

Should we examine sentinel lymph nodes during the operation?

Akimitsu Yamada, Kazuaki Takabe

Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University School of Medicine and Massey Cancer Center, Richmond, VA 23298-0011, United States

Corresponding to: Kazuaki Takabe, MD, PhD, FACS. Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University School of Medicine and Massey Cancer Center, PO Box 980011, West Hospital, Room 7-402, 1200 East Broad Street, Richmond, VA 23298-0011, United States. Email: ktakabe@vcu.edu.



Submitted Sep 30, 2012. Accepted for publication Oct 29, 2012.

DOI: 10.3978/j.issn.2227-684X.2012.10.05

Scan to your mobile device or view this article at: <http://www.glandsurgery.org/article/view/1200/1640>

Axillary lymph node metastasis is one of the most important predictor of outcome in breast cancer (1,2). Currently sentinel lymph node biopsy (SLNBx) has been established as the golden standard to determine the node status (3). The concept of analyzing the first “gate keeper lymph node” to define the likelihood of further lymphatic spread has dramatically transformed the surgical approach against breast cancer. It is very well known that the routine axillary lymph node dissection (ALND) is associated with high complication rate, and the practice of selective SLNBx has significantly reduced its occurrence (4,5).

However, there are several concerns regarding intraoperative evaluation of the SLNBx. First of all, it is quite obvious that more metastases will be identified when more sections from SLNs are evaluated. On the other hand, it is not practical to expect the practicing pathologist to mount, stain, and microscopically examine every single section throughout the every single SLNBx within the operation time. Second, despite the fact that the College of American Pathologists and the American Society of Clinical Oncology did publish their guidelines, the evaluation of SLNs differs significantly between the institutions (6). A recent meta-analysis of 13,000 patients demonstrated an overall sensitivity of 73.6% in accurate diagnosis of macrometastasis (Ma), micrometastasis (Mi) and isolated tumor cells (ITC) combined together by intraoperative frozen section examination. It was pointed out that the sensitivity of Mi/ITC specifically remained low with 40% with frozen section despite the fact that Ma was detected in 94% of the cases (7).

In order to clarify the sensitivity and specificity of SLNBx from intraoperative frozen section and to evaluate

the effectiveness of ALND when Mi or ITC were detected by frozen section, Taffurelli *et al.* analyzed 753 patients who underwent SLNBx (8).

In this study, SLNBx has been selected for patients with T1 (tumor ≤ 2 cm) and T2 (tumor > 2 cm - ≤ 5 cm) disease, without evidence of multifocal involvement or clinically positive lymph nodes. SLNBx for ductal carcinoma *in situ* (DCIS) was included in this study, although its role remains controversial. This was based upon the report that preoperative diagnosis of DCIS has a high probability of underestimation, and 15% of invasive cancer patients have node metastasis (9). Pathological analysis of the intraoperative frozen section was performed on 4-6 slices. When Ma or Mi was detected, radical ALND was performed. The complete lymph node examination was deferred to final pathology, with the purpose of obtaining an intraoperative acceptable Ma detection rate.

A total of 753 patients were enrolled in the study, 158 patients were found to have metastatic disease by frozen section (129 Ma, 27 Mi and 2 ITC) and 156 patients with Ma or Mi underwent completion ALND during the same procedure. A total of 595 SLNs were found to be disease free by frozen section. The final pathological examination revealed 293 patients having a metastatic SLN (158 diagnosed correctly and 135 false negatives by frozen section). Overall, only 16 of 595 patients were diagnosed as Ma by the final pathology of SLN (2.6%), whereas Mi and ITC were found in 70 of 595 (11.8%) and 49 of 595 (8.2%) patients, respectively. All patients with Ma or Mi by final pathology underwent delayed ALND.

Despite the fact that sensitivity of intraoperative frozen section for Mi was found to be very low, it still

spared certain amount of patients from undergoing a delayed ALND as a second operation. Intraoperative examination of SLNBx had a 54% overall sensitivity in detecting any degree of metastatic disease (Ma/Mi/ITC). When Ma was analyzed separately, sensitivity improved to approximately 89%. On the other hand, Mi or ITC were detected by frozen section in only 27% and 4% of the cases, respectively. When the detection rate of Ma and Mi by frozen section were combined together, the sensitivity is 65%, which also means that 156 of the 222 women in their study were spared a delayed ALND.

Whether completion ALND is indicated when Mi is detected in SLN regardless of the timing remains controversial. Chen *et al.* have reported that tumor smaller than 2.0 cm detected by mammogram had little detrimental impact with the presence of Mi in the final pathology of the SLN (6,10). On the other hand, de Boer *et al.* found that neoadjuvant treatment improved overall survival of the patients who were detected with ITC or Mi in the preoperative SLNBx (11).

In this study, 72 out of 222 patients had at least one positive non-SLN found by ALND (32.4%). Fifty-six of 145 patients (38.6%) with Ma in SLN had more than one non-SLNs affected by the disease, while only 8 of 73 (10.9%) in the subgroup with Mi in SLN had metastatic non-SLNs. Sixty-five of 73 patients (89.1%) in this last group underwent radical ALND with no disease found in other axillary nodes. In other words, a delayed ALND as the second procedure was deemed oncologically meaningless in 90% of cases.

Because of the strong results produced from studying SLNBx, many clinicians began to question whether there is any role for completion ALND. American College of Surgeons Oncology Group Z0011, a multicenter, randomized clinical trial conducted by Giuliano *et al.*, evaluated whether a positive SLNBx necessitates ALND in order to improve overall survival in breast cancer patients (12). In order to reach statistical power to be able to determine non-inferiority, this trial had planned to randomize 1,900 patients with one or two positive SLNs to either ALND or no further surgical treatment, with all patients receiving appropriate radiation and systemic therapy. However, the study was published after enrollment of only 891 patients for randomization. After following these patients for a median of 6.3 years, 5 year overall survival was 91.8% versus 92.5%, and 5 year disease free survival was 82.2% versus 83.9%, for ALND versus SLNBx alone, respectively (12). With no statistical difference between the two groups, they concluded that additional

ALND is no longer necessary for SLNBx positive patients, but the others argue that the number of patients studied in this trial may not be statistically sufficient to produce generalizable findings.

Another study from a single center evaluated 5 year disease free survival of 532 patients with T1 breast cancer (tumor ≤ 2 cm) who were randomized to either SLNBx followed by ALND in all cases, or SLNBx alone if it had been negative (13). The results demonstrated that there was no significant difference in disease free survival, which were 92.9% *vs.* 88.9% for SLNBx + ALND *vs.* SLNBx alone, respectively. The results of this trial demonstrated that ALND had no therapeutic impact on breast cancer survival. Because of the importance of lymph node status to appropriately stage and guide treatment in breast cancer, currently there are no recommendations to omit SLNBx.

In conclusion, intraoperative frozen section of sentinel lymph node allows completion axillary lymph node dissection during the same surgical procedure when needed. This report by Taffurelli *et al.* suggests that aggressive surgical approach may not be necessary when micrometastases or isolated tumor cells are detected in the sentinel lymph nodes.

Acknowledgements

Kazuaki Takabe is supported by United States National Institute of Health (R01CA160688) and Susan G. Komen for the Cure [Investigator Initiated Research Grant (IIR12222224)].

Disclosure: The authors declare no conflict of interest.

References

1. Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002;20:3628-36.
2. Woodward WA, Strom EA, Tucker SL, et al. Changes in the 2003 American Joint Committee on Cancer staging for breast cancer dramatically affect stage-specific survival. *J Clin Oncol* 2003;21:3244-8.
3. Rashid MO, Takabe K. Sentinel Lymph Node Biopsy for Breast Cancer: Our Technique and Future Directions in Lymph Node Staging. *J Nucl Med Radiat Ther* 2012;S2:005.
4. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003;349:546-53.

5. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010;11:927-33.
6. Weaver DL. Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale. *Mod Pathol* 2010;23:S26-32.
7. Liu LC, Lang JE, Lu Y, et al. Intraoperative frozen section analysis of sentinel lymph nodes in breast cancer patients: a meta-analysis and single-institution experience. *Cancer* 2011;117:250-8.
8. Taffurelli M, Montroni I, Santini D, et al. Effectiveness of sentinel lymph node intraoperative examination in 753 women with breast cancer: are we overtreating patients? *Ann Surg* 2012;255:976-80.
9. Park HS, Park S, Cho J, et al. Risk predictors of underestimation and the need for sentinel node biopsy in patients diagnosed with ductal carcinoma in situ by preoperative needle biopsy. *J Surg Oncol* 2012. [Epub ahead of print].
10. Chen SL, Hoehne FM, Giuliano AE. The prognostic significance of micrometastases in breast cancer: a SEER population-based analysis. *Ann Surg Oncol* 2007;14:3378-84.
11. de Boer M, van Deurzen CH, van Dijck JA, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med* 2009 Aug 13;361:653-63.
12. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;305:569-75.
13. Veronesi U, Paganelli G, Viale G, et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. *Lancet Oncol* 2006;7:983-90.

Cite this article as: Yamada A, Takabe K. Should we examine sentinel lymph nodes during the operation? *Gland Surg* 2012;1(3):161-163. DOI: 10.3978/j.issn.2227-684X.2012.10.05