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The study of micrometastasis detection in sentinel lymph node of breast cancer

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Background: Although sentinel lymph node biopsy (SLNB) has become the method of choice for axillary staging, the extent of the pathological examination (HE or IHC, the number or intervals of sections) described in the literature differed considerably between studies, particularly for the detection of micrometastases (MMs). Our aim was to evaluate the optimal methods and intervals for the detection of SLN macrometastases, MMs and isolated tumor cells (ITCs).

Material and Methods: Ninety-eight continuous breast cancer patients with 200 SLNs identified "negative" with standard HE stain carried on initial 4 levels were retrospectively analyzed. All SLNs were step sectioned (SS) at 100μm interval, and for each level both HE and IHC with AE1/AE3 were performed. Then HE and IHC detection rates were analyzed at 100-, 200-, 300-, 400-, and 500μm intervals for the detection of macrometastases, MMs and ITCs.

Results: In 98 cases with original SLN negative cases, 18 (18.4%), 25 (25.6%) and 27 (27.6%) cases were found to had metastases with SS HE, SS IHC, and SS HE + IHC, respectively (SS HE + IHC vs. SS HE, $p = 0.004$). In all the 2175 sections, metastases were found in 79 sections (3.6%) by SS HE, and 127 (5.8%) by SS HE + IHC ($p = 0.000$). The metastases included macrometastases 16.7%, MMs 50.0%, and ITC 33.3%. The detection rates of MMs were 9.2%, 15.3%, and 16.3%, respectively (SS HE + IHC vs. SS HE, $p = 0.03$). The detection rates of ITCs were 6.1%, 7.1%, and 9.2%, respectively ($p > 0.05$). The detection rates of metastases at 100-, 200-, 300-, 400-, and 500-μm intervals by SS HE were 18.4%, 14.3%, 13.3%, 12.2%, and 12.2%, respectively. No significant differences were found between 100- and 200-μm intervals ($p = 0.125$), and between 100- and 300-μm ($p = 0.063$), while $p < 0.05$ between 100-μm and other intervals. The detection rates of metastases at 100-, 200-, 300-, 400-, and 500-μm intervals by SS HE + IHC were 27.6%, 23.5%, 18.4%, 20.4%, and 19.3%, respectively. No significant difference was found between 100- and 200-μm intervals ($p = 0.125$), while $p < 0.05$ between 100-μm and other intervals.

Conclusion: SS HE could significantly increase detection rate of SLN metastasis compared to our routine 4 levels HE pathological examination. SS HE + IHC could further significantly improve the detection of SLN metastases, mostly due to the detection of MMs. The optimal interval was 300 μm for SS HE, and 200 μm for SS HE + IHC. Our data will be updated to 244 cases with 4yrs follow-up at the meeting.

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Intraoperative frozen section examination of sentinel lymph node in breast cancer – always, never, sometimes

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Background: Intraoperative frozen section examination of sentinel lymph node (IFSESLN) in breast cancer is controversial and increases the operating time. Partial IFSESLN requests a delayed axillary lymph-node dissection (DALND) in false negative cases increasing costs and psychological distress for patients. The aim of this study is to identify a subset of breast cancer patients candidates for sentinel lymph node biopsy (SLNB) in which IFSESLN can be avoided increasing the number of daily operations, without increasing DALND.

Materials and Methods: 1205 IFSESLN consecutively performed at our department from 2001 to 2007 were reviewed and distribution of positive lymph nodes was considered according to tumor size and results of IFSESLN. IFSESLN was performed as follows: quick freezing was performed with a cooled flat weight to obtain a flat surface and 4 consecutive frozen sections were cut at a microtome setting of 4 microns. Care was taken to waste only the minimum lymph node material when cutting.

Results: Sensitivity of IFSESLN has been 41.9% and in 20.1% of patients a DALND was performed. In T1mic, T1a, T1b breast cancers (427 pts) 71 pts were N+ (16.6%). With IFSESLN the DALND were 51 i.e. 11.9%, with a reduction of 20 DALND (4.7%). In T1c, T2, T3-T4 breast cancers (778 pts) 347 pts were N+ (44.6%). With IFSESLN the DALND were 192 i.e. 24.6%, with a reduction of 155 DALND (19.9%) (Tab1).

Conclusions: According to the results above our future policy will be not to perform IFSESLN in T1mic, T1a, T1b breast cancers and to reoperate N+ patients of this group. On the basis of this experience if we had applied this policy, we would have performed IFSESLN in T1c, T2, T3-T4 breast cancers and DALND in 21.8% (263/1205). This would have increased of 1.7% the number of DALND performed and decreased of 35.4% (427/1205) the number of IFSESLN, allowing to reduce the waiting list by increasing the number of operations per day. On the basis of these data we will follow this policy.

Table 1. Distribution of breast cancer patients according to tumor size, positive lymph nodes and IFSESLN

Tumor size	No. of pts	%	N+	%	IFSESLN +	Sensitivity %	False negatives	%
T1mic	28	2.3	5	17.8	0	0	5	100
T1a	90	7.4	10	11.1	4	40	6	60
T1b	309	25.6	56	18.1	16	28.6	40	71.4
T1c	551	45.6	224	40.6	84	37.5	140	62.5
T2	222	18.4	120	54.1	68	56.6	52	23.4
T3–T4	5	0.4	3	60	3	100	0	0
All	1205	100	418	34.68	175	41.9	243	20.1

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The frozen section is superior to imprint cytology for intraoperative diagnosis of sentinel node biopsy for breast cancer

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Background: Sentinel lymph node biopsy (SNB) has become the preferred alternative to identify or exclude axillary nodal metastasis in breast cancer. Two procedures, intraoperative frozen section (Fs) analysis and imprint cytology (Cy) of sentinel lymph node (SLN) have been to shown to be reliable for detecting breast cancer metastases in SLN. Recently, several techniques such as histo- and cytopathologic methods, immnohistochemistry or molecular biology have been introduced, however, available in not all institutions as routine procedures. In the present study, we compared Fs and Cy to clarify which will be more reliable for intraoperative SLN diagnosis.

Materials and Methods: A total of 118 patients of primary breast cancer, who received SNB treatment at Niigata University Hospital between 2003 and 2006, were entered. The intraoperative SLN diagnosis was performed by Fs, Cy or both. The result of intraoperative diagnosis was compared with postoperative histological diagnosis (Hx). The sensitivity (ST), specificity (SP), accuracy (AC) and false negative rate (FNR) of each method was compared.

Results: SLNs were successfully identified in all 118 patients (100%), and SLN metastases were detected in 30 cases by intraoperative Cy and/or Fs. However, postoperative Hx revealed metastatic SLNs in further 2 cases (ST 93.8%, AC 98.3% and FNR 6.3%). Among 368 removed SLNs, metastases were detected in 48 nodes by intraoperative Cy and/or Fs. However, postoperative histological diagnosis revealed metastatic SLNs in further 2 nodes (ST 96%, AC 99.5%, FNR 4%). The intraoperative Cy diagnosis was performed in 117 cases, and metastatic SLNs was detected in 26 cases, however, postoperative Hx revealed metastatic SLNs in further 3 cases (Cy: ST 89.7%, AC 97.4%, FNR 10.3%). The intraoperative Fs diagnosis was performed in 90 cases, and meatstases were detected in 26 cases, however, postoperative Hx revealed metastatic SLNs in further 2 cases (Fs: ST 92%, AC 97.6%, FNR 8%). In the 89 cases of both Cy and Fs was done simultaneously, metastases were detected in 23 cases by postoperative Hx. Among 23 metastatic cases, metastasis was detected in 19 cases by Cy and in 22 cases by Fs. Among a total of 268 SLNs, metastases were detected in 35 nodes by postoperative Hx. Among 35 metastasic nodes, Cy detected 31 nodes and Fs detected 34 nodes.

Conclusions: Our study suggests that Fs is more accurate and useful method than Cy for the intraoperative diagnosis of SLN metastasis.

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Comparative study of long-term morbidity in patients with breast cancer after sentinel lymph node biopsy and axillary sampling versus axillary dissection

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Background: Intraoperative examination of the sentinel lymph node biopsy may correctly detect axillary node metastases in more than 90% of the

patients with breast cancer. The aims of this study were to assess the usefulness of axillary sampling in conjunction with sentinel node biopsy, and to compare the incidence of lymphoedema after treatment of the axilla.

Patients and methods: Two-hundred and five women who underwent curative surgery for pT1−2, N0−1, M0 primary breast cancer, were retrospectively reviewed.

According to the treatment of the axilla, four groups of age- and stage-matched patients were obtained: Group A (N = 54 patients): sentinel node biopsy alone; Group B (N = 48 patients): sentinel node biopsy and axillary sampling by using ultrasound scissors; Group C (N = 53 patients): axillary dissection by using ultrasound scissors; Group D (N = 50 patients): traditional axillary dissection. Patients were followed-up for at least 18 months. The diagnosis of lymphoedema was made when a difference of 2 cm or more was observed in the arm circumference between affected and non affected arms.

Results: Final pathology showed axillary node metastases in 20, 17, 16, and 17 patients in Groups A, B, C, and D, respectively (p = NS, chi-squared test). In Group A and B patients frozen section examination of the sentinel node biopsy showed axillary node metastases in 16 of 20 (sensitivity = 80%), and 16 of 17 cases (sensitivity = 94.1%) patients, respectively (p=NS). At follow-up patients with lymphoedema were 2 (3.7%), 2 (4.2%), 3 (5.6%), and 8 (16%) in Groups A, B, C, and D, respectively (p = NS).

Conclusions: Axillary sampling is a safe and low-morbidity procedure that in conjunction with sentinel node biopsy may reduce the number of false-negative results of sentinel node biopsy alone. Lymphoedema is a rare occurrence both in patients who underwent sentinel node biopsy alone, and in those who underwent axillary sampling. The use of US may reduce such late complication especially when axillary dissection is required.

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How many nodes are enough in sentinel lymph node biopsy for breast cancer?

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Backgrounds: Sentinel lymph node (SLN) biopsy is as a minimally invasive alternative to axillary lymph node dissection for breast cancer. SLN biopsy is performed by injection a vital blue dye, radioactive colloid, or both around the site of the primary breast cancer. A dual tracer technique with blue dye and radioisotope increases both the success rate and the accuracy of the procedure, but also increases the number of lymph nodes removed per case. The purpose of this analysis was to determine whether there is a threshold (based on number of SLNs removed) after which the surgeon does not need to excise additional lymph nodes.

Material and Methods: Medical records were reviewed for 136 breast cancer patients who underwent successful lymphatic mapping and SLN biopsy between Dec 2005 and March 2007 at the Kyungpook National University Hospital. All patients underwent SLN biopsy using both radioactive colloid and blue dye. Lymph nodes were removed and labeled as SLNs if they were palpably suspicious, blue, or were hot, defined as the hottest node plus any lymph node with the radioactive counts greater than the count in the axilla. A preliminary frozen section was performed on all SLNs. In 122 patients with a positive SLN or with invasive cancer, axillary lymph node dissection was done after SLN biopsy.

Results: The median age was 51 years (range, 26−76 years) and all patients were female. The mean number of SLNs removed per patient was 5.8(±3.2) and 86.0% of patients had three or more SLNs removed. The false negative rate in patients who had 3 or more sentinel node removed was 3.4%.

Of the 34 patients with SLN metastases, 100% were positive by the 3rd node.

Conclusions: SLN biopsy has an inherent false negative rate in the range of 4−10%. Based upon the findings of this study, terminating the SLN biopsy procedure at 3 nodes should identify a positive SLN in almost all cases. As long as the surgeon is confident that the blue and hottest node(s) have been removed, it is reasonable to limit sentinel node removal to 3 nodes in order to reduce both cost as well as the morbidity of the procedure.

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Intraoperative frozen section for sentinel lymph node – a pathologic experience of 262 patients with breast cancer

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Background: Sentinel lymph node biopsy (SLNB) has been developed to access the staging of breast cancer patients to minimize the morbidity of complete axillary lymph node dissection (ALND). Intra-operative frozen section (FS) of SLNB is becoming a common procedure in breast cancer operation and patients with a positive result may undergo immediate complete ALND and patients with negative result may be freed from the morbidity of complete ALND. This study evaluates the sensitivity and specificity of intra-operative frozen section examination of SLNB.

Material and Methods: Between January 2000 and February 2004, breast cancer patients from Taichung Veterans General Hospital underwent SLNB and intra-operative FS were collected. The residual tissue after intra-operative FS was sent for standard histological tissue processing and sectioning. The result was regarded as the gold standard of intra-operative FS. Most of these patients had a subsequent ALND no matter the result of SLNB.

Results: A total of 952 sentinel lymph nodes from 262 patients were harvested. The overall sensitivity and specificity for intra-operative FS are 68.57% (72/105) and 99.65% (844/847). When further stratified on metastatic tumor size, the sensitivity for macrometastases, micrometastases, and submicrometastases were 95.52% (64/67), 25% (6/24), and 14.29% (2/14). 247 patients (172 SLNB negative and 75 SLNB positive) underwent subsequent ALND.

Conclusions: Intra-operative FS of SLNB was a highly specific and highly sensitive method for detecting macrometastases; highly specific but low sensitive method for detecting micrometastases and submicrometastases. For micrometastases and submicrometastases, more complicated methods with serial sections, imprint cytology or ultra-rapid immunohistochemistry might help in accurate diagnosis if these facilities and trained personnel are available. Following the histological sections of residual tissue from FS negative nodes was necessary to find occult metastases and the two step operation was essential for these patients.

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Efficacy of sentinel lymph node biopsy under local anesthesia prior to breast-conserving surgery for early breast cancer

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Background: Sentinel lymph node biopsy (SLNB) is a technique to evaluate axillary lymph node (ALN) metastasis for early breast cancer. A standard SLNB is performed with breast-conserving surgery (BCS) under general anesthesia and the need for axillary lymph node dissection (ALND) is determined by the results of intraoperative frozen section analysis. However, the possibility of false-negative cases cannot be avoided, and ensuing ALND will be required. In our institution, we perform SLNB under local anesthesia prior to BCS and decide the indication for ALND based on the permanent section evaluation. In this report, we discuss the results of 117 cases between October 1999 and December 2007 in which we performed SLNB under local anesthesia prior to BCS.

Patients and Methods: Early breast cancer patients with non-invasive or invasive breast carcinoma of less than 20 mm, with no ALN metastasis on contrast-enhanced CT images were indicated.The two-mapping method using dye (2% patent blue, 1 ml) and radioisotope (phytate Tc, 1 mCi) was performed. The location and the number of sentinel lymph nodes (SLN) were examined by lymphoscintigraphy. A gamma probe was used to locate the SLN, and a 2-cm skin incision was performed. Each SLN was cut into 3 valves and studied with H&E and immuno-histochemical staining for cytokeratin.

Results: SLNs were detected in 100% of the patients. Out of the 117 patients studied, 86 patients (73.5%) were negative for metastasis in SLN and therefore did not receive ALND. Four cases (4.6%) of these patients recurred in the ALN. Thirty-one patients (26.5%) were positive for metastasis in SLN; of the cases, 9 cases had micrometastasis, and 3 cases had isolated tumor cells. These 29 patients received BCS with ALND under general anesthesia, and two patients had metastasis in ALN.

The average operating time of SLNB in the recent 50 cases was 36.4 minutes. The amount of lidocaine was less than 200 mg in all cases. There were no complications regarding the SLNB procedures.

Conclusion: The out-patient SLNB under local anesthesia reported here is not a difficult method. This method is a feasible procedure in deciding the indication of ALND prior to BCS for early breast cancer patients.