The Breast Journal

ORIGINAL ARTICLE

The role of Micrometastatic Disease in Sentinel Lymph Node in Breast Cancer

Francesca Rovera, MD, Francesco Frattini, MD, Corrado Chiappa, MD, Cristiano Piscopo, MD, Veronica Bianchi, MD, Gianlorenzo Dionigi, MD, FACS, Stefano Rausei, MD, Luigi Boni, MD, FACS, and Renzo Dionigi, MD, FACS

Department of Surgical Sciences, University of Insubria, Varese, Italy

■ **Abstract:** Sentinel lymph node (SLN) biopsy is the standard procedure for axillary node staging in breast cancer. Improvements in histopathological analysis and immunohistochemistry have recently increased the rate of detection of lymph nodal micrometastases. The clinical implications and prognostic significance of micrometastases in SLN still remain a controversial issue. Literature review was analyzed by searches of Medline and PubMed data bases. Whereas most studies carried on small groups of patients did not show differences in survival, recently some studies with longer follow-up and with larger populations demonstrated that prognosis of patients with micrometastases is worse compared to that of patients with SLN free of disease. To date, completion axillary dissection remains the standard option when a macro or micrometastasis (0.2–2 mm) in the SLN is found. However, in absence of level-1 evidence guidelines, each case requires discussion in the context of a multi-disciplinary team. ■

Key Words: axillary surgery, micrometastases, sentinel lymph node biopsy

Axillary lymph node status represents the most significant prognostic factor in breast cancer. Sentinel node biopsy has been validated as the standard technique in lymph nodal staging in breast cancer presenting high accuracy and minimal morbidity.

The development in the anatomopathological techniques of evaluation of sentinel lymph node (SLN) with serial sectioning and immunohistochemistry (ICH) has increased the identification rate of micrometastatic disease.

DEFINITION

Definition of micrometastasis is still controversial. The V Edition of the American Joint Committee (AJCC) Cancer Staging Manual defined "micrometastasis" a single cluster of metastases till 2 mm of size. The VI Edition of AJCC considered micrometastases a single cluster of metastatic cells of 2.0 mm or less and larger than 0.2 mm. Moreover, the same edition introduced the term of "Isolated Tumor Cells" (ITC) to consider single cells or small groups of cells of 0.2 mm or less (1).

The prevalence of micrometastatic disease in SLN ranges from 8% to 59% (mean 38%) (2).

DETECTION OF MICROMETASTASES

To date, most guidelines recommend a detailed analysis of SLN through multilevel sectioning coupled with cytokeratin ICH (2). However, a recent review by Cserni et al. (3) from about 240 pathology laboratories in Europe revealed a great variability in the work-up of nodes. On the basis of the survey by the European Working Group for Breast Screening Pathology (3), the most common methods, consisting of the evaluation of six levels separated by 150 μm, were used by only eight departments. A systematic and complete sampling is carried out in 25% of cases. The distance between sections also shows great variability, ranging from 2 to 500 μm. The immunohistochemical technique is not considered mandatory, but may be performed when the hematoxylin and eosin-stained slides have suspicious

Address correspondence and reprint requests to: Francesca Rovera, MD, Director, Senology Research Center, Department of Surgical Sciences, University of Insubria, Via Guicciardini 21100 Varese, Italy, or e-mail: francesca.rovera@uninsubria.it.

DOI: 10.1111/j.1524-4741.2010.00999.x

cells that are equivocal. With the introduction of a more detailed and intensive use of SLN, an upstaging would be expected. In a recent review (3,4), the upstaging rate ranged between 9% and 47% and upstaging was seen to be enhanced by the use of ICH staining for anticytokeratin. ICH seems to increase the ability of detecting metastatic cells in lymph node tissue. In addition, in recent years, advances in molecular biology have enabled highly sensitive techniques to be applied to SLN analysis. Reverse transcriptase polymerase chain reaction (RT-PCR) method is capable of detecting trace amounts of keratin messenger RNA produced by epithelial cells. RT-PCR has recently been reported to reach a sensitivity of 89.5% and a specificity of 96.7% on frozen sections (5). RT-PCR is even more sensitive than cytokeratin ICH and may identify very low-volume nodal involvement but, on the contrary, may also condition false signals. The VI AJCC Cancer Staging system considers a pN0 (mol+) (sn) a SNL found to be positive only by molecular methods (1).

PREDICTION OF NONSENTINEL LYMPH NODE METASTASES

Prevalence of micrometastases in nonsentinel lymph node in patients with sentinel node positive for micrometastases ranges from 0% to 57%. Several studies evidenced in multifactorial analysis that size of metastases in SLN is the most powerful risk factor of metastases in nonsentinel lymph nodes (6).

Viale and colleagues (7) published a study specific addressing the risk of further axillary metastases in patients with ITC-positive SLN. In this large single-institution series, 1228 patients with positive SLN were reclassified according to the VI AJCC Cancer Staging as follows: 64.6% macrometastases, 26% micrometastases, and 9.4% ITC. Interestingly, further nonsentinel metastases after axillary lymph node dissection (ALND) have been found in 50.3%, 21.4%, and 14.4% of these groups, respectively. Therefore, the finding of ITC in SLN is associated with a small (14.4%) but not negligible risk of further axillary involvement, as well as micrometastases of up to 1 mm in size (17%). If both groups are considered together, patients with ITC only or SLN metastasis smaller than 1 mm have the lowest risk of additional metastases compared with those with micrometastases 1–2 mm and those with SLN macrometastases.

Of 2929 cases with breast carcinoma not larger than 15 mm and staged with SLN biopsy, Cserni *et al.* (8) found no further axillary involvement in the other nodes dissected if the SLN had ITC (26 cases of 71 had ALND). In cases with micrometastases, 12% had further axillary node involvement (178 cases of 234 cases had ALND). SLN macrometastases were followed by axillary node involvement in 37% of cases (299 of 335 cases had ALND). In a predictive model considering the size of metastasis in the SLN combined with other significant predictors (number of positive SLNs and presence of vascular invasion of the primary tumor), patients with the most favorable combination of predictive factors still have a 13% risk of developing nonsentinel node metastases. So, even if most surgeons would not recommend completion axillary dissection in ITC-positive SLN, in others' opinions, it should be offered outside clinical trials.

PROGNOSTIC IMPLICATIONS OF MICROMETASTATIC DISEASE

Despite intensive working on the prognostic significance of micrometastases and ITC in the SLN, their clinical implications remain unknown.

Whereas the first studies on small groups of patients did not evidence differences in survival, recently several studies with longer follow-up (4–25 years) and with larger populations demonstrated that prognosis of patients with micrometastases is quite different from patients with SLN free of disease. The International Breast Cancer Study Group on 921 patients evidenced an increased risk of local recurrence in patients with micrometastases (9). The study of Grabau et al. (10), to date that with the largest population, has demonstrated a significantly worse overall survival in patients with micrometastases (RR 1.20, 95% CI, $p = 0.04$) compared with node-negative patients. Similar results have been reported by Colleoni (11) and Kujit (12). Chen et al. (13) reported SEER data of 209720 cases among which, in multivariate analysis of overall survival, cases with micrometastases had a HR of 1.35 compared with node-negative patients and of 0.82 compared with cases with macrometastases.

PRACTICAL APPROACH TO MICROMETASTATIC DISEASE

It is still a controversial issue what is the best procedure to perform in case of micrometastatic disease in SLN. In approximately 80% of patients with SLN

micrometastases, the SLN is the only involved axillary lymph node; therefore, further axillary surgery may be considered an overtreatment. The guidelines of the American Society of Clinical Oncology (ASCO) (14) recommend ALND in patients with micrometastases in SLN. To date, completion axillary dissection remains the standard option when a macrometastasis or micrometastasis (0.2–2 mm) in the SLN is found, while in the case of detection of ITC-positive SLN axillary dissection may be omitted, even if the low risk of further axillary involvement should be considered.

ONGOING RANDOMISED CLINICAL TRIALS

In the few next years, the ongoing large randomised trials will issue their preliminary results, both in Europe (Trial 23-01 of the International Breast Cancer StudyGroup [IBCSG]) and the USA (the ACOGSOG study Z0010 and NSABP study B-32). Results from these trials are expected to give an important contribution to clarify the prognostic value of micrometastasis and ITCs in SLN and whether sparing an axillary dissection in micrometastatic SLN is safe.

REFERENCES

1. Greene GL, Page DL, Fletcher C, editors. *AJCC Cancer Staging Manual*. 6th edn. New York: Springer; 2002.

2. Cserni G, Gregori D, Merletti F, *et al.* Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. *Br J Surg* 2004;91:1245–52.

3. Cserni G, Amendoeira I, Apostolikas N, *et al.*; European Working Group for Breast Screening Pathology Pathological work-up of sentinel nodes in breast cancer. Review of current data to be considered for the formulation of guidelines. *Eur J Cancer* 2003;39:1654–67.

4. Ryden L, Chebil G, Sjostrom L, Pawlowski R, Jonsson PE. Determination of sentinel lymph node status in primary breast cancer by prospective use of immunohistochemistry increases the rate of micrometastases and isolated tumor cells: analysis of 174 patients after SLN biopsy. *Eur J Surg Oncol* 2007;33:33–8.

5. Kurosumi M, Takei H. Significance and problems of histopathological examination and utility of real-time reverse transcriptase-polymerase reaction method for the detection of sentinel lymph node metastasis in breast cancer. *Breast Cancer* 2007;14:342–9.

6. Cserni G. Histopathologic examination of the sentinel lymph nodes. *Breast J* 2006;12(Suppl 2):S153–6.

7. Viale G, Maiorano E, Pruneri G, *et al.* Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. *Ann Surg* 2005;241: 319–25.

8. Cserni G, Bianchi S, Vezzosi V, *et al.* Sentinel lymph node biopsy in staging small (up to 15 mm) breast carcinomas. Results from a European multi-institutional study. *Pathol Oncol Res* 2007;13:5–14.

9. International (Ludwig) Breast Cancer Study Group. Prognostic importance of occult axillary lymph node micrometastases from breast cancers. *Lancet* 1990;335:1565–8.

10. Grabau D, Jensen MB, Rank F, Blichert-Toft M. Axillary lymph node micrometastases in invasive breast cancer: national figures on incidence and overall survival. *APMIS* 2007;115:828–37.

11. Colleoni M, Rotmensz N, Peruzzotti G, *et al.* Size of breast cancer metastases in axillary lymph nodes: clinical relevance of minimal lymph node involvement. *J Clin Oncol* 2005;23:1379–89.

12. Kuijt GP, Voogd AC, van de Poll_franse LV, Scheijmans LJ, van Beek MW, Roumen RM. The prognostic significance of axillary lymph-node micrometastases in breast cancer patients. *Eur J Surg Oncol* 2005;31:500–5.

13. Chen SL, Hoehne FM, Giuliano AE. The prognostic significance of micrometastases in breast cancer: a SEER population-bases analysis. *Ann Surg Oncol* 2007;14:3378–94.

14. Lyman GH, Giuliano AE, Somerfield MR, *et al.* American Society of Clinical Oncology Guideline Recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005;23:7703–20.