福岡大医紀（*Med. Bull. Fukuoka Univ.*）：37(2), 67–72, 2010

Micrometastasis of Breast Cancer in the Sentinel Lymph Nodes

Yasuteru YOSHINAGA[1)], Yasuko HAGIO[1)], Maya FUKUYO[1)], Akinori IWASAKI[1)], Mikiko IDA[2)], Ritsuko FUJIMITSU[2)], Makoto HAMASAKI[3)] and Kazuki NABESHIMA[3)]

[1)] *Department of Thoracic, Breast, Endocrine, and Pediatric surgery,*
[2)] *Department of Radiology*
[3)] *Department of Pathology, Faculty of Medicine, Fukuoka University*

Abstract：The surgical procedure for early breast cancer patients with negative axillary lymph nodes has changed from routine axillary clearance to a sentinel lymph node biopsy (SLNB). The presence of metastatic lymph nodes and the number of involved lymph nodes helps to determine the appropriate adjuvant systemic therapy. The significance of micrometastasis in the sentinel lymph nodes has been the subject of much debate, because the prognostic and therapeutic implication of micrometastasis to these lymph nodes remains unclear. This study retrospectively evaluated the clinical features of breast cancer patients with axillary micrometastasis. Two hundred and eighteen patients with early stage breast cancer underwent surgery including a SLNB between June 1996 and April 2009. A total 201 of SLNB procedures were successful and analyzed. The median follow-up was 37.7 months. A metastatic lesion was located in sentinel lymph nodes in 39 (19.4%) patients. The sentinel lymph nodes contained micrometastases in 9 of 201 patients (4.5%). Metastatic foci in non-sentinel lymph nodes were detected as macrometastases in one patient with micrometastases. None of the patients with micrometastases developed local recurrence or distant metastasis. The results suggest that avoiding an axillary lymph node dissection was not appropiate for a patient with micrometastases in the sentinel lymph nodes.

Key words：**Micrometastasis, Breast cancer, Sentinel lymph node, Axillary lymph node dissection**

Introduction

The surgical procedure for early breast cancer patients with negative axillary lymph nodes has changed from routine axillary clearance to a sentinel lymph node biopsy (SLNB). An axillary lymph node dissection is considered unnecessary in patients where the sentinel lymph node appear to be free of tumor by a pathological examination. Large randomized studies have confirmed by the efficacy and reduced morbidity of an axillary lymph node dissection associated with a SLNB as an axillary staging procedure.[1)] Adjuvant systemic therapy is planed after surgery according to various prognostic factors (i.e. invasive tumor size, number of involved lymph nodes and others)and predictive factors (i.e. status of hormone receptor and HER2). A SLNB can reduce the number of lymph nodes extirpated, so the pathological analysis is more detailed for only selected lymph nodes than before. Consequently, there are patients with only small metastatic foci or micrometastasis in the lymph nodes. These terms are defined by the International Union Against Cancer (UICC) TNM classification[2)]：macrometastasis larger than 2.0 mm, micrometastasis larger than 0.2 mm but none larger than 2.0 mm and isolated tumor cells no longer than 0.2 mm. However the significance of these micrometastases without macrometastases has not yet been clarified.

This article retrospectively evaluated the clinical

Correspondence to：Yasuteru Yoshinaga M. D.,
Department of Thoracic, Breast, Endocrine, and Pediatric surgery 7-45-1, Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan
Tel：+81-92-801-1011 Fax：+81-92-861-8271 E-mail：srk@fukuoka-u.ac.jp

features of breast cancer patients with axillary micrometastasis.

Patients and methods

Two hundred and eighteen patients with early stage breast cancer underwent surgery including a SLNB at Fukuoka University Hospital between June 1996 and April 2009. Inclusion criteria for this study were (1) breast cancer diagnosed histologically or cytologically before the surgery, (2) absence of clinically involved axillary lymph nodes by physical and ultrasound examination, (3) acceptance of informed consent concerning the SLNB.

SLNB procedure

SLNB was performed by three methods using blue dye only or a combination of blue dye and a radiolabeled colloid, or blue dye and CT lymphography.

Ninety-one primary breast cancer patients underwent SLNB only using blue dye (2ml, 2.5% patent blue violet) that was injected subdermally above the tumor or subareolar 10–15 minutes prior to incision. 119 patients received CT lymphography on the day before surgery using Iodinated contrast medium injected in the same regions. CT lymphography was performed preoperatively to identify the lymphatic drainage route to the ipsilateral axillary area and the presence of sentinel lymph nodes. Eight patients were received radioisotope technique as described others.[3] All blue or hot nodes and surrounding these nodes were extirpated as the sentinel lymph nodes.

Frozen sections of the sentinel lymph node were routinely performed intraoperatively. All removed lymph nodes were sectioned at 2.0 mm intervals. The sections were stained with hematoxylin and eosin, and immunohistochemical staining after surgery if necessary. The patients with negative sentinel lymph nodes, as diagnosed by frozen sections, could thus avoid an axillary node dissection after a feasibility study of 40 cases. A subsequent axillary dissection was carried out when macrometastases or micrometastases were diagnosed in frozen sections. Conversely, no additional axillary dissection was performed when only micrometastsis was diagnosed on a permanent section after surgery.

Adjuvant therapy

Patients received radiation therapy with 50 Gy and a boost of 10 Gy when indicated after breast-conserving surgery. Adjuvant systemic therapy was administered with hormone treatment (when hormone receptor positive) and/or chemotherapy based on the recommendations of the St. Gallen Consensus Conference.[4]

Postoperative follow-up

The patients were followed up every three months by means of physical and ultrasound examinations in the first year after the surgery and every six months from the second and all following years until the 10th year of follow-up, as well as undergoing mammography annually.

Results

Two hundred and eighteen patients underwent SLNB by three methods. Table 1 shows that the identification rate of sentinel lymph node was superior by blue dye + CT or blue dye + RI methods in comparison to blue dye only. The SLNB procedure failed in seventeen patients. A total 201 of SLNB procedures were analyzed. The median follow-up was 37.7 months.

The characteristics of a successful SLNB are

Table 1 Sentinel lymph node biopsy procedure

technique	Blue dye	Blue dye + CT	Blue dye + Rl
Number	91	119	8
Identification rate of SLNs (%)	84.6	97.5	100
Number of removed SLNs (mean)	2.2	1.6	3.1
Number of patients with metastasis	19	24	4
Number of patients with micrometastasis	1	7	1

SLN : sentinel lymph node

listed in Table 2. The mean age was 69.0 years. The mean tumor size was 19.8 mm. One hundred and seventy-eight patients showed an invasive tumor (88.6%) cases and 23 showed a non-invasive tumor (11.4%). A partial mastectomy, indicating breast- conserving surgery, was performed in 105 patients. An average of 2.0 sentinel lymph nodes were harvested per patient. Eighty-six (42.8%) patients underwent an axillary lymph node dissection after SLNB. Metastases were detected in the dissected non-sentinel lymph nodes after a negative diagnosed in the sentinel lymph nodes in five patients after surgery. But the metastasis appeared at only one lymph node each in these five patients.

Metastatic lesions were located in the sentinel lymph nodes in 39 (19.4%) patients. The characteristics of the patients with positive sentinel lymph nodes are summarized in Table 3. All of those patients were female and had invasive tumors. The sentinel lymph nodes contained micrometastases in 9 of 201 patients (4.5%). Micrometastases were detected intraoperatively in 4 of 9 and in 5 after surgery (Fig. 1). No axillary lymph node dissection was performed in 4 of 9 patients. There was no statistical difference in

Table 2 Patients and tumor characteristics of successful SLNB

Gender (M : F)	3 : 198
Age (mean)	69.0
Menopausal status	
Premenopausal	57
Postmenopausal	141
Tumor size (mean, mm)	19.8
Histology	
Invasive	178
Non-invasive	23
Operation	
Partial mastectomy	105
Total mastectomy	87
Others	9
Hormone receptor status	
Positive	158
Negative	43
HER2 status	
Positive	22
Negative or unknown	189
No. of SLN per patients	2.0
No. of patients with axillary dissection	86

Table 3 Characteristics with metastatic SLN (n=39)

	macrometastasis (n=30)	micrometastasis (n=9)
Age (mean)	56.4	59.2
Menopausal status		
Premenopausal	9	2
Postmenopausal	21	7
Tumor size (mean, mm)	23.5	16.9
Operation		
Partial mastectomy	14	5
Total mastectomy	15	4
Others	1	0
Hormone receptor status		
Positive	28	7
Negative	2	2
HER2 status		
Positive	3	1
Negative or unknown	27	8
No. of SLN per patients (mean)	2.3	2.3
No. of metastatic nodes per patients (mean)	2.5	2.0
No. of patients with non-SLN metastasis	11	1

the mean age, menopausal status, mean tumor size, operation, hormone status, HER2 status, number of sentinel lymph nodes per patients and number of metastatic lymph nodes per patients between the macrometastases group and the micrometastasis group. Additional metastases were found in non-sentinel nodes in 36.7% of patients (11/30) with macrometastases in sentinel node, in 11.1% of patients (1/9) with micrometastases. These figures are not significantly different (Chi-square χ^2 p=0.11). Metastatic foci in were detected as macrometastases in the non-sentinel lymph node of the patient with micrometastases in sentinel node (Fig. 2). One sentinel node was the only the site of metastasis in another eight patients with micrometastases.

All of patients with macro or micro metastatic lymph nodes were received adjuvant systemic therapy (Table 4). Hormonal and chemotherapy was administered more frequently in macrometastases group. Three patients with macrometastases were diagnosed with recurrence during the follow-up period 2 had distant metastases and 1 had local recurrence. The patients that developed distant

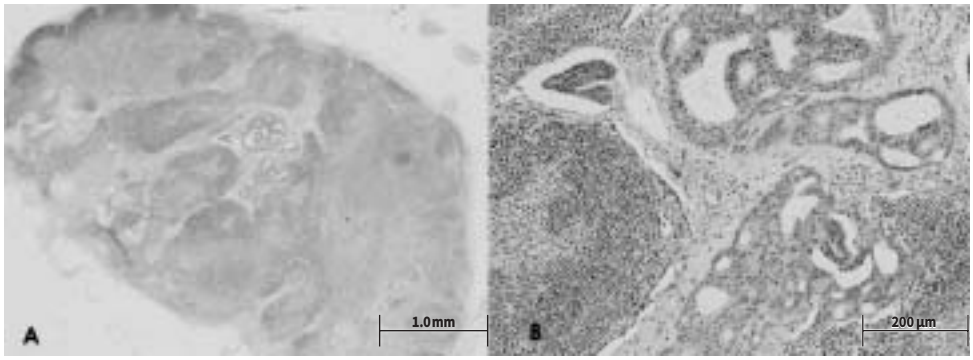

Fig. 1 Micrometastases in a sentinel lymph node, hematoxylin and eosin stained : (A) low power 20× and (B) high power 100×

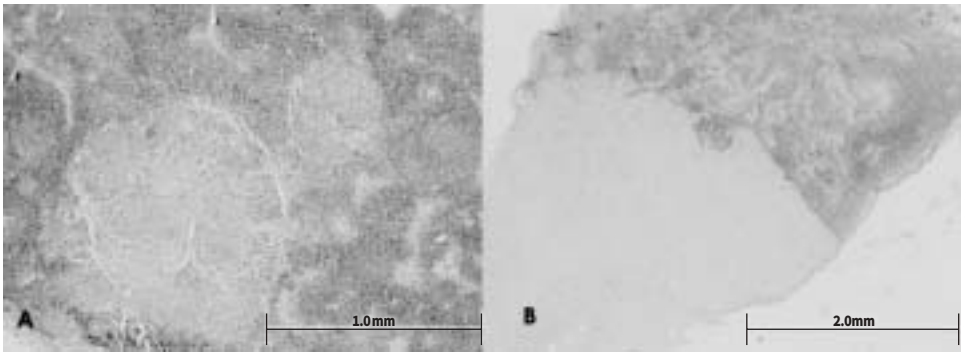

Fig. 2 Micrometastases in a sentinel lymph node 40× (A) and macrometastases in a non-sentinel lymph node 20× (B), hematoxylin and eosin stained

Table 4 Adjuvant therapy and prognosis (n=39)

	macrometastasis (n=30)	micrometastasis (n=9)
Adjuvant therapy		
Hormone therapy alone	8	4
Chemotherapy alone	2	2
Hormone + Chemotherapy	20	3
None	0	0
Prognosis		
Metastatic disease	3	0
Death	1	0

metastases in the bone died. None of the patients with micrometastases developed local recurrence or distant metastasis.

Discussion

Axillary lymph node status is one of the most important prognostic factor for patients with breast cancer.[5] The presence of metastatic lymph node and number of involved lymph nodes help to determine the appropriate adjuvant systemic therapy.

The significance of micrometastasis in the sentinel lymph nodes has been the subject of much debate, because the prognostic and therapeutic implications of micrometastasis in that tissue remain unclear.

Some of the earliest studies comparing node negative patients to those with micrometastasis in the axillary nodes found associations with poorer prognosis.[6] Bettelheim et al. revealed that the patients with micrometastases, in 9% of 921 patients, had a significantly poorer disease free and overall survival of five years.[7]

None of the patients in the micrometastasis group in the current series have developed recurrence. However, the small number of patients examined in this study might misrepresent these results.

Recent prospective trials have demonstrated that micrometastases have no prognostic implications when there are no further signs of axillary metastases.[8] It is noteworthy that there are many examples especially in the earlier literature where the definition of micrometastases has differed. Viale et al. have found that micrometastases in the sentinel nodes and the increasing size of micrometastatic site are significant predictors of non-sentinel metastasis.[9] Schrenk et al. reported that non-sentinel nodes are positive in 18% of those with micrometastases in the sentinel nodes in comparison to 51.1% of those with macrometastases.[10] On the other hand, Rutldge et al. reported that the risk of finding non-sentinel lymph node positivity was significantly lower in patients with micrometastases in the sentinel nodes (3%) in comparison to macrometastases (63%).[11]

Non-sentinel lymph node metastasis was found as a macrometastasis in a patient with micrometastases in the sentinel node. It is important to remove lymph nodes around blue or hot nodes and palpable nodes. Noguchi reported that it is impossible to indentify a subset of patients in whom axillary dissection can be omitted in a group of patients with micrometastases as well as macrometastases in the sentinel lymph nodes.[12] Axillary lymph node dissection should be considered necessary, when micrometastasis was found in frozen sections.

The identification of micrometastasis remains highly dependent on the analytical technique. Hematoxylin and eosin stain is complemented by immunohistochemical staining and molecular techniques, including PCR and RT-PCR, thus more micrometastases or isolated tumor cells are detected. There is the potential for stage migration and an impact on management decisions. Large prospective trials that assess the clinical implications of SLNB are ongoing.[13)-15)] These trials are expected to provide much information regarding the clinical significance of micrometastases in the axillary lymph node.

Patani et al. recommended that in the absence of evidence concerning the management of patients with micrometastases in the sentinel lymph nodes, each case requires discussion with regard to other tumors and patient related factors in the context of a multidisciplinary team.[16]

References

1) Veronesi U, Pagnelli G, Viale G. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 349 : 546-553, 2003.
2) Wittekind G, Greene FL, Hutter RVP et al. TNM Atlas, Illustrated Guide to the TNM/pTNM Classification of Malignant Tumors. pp. 207-223. Springer, New York, 2005
3) Krag D, Weaver D, Ashikaga T et al. The sentinel node in breast cancer- a multicenter validation study. N Engl J Med 36 : 941-946, 1998.
4) Goldhirsch A, Ingle JN, Gelber RD, Coates AS et al. Thresholds for therapies : highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2009. Ann of Oncol 20 : 1319-1329, 2009.
5) Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24, 740 breast cancer cases. Cancer 63 : 181-187, 1989.

6) Fisher ER, Palekar A, Rockette H, Redmond C, Fisher B. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol No. 4). V. Significance of axillary nodal micro- and macrometastases. Cancer 42 : 2032-2038, 1978.
7) Bettelheim R, Price KN, Neville AM. For the international (Ludwig) Breast Cancer Study Group : prognostic importance of occult axillary lymph node micrometastases from breast cancers. Lancet 335 : 1565-1568, 1990.
8) Cox C, Vrcel V, Riker A. Significance of sentinel lymph node micrometastasis on survival for patients with invasive breast cancer. Newsletter San Antonio Breast Cancer Symposium Issue3, December 10, 2005.
9) 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 241 : 319-325, 2005.
10) Schrenk P, Konstantiniuk : Wolfl S, Bongner S, Haid A, Nemes C, Jagoutz-Herzlinger M, Redtenbacher S. Prediction of non-sentinel lymph node status in breast cancer with a micrometastatic sentinel node. Br J Surg 92 : 707-713, 2005.
11) Rutledge H, Davis J, Chiu R, Cibull M, Brill Y, McGrath P, Samayoa L. Sentinel node micrometastasis in breast carcinoma may not be an indication for complete axillary dissection. Mod Pathol 18 : 762-768, 2005.
12) Noguchi M. Avoidance of axillary lymph node dissection in selected patients with node-positive breast cancer. Eur J Surg Oncol 34 : 129-134, 2008.
13) Rutgers EJ, Meijnen P, Bonnefoi H. Clinical trials update of the European Organization for Research and Treatment of Cancer Breast Cancer Group. Breast Cancer Res 6: 165-169, 2004.
14) Mansel RE, Goyal A. European studies on breast lymphatic mapping. Semin Oncol 31 : 304-310, 2004.
15) White RI, Wilke LG. Update on the NSABP an ACOSOG breast cancer sentinel node trials. Am Surg 70 : 420-424, 2004.
16) Patani N, Mokbel K. The clinical significance of sentinel lymph node micrometastasis in breast cancer. Breast Cancer Res Treat 114 : 393-402, 2009.

(Received on January 9, 2010,
Accepted on March 2, 2010)