological
					CR	PR	NR	CR
Breslin et al [15]	Dye 45% (23/51) Dye + Isotope 55% (28/51)	T1 (NA) T2 (NA) T3 (NA)	IIA: 49% (25/51) IIB: 24% (12/51) IIIA: 27% (14/51)	FAC: 69% (35/51) High-dose FAC: 4% (2/51) Paclitaxel + FAC: 15% (8/51) AT: 10% (5/51) Tamoxifen: 2% (1/51)	NA	98% (40/41)	2% (1/41)	NA
Nason et al [16]	Dye (NA) Isotope (NA) Dye + Isotope (NA)	T2 (NA) T3 (NA)	NA	AC	15% (2/13)	62% (8/13)	23% (3/13)	NA
Fernandez et al [17]	Isotope 100% (40/40)	T1: 10% (4/40) T2: 42.5% (17/40) T3: 40% (16/40) T4: 7.5% (3/40)	I: 10% (4/40) IIA: 25% (10/40) IIB: 47.5% (19/40) IIIA: 10% (4/40) IIIB: 7.5% (3/40)	NA	NA	NA	NA	NA
Haid et al [18]	Dye + Isotope 100% (33/33)	T1: 6% (2/33) T2: 91% (30/33) T3: 3% (1/33)	NA	CMF, EC, TE	37% (12/33)	33% (11/33)	30% (10/33)	9% (3/33)
Tafra et al [19]	Dye + Isotope 100% (29/29)	NA	NA	NA	NA	NA	NA	NA
Balch et al [20]	Dye + Isotope 100% (26/26)	T2 (NA) T3 (NA) T4 (NA)	II: 50% (13/26) III: 50% (13/26)	AC or FAC : 81% (21/26) Paclitaxel and RT: 19% (5/26)	NA	85% (22/26)	NA	8% (2/26)
Mamounas et al [25]	Dye 30% (126/420) Isotope 16% (67/420) Dye + Isotope 54% (227/420)	NA	NA	AC or AC + T	NA	NA	NA	18% (56/312)
Stearns et al [21]	Dye (NA) Isotope (NA) Dye + Isotope (NA)	T3: 74% (25/34) T4: 26% (9/34)	NA	AC: 21% (7/34) A + paclitaxel ± C: 70% (24/34) AC + paclitaxel/trastuzumab: 3% (1/34) Endocrine: 6% (2/34)	NA	NA	NA	NA
Brady [22]	Dye 93% (13/14) Dye + Isotope 7% (1/14)	NA	I: 7% (1/14) IIA: 36% (5/14) IIB: 29% (4/14) IIIA: 14% (2/14) IIIB: 14% (2/14)	AC: 72% (10/14) AC + T: 14% (2/14) AC + paclitaxel: 7% (1/14) AC + paclitaxel/trastuzumab: 7% (1/14)	14% (2/14)	43% (6/14)	43% (6/14)	NA
Julian et al [23]	Dye (NA) Isotope (NA) Dye + Isotope (NA)	T1 (NA) T2 (NA) T3 (NA)	I–IIIA	AC: 74% (25/34) AC + T: 26% (9/34)	59% (20/34)	12% (4/34)	29% (10/34)	18% (6/34)
Piato et al [24]	Isotope 100% (42/42)	T1: 60% (25/42) T2: 40% (17/42)	I–II	AC	45% (19/42)	50% (21/42)	5% (2/42)	NA

SNB = sentinel node biopsy; CR = complete response; PR = partial response; NR = no response; NA = not available; FAC = fluorouracil/doxorubicin/cyclophosphamide; AT = doxorubicin/docetaxel; AC = doxorubicin/cyclophosphamide; CMF = cyclophosphamide/methotrexate/fluorouracil; EC = epirubicin/cyclophosphamide; TE = docetaxel/epirubicin; RT = radiotherapy; T = docetaxel; A = doxorubicin; C = cyclophosphamide.

98%.[15,16,18,20,22–24] Pathological complete response was reported in four studies and ranged from 8–18%.[18,20,23,25]

Test characteristics

Relevant test characteristics for sentinel node biopsy (SNB) were calculated or recalculated for the published trials using the following formulas:

- Identification rate = patients with successful SNB/patients undergoing SNB
- False-negative rate = false negatives/(true positives + false negatives)
- Sensitivity = true positives/(true positives + false negatives)
- Specificity = true negatives/(true negatives + false positives)
- Positive predictive value = true positives/(true positives + false positives)
- Negative predictive value = true negatives/(true negatives + false negatives)
- Overall accuracy = (true positives + true negatives)/patients with successful SNB

A true positive was defined as a node positive on both SNB and axillary lymph node dissection, a false positive as a node positive on SNB and negative on axillary lymph node dissection, a true negative as a node negative on both SNB and axillary lymph node dissection, and a false negative as a node negative on SNB and positive on axillary lymph node dissection.

The test characteristics of SNB following preoperative chemotherapy in patients with operable breast cancer are outlined in Table 3. Ten of the 11 studies demonstrated favourable results, with overall accuracy ranging from 88–100%.[15,17–25] The identification rate of sentinel lymph nodes following preoperative chemotherapy was 84–98%. The false-negative rates ranged from 0–20%. The remaining study by Nason et al reported a false-negative rate of 33% and an overall accuracy of 77%.[16] This study was limited in that only nine of 15 patients had positive lymph nodes and three of these patients had a false-negative sentinel lymph node. The ability of such a small study to define the accuracy of sentinel lymph node biopsy following chemotherapy is highly questionable.

Discussion

While neoadjuvant chemotherapy is currently considered the standard of care for patients with locally advanced breast cancer, the indications for its use in patients with early-stage disease are still evolving. The primary rationale is earlier treatment of occult systemic metastases; however, trials directly comparing neoadjuvant with adjuvant chemotherapy have not conclusively demonstrated a survival advantage for patients treated with the neoadjuvant approach. Patients treated with chemotherapy first are more likely to be candidates for breast-conserving surgery and less likely to have positive lymph nodes.[6]

Based on the available literature, it appears that lymphatic mapping and sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer are both feasible and accurate. Most studies to date are retrospective and include a heterogeneous patient population treated with different chemotherapy drugs and treatment schedules. Thus far, the combination approach using blue dye with radioisotope resulted in maxi-

Table 3. Test characteristics of sentinel node biopsy after preoperative chemotherapy

Authors	Identification rate *n* (%)	False-negative rate *n* (%)	Sensitivity *n* (%)	Specificity *n* (%)	Positive predictive value, *n* (%)	Negative predictive value, *n* (%)	Overall accuracy *n* (%)
Breslin et al [15]	43/51 (84)	3/25 (12)	22/25 (88)	18/18 (100)	22/22 (100)	18/21 (86)	40/43 (93)
Nason et al [16]	13/15 (87)	3/9 (33)	6/9 (67)	4/4 (100)	6/6 (100)	4/7 (57)	10/13 (77)
Fernandez et al [17]	34/40 (85)	4/20 (20)	16/20 (80)	14/14 (100)	16/16 (100)	14/18 (77)	30/34 (88)
Haid et al [18]	29/33 (88)	0/18 (0)	18/18 (100)	11/11 (100)	18/18 (100)	11/11 (100)	29/29 (100)
Tafra et al [19]	27/29 (93)	0/26 (0)	26/26 (100)	NA	NA	NA	NA
Balch et al [20]	25/26 (96)	1/14 (7)	13/14 (93)	11/11 (100)	13/13 (100)	11/12 (92)	24/25 (96)
Mamounas et al [25]	357/420 (85)	15/138 (11)	123/138 (89)	202/202 (100)	123/123 (100)	202/217 (93)	325/340 (96)
Stearns et al [21]	23/26 (88)	1/16 (6)	15/16 (94)	7/7 (100)	15/15 (100)	7/8 (88)	22/23 (96)
Brady [22]	13/14 (93)	0/10 (0)	10/10 (100)	3/3 (100)	10/10 (100)	3/3 (100)	13/13 (100)
Julian et al [23]	31/34 (91)	0/12 (0)	12/12 (100)	19/19 (100)	12/12 (100)	19/19 (100)	31/31 (100)
Piato et al [24]	41/42 (98)	3/18 (17)	15/18 (83)	23/23 (100)	15/15 (100)	23/26 (88)	38/41 (93)

NA = not available.

mum sentinel node identification rates. With the exception of Nason et al's report,[16] the false-negative rates are comparable to early reports of SNB in early-stage untreated breast cancer patients.

Since the fibrotic response to chemotherapy in treated breast tissue and nodal basins is known to result in increased difficulty with surgical dissection and pathological assessment of tissues, the learning curve may be different for surgeons attempting sentinel lymph node biopsy in patients treated with neoadjuvant chemotherapy compared with surgeons performing it in untreated patients. It would seem prudent that each individual surgeon examine their cases of sentinel lymph node biopsy after chemotherapy separately from those patients treated with surgery first, in order to evaluate his or her learning curve.

There are a number of clinical questions that must be addressed in future clinical trials. Is complete axillary node dissection necessary in patients with micrometastatic disease in the sentinel node? The American College of Surgeons Oncology Group Trial Z0011 was designed to specifically address this question. It is actively accruing patients but is unlikely to provide a definitive answer for another 5 years. Several groups, including our own here at the M.D. Anderson Cancer Center, have developed models based on clinical and pathological factors to determine the likelihood that a patient with disease in the sentinel node will harbour additional disease in the remaining axillary lymph nodes.[26] While these tools may be useful for patients treated with surgery first, it is unlikely that they will be immediately translated into a prognostic model for patients treated with neoadjuvant chemotherapy prior to surgery.

Another critical question is whether or not axillary irradiation can be used as the sole form of local treatment of the axilla in select patient populations. Several studies have been published on the use of axillary irradiation in clinically node-negative breast cancer patients and demonstrate failure rates of 1–2%.[27] In patients treated with breast-conserving surgery, tangential breast irradiation will include most of the sentinel node dissection field and, in fact, includes about one-third to two-thirds of the level I and level II axillary lymph nodes.[28] Although there is less experience with radiation therapy in the treatment of the clinically node-negative axilla following neoadjuvant chemotherapy, there are sufficient data to support the use of radiation therapy as an adjunct to SNB in this patient population.

As the use of neoadjuvant chemotherapy continues to increase in the treatment of breast cancer patients, it is important that we carefully assess the role of SNB in these patients. Just as breast-conserving surgery is now an accepted treatment modality for selected patients following neoadjuvant chemotherapy, there will be a role for SNB as well. Single-institution studies will provide useful information; however, national trials with multiple participating institutions will ultimately be needed in order to clearly define this role.

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