ORIGINAL ARTICLE

Validity of Sentinel Lymph Node Biopsy in Taiwanese Breast Cancer Patients

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Background/Purpose: The clinical validity of sentinel lymph node (SLN) biopsy in Taiwanese breast cancer patients from 16 institutes in two consecutive periods was analyzed.

Methods: Data from the initial period between January 3, 1999 and July 2004 and data from the later period after August 2004 to February 2005 were compared. Data on the use of a tracer, SLN identification, harvest and examination, false negative rate (FNR) and the number of patients spared axillary lymph node dissection (ALND) were analyzed.

Results: A total of 3308 patients with clinical axilla negative breast cancer underwent SLN biopsies in 16 hospitals (11 in both periods and 5 in the period before August 2004). Comparison of data from the two periods revealed that in the later period, use of combined blue dye and isotope tracer increased from 40% to 80%, the 95% SLN biopsy success rate increased from 50% to 80%, hospitals conducting intraoperative SLN examination increased from 80% to 93%, and the 95% match to permanent section rate increased from 30% to 80%. In the initial period, eight hospitals had less than 7% FNR, while in the later period this had decreased to 4.1% in these hospitals. Another three hospitals had FNR greater than 7% in the initial period, which had decreased to 0% in the later period. Hospitals with more than 100 cases of SLN biopsy had an average 3.8% FNR, whereas hospitals with less than 100 cases of SLN biopsy experience had an 8.2% FNR ($p < 0.01$).

Conclusion: This study found that the SLN biopsy success rate increased after the use of combined tracers and with experience. FNR was controlled to within 5% among breast surgeons with accumulated experience exceeding 100 cases. It is recommended that ALND-sparing surgery be suspended temporarily in hospitals with FNR greater than 5%. [*J Formos Med Assoc* 2007;106(2):126–133]

Key Words: breast cancer, false negative rate, sentinel lymph node

Accurate detection of sentinel lymph node status in the axilla of breast cancer patients is essential to avoid unnecessary axillary lymph node dissection (ALND).[1–3] Even for breast cancer patients with clinically negative sentinel lymph nodes (SLNs), the standard of care involves an integrated team consisting of breast surgeons, nuclear medicine experts and pathologists. Validation of the existence of SLNs is necessary because it provides a 95% interval of confidence in assessing the pathologic status of axilla. The false negative result (FNR) should be as low as possible and a less than 5% FNR is accepted universally.[4] Once validation is achieved, sparing the SLN negative breast cancer patient from ALND surgery is considered safe.

The incidence of pathologically negative axilla in Taiwanese breast cancer patients increased from 24% (stage 0, 12%; stage I, 12%) to 46.2% (stage 0,

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15.4%; stage I, 30.8%) after vigorous promotion of a breast cancer screening program.[5] In 1998, breast surgeons in Taiwan began performing SLN biopsy validation in an attempt to spare clinically negative axilla breast cancer patients from ALND. Two years later, the first SLN workshop was held on July 3, 2000 at Taichung Veterans General Hospital with the participation of an SLN biopsy team from the University of California at San Francisco.[6] Thereafter, many other breast surgeons from Taiwan have adopted this new approach. After the SLN symposium in the 4th Asian Breast Cancer Conference in Taipei in February 2004,[7] data were collected nationwide to evaluate the results of SLN biopsy validation in Taiwanese breast cancer patients. The first set of collaborative data were collected from 11 institutions and presented at the second SLN biopsy workshop in August 2004 at Tri-Service General Hospital.[8] A second set of collaborative data was accrued from the original 11 and an additional five hospitals. This study analyzed the validity of the clinical data collected in these two periods.

Materials and Methods

Study period and subjects

Data collected in the period January 1999 to July 31, 2004 were compared with data from August 1, 2004 to February 28, 2005. Patients < 80 years old with pathologically confirmed breast cancer with *c*T2 (< 5 cm) tumor, without palpable lymphadenopathy at axillary fossa were included. Data on pathologic staging was not collected, but a clinically negative axilla was required to validate whether SLN biopsy could replace conventional ALND.

Questionnaire

Breast surgeons from 11 hospitals provided data in both periods, and those from five additional hospitals only responded in the later period. Data collected by questionnaire included the kinds of tracer used, timing and location of tracer injection, SLN success biopsy rate, average and maximum number of SLNs harvested, background and criteria of SLN biopsy completion when using isotope as the tracer, intraoperative SLN examination and its agreement with permanent section rate, case number of positive cytokeratin staining and its conversion pathologic diagnosis from negative to positive. Results obtained for SLNs and axillary lymph node (ALNs) were compared with regard to final pathology, FNR and the number of patients who were spared ALND.

Statistical analysis

Student's *t* test was used to compare the difference in FNR between surgeons who had experience with more than or less than 100 cases. The difference between two groups was considered significant if p was less than 0.05.

Results

A total of 3308 patients were included in this study. Of them, 1964 were treated in one of 11 hospitals in the initial period and 1344 were treated in one of 16 hospitals in the later period. ALND-sparing surgery was performed on 340 patients in the initial period and on 350 patients in the later period.

SLN biopsy methods

Table 1 compares the SLN biopsy methods used in the two study periods.

Tracer

In the initial period, 45% (5/11) of hospitals used combined blue dye and isotope as tracer, and in the later period, 80% (13/16) of the hospitals used combined tracers. Uncharacteristically, one hospital preferred to use blue dye alone and two others preferred to use isotope alone as the tracer throughout the two periods. The blue dyes used as the tracer in the initial period were methylene blue, patent blue V and charcoal. No hospital used lymphozurin as the tracer during the entire study. One hospital used charcoal in the initial period but discontinued it in the later period

Table 1. Comparison of lymph node biopsy methods used in the two study periods

Period	Initial*	Later*
Tracer		
Blue dye	2	1
Isotope	4	2
Combined	5	13
Blue dye		
Methylene blue	3	2
Patent blue V	3	12
Charcoal	1	0
Isotope dose		
1 mCi	8	14
2 mCi	1	1
Colloid size		
< 200 nm	7	13
> 1000 nm	2	2
Time of isotope injection		
Day of operation	3	1
Day before operation	3	10
Both	3	4
Background of isotope		
Hottest node in axilla (1)	3	2
Abdomen (2)	4	12
0 radioactivity in axilla	0	1
(1) + (2)	1	0
No need	1	0

**The number in both periods represents the number of hospitals in which the procedure was used.*

and instead used combined methylene blue and isotope. Patent blue V was the most frequently used blue dye tracer of choice in the later period (12/14). Filtered sulfur colloids (< 200 nm) were the primary legend agent used in isotope tracer in all hospitals except two, which preferred to use unfiltered (> 1000 nm) sulfur colloids in both periods. Labeling 1 mCi technetium-99m was used in all hospitals except one, which used 2 mCi and unfiltered sulfur colloids as well. When isotope was used as the tracer, use of the abdomen as the background increased from 60% (3/5) in the initial period to 87% (13/15) in the later period. The remaining hospitals favored 10% radioactivity in the hottest node in the axilla as the background.

Timing of tracer use and injection site

Blue dye was injected just before incision in all cases. Isotope was most often injected before the day of operation in all hospitals. Three hospitals in the initial period and one in the later period preferred to inject isotope on the day of operation. The periareola plus subdermal areas were the most common injection site in both periods, and three hospitals also preferred to perform an additional injection in the peritumor area. Only one hospital favored injecting in the subdermal area alone.

Background and SLN biopsy completion criteria

Three hospitals in the early and two in the later period chose the hottest node in the axilla as the basic background, i.e. they selected 10% radioactivity in the hottest node as the threshold for completed SLN resection. The remaining hospitals preferred abdominal radioactivity as the background. Notably, one hospital in the early period did not use any specific location as the background and had no specific criteria for SLN completion. This hospital chose the abdomen as background in the later period. One hospital in the early period used both methods but omitted the hottest node in the later period. One newly participating hospital preferred zero radioactivities at the axilla as the SLN completion criteria.

SLN biopsy results

Table 2 compares the SLN biopsy results in the two periods.

SLN identification/biopsy success rate

After tracer injection, only 45.5% (5/11) of institutes in the early period achieved a 95% SLN identification success rate, whereas five other hospitals (45.5%) had a lower than 85% or 90% rate and one hospital had only an 80% success rate for SLN identification. In the later period, 12 out of 16 hospitals (75%) achieved a 95% success rate for SLN identification. Of the remaining three new participating hospitals, two had a success rate of at least 90% and one had an 85% success rate for SLN identification. Another one hospital using large colloid for SLN biopsy clinical trial

Table 2. Comparison of sentinel lymph node (SLN) biopsy results in the two study periods

Period	Initial*	Later*
SLN biopsy success rate (%)		
100	0	0
95	5	12
90	4	3
85	1	1
80	1	0
Average/maximal SLN number		
1–2/3	3/2	3/2
2–3/6	3/4	4/7
3–4/9	4/2	8/3
> 4/12	1/3	1/4
Intraoperative SLN examination		
Not done	2	1
Frozen section	5	11
Cyto-print	2	2
Both	2	2
Match with permanent section (%)		
100	1	0
95	2	13
90	6	2
85	0	0
Cytokeratin conversion cases (*n*)		
Not done/not available	6/3	4/2
1–3	1	6
4–6	0	2
7–9	1	2

**The number in both periods represents the number of hospitals in which the procedure was used.*

in the early period still had a 90% SLN biopsy success rate in the later period. None of the hospitals had a 100% successful identification rate.

Average and maximum number of SLNs harvested

Hospitals using blue dye only harvested one to two SLNs on average and a maximum of three SLNs. The percentage of cases with a maximum number of harvested SLNs of three to four or more on average increased from 45% in the early period to 63% in the later period. The percentage of patients with a maximum number of harvested SLNs of more than six increased from 82% in the early period to 88% in the later period. Three hospitals in the early period and four hospitals in the later period harvested a maximum of 12 or more SLNs respectively.

Intraoperative SLN pathologic examination and its rate of agreement with permanent section

Two hospitals in the early period and one in the later period did not conduct any intraoperative SLN examination. In the early period, five hospitals used frozen section, two used Cyto-print and two used both methods. In the later period, 11 hospitals used frozen section; of them, five were from the original group of hospitals, five were from the new group and one was from a hospital not originally performing intraoperative examination. One hospital had a 100% match rate between the results of frozen section and permanent section in the early period, but the match rate decreased to 95% in the later period. In the early period, only two hospitals had a 95% match rate and another six hospitals had a 90% match rate. In the later period, the majority (13/15) of included hospitals had a 95% match rate, and only two of the newly included hospitals had a 90% match rate.

Cytokeratin staining

All cytokeratin staining results on the negative SLNs were obtained from subsequent permanent sections. Two hospitals in the early period and 10 in the later period used this method. Upstaging of breast cancer based on cytokeratin staining results occurred in 10 out of 359 patients in the early period and 31 out of 912 patients in the later period. Of these 41 patients, no cancer metastasis was found in other non-SLNs after ALND.

False negative rate and sparing of ALND

The FNR in the early period was < 7% in eight hospitals and > 7% FNR in three hospitals. Table 3 compares results for the two periods including the number of SLN biopsy cases, number of positive SLN versus false negative cases, FNR, and the number of ALND-sparing cases in the eight hospitals with FNR < 7% in the early period. Two of these hospitals did not report the number of cases with SLN biopsy or the FNR, but did report the

Table 3. Comparison of false-negative rate (FNR) and number of patients spared axillary lymph node dissection (ALND) in hospitals with initial FNR < 7%

SLN cases (*n*)		SLN+/F		FNR (%)		ALND spared (*n*)	
Initial	Later	Initial	Later	Initial	Later	Initial	Later
140	NA	46/0	NA	0	NA	134	41
124	NA	43/0	NA	0	NA	4	32
43	36	30/1	33/1	3.3	3.1	92	17
814	355	286/10	18/0	3.5	0	30	36
111	63	22/1	16/1	4.3	5.8	18	16
219	71	73/5	23/1	6.4	4.2	8	18
165	58	45/3	18/1	6.4	5.8	20	22
251	77	66/5	33/2	7.0	5.7	20	12

SLN = sentinel lymph node; SLN+/F = SLN positive number/false negative number; NA = not available.

Table 4. Comparison of false-negative rate (FNR) and number of patients spared axillary lymph node dissection (ALND) in hospitals with FNR > 7% in the initial period and newly participating hospitals

SLN cases (*n*)		SLN+/F		FNR (%)		ALND spared (*n*)	
Initial	Later	Initial	Later	Initial	Later	Initial	Later
50	51	7/2	8/0	22	0	6	0
32	42	10/2	5/0	17	0	6	0
15	28	3/1	7/0	33	0	2	0
	131		113/2		1.7		10
	35		5/3		37.5		15
	204		55/2		3.5		36
	114		23/1		4.2		19
	79		19/1		5.0		76

SLN = sentinel lymph node; SLN+/F = SLN positive number/false negative number.

number of cases spared ALND in the later period. Comparison of the FNR in the two periods for the other six hospitals revealed a decrease of FNR around 5% in the later period but the number of patients spared ALND did not increase in proportion with the increased number of SLN biopsy cases. Table 4 compares the FNR and number of patients spared ALND in hospitals with FNR > 7% in the initial period, including the five newly participating hospitals in the later period. The three hospitals with FNR > 7% in the initial period had a decrease in FNR to 0% and did not perform ALND-sparing surgery in the later period. Of the five newly participating hospitals in the later period, four had FNR < 5%, and one had an FNR of 37.5%; the surgeon-in-charge in that hospital performed ALND-sparing surgery on 15 patients.

Analysis of the accumulated case number in each institute and its relation to the resulting FNR revealed that breast surgeons with more than 100 cases of experience had significantly lower FNR than those with a case experience of less than 100 (average FNR 3.8 *vs.* 8.2, $p < 0.01$).

Discussion

Blue dye has the advantages of no radiation damage, easy injection during surgery, clear demonstration of the lymphatic channel near a SLN, short waiting time for tracer spread, and no need for a sophisticated detection instrument. However, its disadvantages include harvest of a small number of SLNs due to short staining time, difficulty in

identifying SLNs due to bleeding during operation, blue coloration in the breast and urine and anaphylactic reaction.[9] While the lethal complication in previous studies was usually caused by lymphozurin, this blue dye is not available in Taiwan. This explains why anaphylactic reaction did not occur in this study.

Use of an isotope has the advantages of harvest of a large number of SLNs, no interference from bleeding during SLN identification, and a small incision wound. However, the procedure requires a special gamma detector, is limited to hospitals with nuclear medicine facilities, requires at least 2 hours of waiting time after injection, and may expose patients, surgeons and pathologists to harmful radiation.[10] The radiation dose of 1–2 mCi technetium-99 is in the accepted safety range according to the Medical Internal Radionuclide Dosimetry Committee of the Society of Nuclear Medicine in the USA.[11] When using legend colloid, the smaller the molecule, the more SLNs will be shown and vice versa. Unfiltered colloid smaller than 1000 nm is universally accepted as adequate to identify SLN.[12]

Both blue dye and isotope can identify SLNs in the axilla during surgery with rates of 90% to 92% respectively. However, previous studies showed that combined use of these two agents could provide an extra capability of identifying SLN during surgery, with an increase of up to 98% compared to using either agent alone.[10,13] In this study, the number of hospitals that used the combined tracer method doubled in the later period. This is partially reflected by the 95% increase in the SLN biopsy success rate in the later period. Nevertheless, hospitals, which used only one tracer, still had a SLN biopsy success rate > 95%. This is largely attributable to having acquired enough experience to conduct this procedure. However, one hospital that used 2 mCi Tc-99 legend with more than 1000 nm colloid had only an 85% SLN biopsy success rate. It is possible that the use of a too large colloid was responsible for the decreased number of SLNs identified and harvested. In addition, use of a higher dose of isotope did not improve the SLN biopsy success rate in this hospital. The isotope was usually injected on the day before biopsy to allow more time for surgery on the following day and to improve the SLN biopsy success rate.[14] A previous study found that multiple injections of tracer on the tumor and nipple-areola complex revealed more SLNs through different lymphatic drainage channels.[15] In the later period of this study, more hospitals advocated this approach, which may partly explain the higher SLN biopsy success rate. When isotope was used in SLN biopsy, the background was essential for SLN identification based on the comparative radioactivity count between SLN and background.[16] A procedure, which requires > 10% radioactivity count in the hottest node in the axilla, has been outlined in many studies and was performed at two hospitals in this study. Such a procedure might pose a risk of concealing a hot node with cancer metastasis in the axilla due to missing the hottest node in the first biopsy step.[3] When using the abdomen as background, every hot node in the axilla, whether positive or negative for cancer metastasis, will be found. The only drawback to this approach is that it requires more biopsy steps and takes more time to complete in a patient with multiple SLNs. In this study, more hospitals (87%) selected the abdomen as the background in the later period compared to the early period (56%). A standard assumption in SLN biopsy is that the more SLNs harvested, the lower the resulting FNR.[17] In this study, the increased identification success rate and decreased FNR showed that it was worthwhile to take more time during surgery.

Intraoperative SLN pathologic examination can provide information regarding cancer metastasis and ALND can be performed immediately afterwards. In this study, all but two hospitals in the early period and one in the later period used such a procedure. Some pathologists were concerned that a frozen section procedure would consume tissue, which could harbor microscopic metastatic lesions. As pathologists accumulated more experience, the diagnostic accuracy rate increased. A previous study reported that the key to increasing the matching rate was to use multiple

sections on each SLN instead of the traditional bi-halved method,[18] and this method was introduced in the two SLN workshops in February 2003 and August 2004. A more than 95% increase in accuracy rate occurred from 22% in the early period to 87% in the later period. One hospital had a 100% matching rate in the early period despite experience with less than 20 cases; the rate decreased to 95% in the later period, after treatment of a total of 50 cases. The Cyto-print method has the advantage of zero tissue consumption with results equivalent to frozen section. However, according to previous reports, nearly 20% of findings are suspicious and a subsequent permanent section is required for proof. Besides, an experienced cytologist is needed to use this approach.[19] Micrometastatic lesions can also be found by meticulous intraoperative review of multiple sections of SLN. Cytokeratin immunohistochemical staining can highlight micrometastasis, which may be hidden on hematoxylin and eosin staining in SLN, resulting in a change in the staging of breast cancer. Surgeons and pathologists who participated in this study were highly in favor of this examination during the later period. In this study, the number of cases, which were converted from a negative SLN result to a positive result increased as more hospitals performed this examination routinely.

The SLN biopsy confidence rate for solid cancer should be validated based on the results for FNR; too high a value of FNR is not acceptable.[20] It has been well documented that breast cancer metastasis to axillary lymph node has a 3–5% skip metastatic rate; positive lymph nodes have been found in higher level axilla but not in lower axilla.[21] Therefore, a 5% FNR is acceptable in SLN biopsy of breast cancer patients.[4] In the initial period of this study, eight hospitals had an FNR $< 7\%$, while in the later period this rate decreased to $< 5\%$. Notably, seven of these hospitals had more than 100 cases of accumulated experience in the initial period. The remaining three hospitals had an initial FNR $> 7\%$ and had less than 50 cases of experience in the initial period. The FNR in these hospitals, however, decreased to 0% in the later period as with the accumulation of accumulated over 100 cases of experience. In addition, ALND-sparing surgery was not performed in these three hospitals in the later period for the sake of patient safety. The impact of the two SLN workshops was apparent and more experience was required to improve the skill levels for every breast surgeon. The five newly participating hospitals in the later period had an FNR similar to that of the original 11 hospitals. Another hospital with only 35 cases of experience had an FNR of 37.5% and performed ALND-sparing surgery on 15 patients. The surgeon responsible for all case data in that hospital was asked to suspend future ALND-sparing surgery until his FNR in SLN biopsy decreased to less than 5%.

Bass et al analyzed the relation between case experience and FNR and concluded that at least 30 cases were needed to reach a 5% FNR,[22] and that a false-negative event was usually encountered in the first 30 cases of SLN biopsies. However, this study found that experience with at least 100 cases resulted in an acceptable FNR and that patients undergoing ALND-sparing surgery in such environments will be safe. Recently, the axillary recurrence rate in ALND-sparing surgery patients with negative SLN was estimated to be around 0.32% after 2.5 years of follow-up.[23] Although many institutes have reached a safe range with regard to FNR, breast surgeons in Taiwan are still reluctant to perform ALND-sparing surgery on breast cancer patients with negative SLN due to a lack of nationwide collaborating supporting evidence. Further, current practices are not based on validation from a large population. Based on the results of the study of Bass et al[22] and the results of this study, the Taiwan Breast Society developed compromised guidelines stating that experience with at least 50 cases of SLN biopsy validation is needed for a breast surgeon to safely perform ALND-sparing surgery on breast cancer patients with negative SLN. This is also in agreement with the findings of the EORTC Breast Cancer Group.[24] Therefore, a nationwide one-arm SLN biopsy protocol in breast cancer requiring that breast surgeons have validated experience of at least 50

SLN biopsies with FNR < 5% will be recommended by the Taiwan Breast Society and the National Health Research Institute in order to ensure the best quality of life for breast cancer patients with negative SLN undergoing ALND-sparing surgery.

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References

1. Krag DN, Weaver DL, Alex JC, et al. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 1993;2:335–9.
2. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391–8.
3. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph nodes. *Lancet* 1997;349:1864–7.
4. Schwartz GF, Giuliano AE, Veronesi U. Consensus Conference Committee. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast. April 19–22, Philadelphia, Pennsylvania. *Cancer* 2002;94:2542–51.
5. Yu CC. Breast cancer registration in Tri-Service General Hospital, 2005. [Unpublished data]
6. Bulletin of Combined Workshop of Sentinel Lymph Node Biopsy in Breast Cancer, July 3, 2000, Taichung Veterans General Hospital, Taichung, Taiwan, ROC.
7. Abstract book of 4th Asian Breast Cancer Conference. February 27–29, 2004. Taipei, Taiwan, ROC.
8. Bulletin of Sentinel Node Biopsy in Breast Cancer Workshop, Taiwan Breast Society August 7, 2004.
9. Giuliano GE, Jones RC, Brennan M, et al. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997;15: 2345–50.
10. Tafra L, Lannin DR, Swanson MS, et al. Multicenter trial of sentinel lymph node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. *Ann Surg* 2001;233:51–9.
11. Stratmann SL, McCarty TM, Kuhn JA. Radiation safety with breast sentinel node biopsy. *Am J Surg* 1999;178:454–7.
12. Pijpers R, Meijer S, Hoekstra OS, et al. Impact of lymphoscintigraphy on sentinel node identification with technetium-99m-colloidal albumin in breast cancer. *J Nucl Med* 1997;38:366–8.
13. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996;276:1818–22.
14. Liu TJ, Yeh DC, Wu CC, et al. Selective sentinel lymph node dissection in breast cancer: experience from Taiwan. *Surg Clin North Am* 2000;80:1779–86.
15. Canavese G, Gipponi M, Gatturich A, et al. Pattern of lymphatic drainage to the sentinel lymph node in breast cancer. *J Surg Oncol* 2000;74:69–74.
16. Duncan M, Cech A, Wechter D, et al. Criteria for establishing the adequacy of a sentinel lymphadenectomy. *Am J Surg* 2004;187:639–42.
17. Wong S, Edwards M, Chao C, et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes on the false negative rate. *J Am Coll Surg* 2001; 192:684–9.
18. Turner RR, Giuliano AE, Hoon DSB, et al. Pathological examination of the sentinel lymph node for breast carcinoma. *World J Surg* 2001;25:798–805.
19. Van Diest PJ, Torrenga H, Borgstein PJ, et al. Reliability of intraoperative frozen section and imprint cytological investigation of sentinel lymph node in breast cancer. *Histopathology* 1999;35:14–8.
20. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer: a multicenter validation study. *N Engl J Med* 1998;339:941–6.
21. Veronesi U, Luini A, Galimberti V, et al. Extent of metastatic axillary involvement in 1446 cases of breast cancer. *Eur J Surg Oncol* 1990;16:127–33.
22. Bass SS, Cox CE, Ku NN, et al. The role of sentinel lymph node biopsy in breast cancer. *J Am Coll Surg* 1999;189: 183–94.
23. Jeruss JS, Winchester DJ, Sener SF, et al. Axillary recurrence after sentinel node biopsy. *Ann Surg Oncol* 2005; 12:34–40.
24. *Manual for Clinical Research in Breast Cancer*, 5th edition. EORTC Breast Cancer Group. London, UK: Greenwich Medical Media, 2004:57–8.