Recent Development of Sentinel Lymph Node Biopsy for Breast Cancer in Japan

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The number of breast cancer cases undergoing sentinel lymph node biopsy (SLNB) has been increasing with the number of articles published in Japan. SLNB using the dye method alone is performed in about one-third of patients. Analysis of questionnaire responses from 40 institutions in Japan revealed an identification rate by the dye method alone of 87%, compared with 96% using the combined method; the combined method is now recognized in Japan as superior to the dye method alone. No dyes have been specifically approved by the government for use in SLNB, and physicians have been using several inappropriate dyes as tracers for SLNB, such as indocyanine green, patent blue, indigo carmine, and isosulfan blue. The colloidal radiotracers used in Japan include tin colloid, stannous phytate, rhenium sulfate and human serum albumin. Albumin colloid and sulfur colloid are not commercially available in Japan. Small-size tin colloids, stannous phytate and rhenium sulfate all yield good results in terms of detection and false-negative rates. Provided that the surgeon has adequate experience in SLNB, a negative sentinel node can serve as a substitute for negative results from axillary lymph node dissection. Although many institutions have introduced SLNB, few reports have focused on the results of SLNB without axillary dissection because of short follow-up times and small number of patients. The final decision as to whether SLNB is an adequate substitute for axillary dissection awaits the results of prospective randomized trials. [*Asian J Surg* 2004;27(4):275–8]

Current status of SLNB in Japan

Sentinel lymph node biopsy (SLNB) has been used in Japan since about 1998,[1] and rapidly came into widespread use. About half of the major institutions in Japan perform SLNB at present, and in 1999, the Sentinel Node Navigation Surgery Society (SNNSS) was established to determine good practice for SLNB. The society consists of surgeons, radiologists and pathologists, and its activities include preparation of guidelines, investigation of the current status of SLNB in Japan by conducting questionnaire surveys, and annual scientific meetings. In spite of these efforts, there are many issues that need to be resolved in Japan, including government approval of dyes such as isosulfan blue, government insurance approval of SLNB, education and certification. These issues have arisen because of the rapid adoption of SLNB, and the SNNSS has not had enough time to deal with them.

The problem regarding radioisotopes (RIs) is that, by law, they can only be used in radiologically controlled areas. However, patients leave the controlled area after injection of radioactive agents. The situation is the same whether a physician uses carbon 14, a large amount of ^{99m}Tc for bone scintigraphy or a small amount of ^{99m}Tc for SLNB. Concerns about the adverse effects of RIs are an important problem for paramedical staff, but the dose of RI used to perform SLNB is very small (e.g. about 1/10 to 1/100 of doses used in bone scan and myocardial perfusion scan), and the measured RI count is very low compared to the dose recommended by the International

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Commission on Radiological Protection (ICRP).[2] Data confirm that an operator can perform more than 500 cases a year according to the ICRP recommendation. In fact, no radiation exposure was noted at the abdomen of assisting nurses using the conventional radiation monitor. It is also thought that pathologists and paramedical staff can perform SLNB safely in terms of radiation hazard. Paramedical staff and patients need to be provided with accurate information about RIs.

The entire population of Japan is covered by national health insurance. Thus, it is important for SLNB to be approved by the insurance system so that it becomes a routine procedure. Japanese investigators are asking the government to approve coverage of SLNB by the national health insurance.

There is no systematic education concerning SLNB in Japan, and each investigator must obtain information independently. A learning curve has been reported to exist for SLNB,[3] and we have also noted a learning curve from a questionnaire survey conducted in Japan.[4] It is important to perform SLNB only after experience has been gained from an adequate number of cases, but what should be the minimum requirement? Cox et al reported a decrease in the false-negative rate after 20 cases,[3] whereas Sanidas et al reported that while 20 cases are adequate for breast surgeons, 60 cases should be required for general surgeons.[5] These criteria should be considered carefully, because in the experience of 20 cases before routine practice, there may be about 10 node-positive cases and the false-negative rate may exceed 10%, even if there was only one false-negative case. Since false-negative cases occur not only because of poor surgical technique but because of the method of pathological examination, thorough education in the surgical, radiological and pathological techniques is important. The Japan Society of Nuclear Medicine issued a guideline for RI use in SLNB in 1999,[6] and the SNNSS issued a guideline for the use of SLNB in 2003.[7] However, the application of these guidelines has never been evaluated, and it is unclear how many surgeons follow them.

Technical aspects of SLNB in Japan

A questionnaire survey under the auspices of SNNSS in 2002 revealed that the combined method was more popular than the RI or dye methods alone,[8] probably because of the superiority of the combined method in terms of the identification and false-negative rates, despite some obstacles, including government regulations and expensive instruments. Several colloids are used in Japan. Large-particle tin colloid was popular at first,[9] but since nodal uptake was relatively poor because of the large particle size, small-particle tin colloid,[10] phytic acid[11] and rhenium colloid[12] are now used, and good results have been reported for them all. The timing of the RI injection depends on the colloid used. If a large-particle colloid such as tin colloid is used, the injection is administered 3–15 hours before surgery. The RI method allows physicians to confirm the presence of an SLN preoperatively and to confirm lymphatic flow to the internal mammary chain. Peritumoural injections are performed to detect lymphatic flow to the internal mammary chain by the RI method. Lymphoscintigraphy is usually performed after RI injection in Japan.

The blue-dye method is being rapidly adopted in Japan. As no dye has been formally approved for SLNB in Japan, various dyes are used.[13] Isosulfan blue (Lymphazurin; Ben Venue Laboratories Inc, Bedford, OH, USA) is a standard dye in the USA, but because it is not yet approved in Japan, physicians are forced to import it privately. Patent blue dye has also not been approved as a drug, and it is prepared in the hospital. Indocyanine green and indigo carmine have been approved as testing drugs, so they are easy to use, although their migration to lymph nodes is poorer than that of other agents. Blue dye is injected just before the operation. It may be injected intradermally, subcutaneously, peritumourally or subareolarly. Since migration to SLNs is better after intradermal or subareolar injection than peritumoural injection,[14,15] intradermal or subareolar injections are used more frequently.

Current status of SLNB in daily practice

Centres that do not fulfill standard criteria cannot participate in clinical trials in the USA. Many training courses are held in the USA, but none have been held in Japan. Each institution performs SLNB as a routine procedure after approval by its institutional review board. Many institutions have already started to perform SLNB without back-up dissection.[16] The existence of a learning curve has been reported, especially with the blue-dye method, and the importance of training is obvious.

Methods of pathological examination of SLNs

One of the advantages of SLNB is the meticulous examination of sentinel nodes, because the pathologist can concentrate on examining only a few SLNs instead of 20–30 axillary nodes. The issue of micrometastasis arises as a result of meticulous examination of SLNs. The clinical significance of micrometastasis is unclear, and the American Joint Committee on Cancer staging system for breast cancer revised its general

rules, with a definition of lymph node metastasis as an isolated cancer cell nest smaller than 0.2 mm and micrometastasis as smaller than 2 mm, compared to conventional metastasis as larger than 2 mm.[17] Isolated cancer cell nests are not considered metastases. However, this definition is not absolute and it will be necessary to revise it as more data become available in the future. Currently, many centres diagnose metastasis based on pathological examination of a single haematoxylin and eosin (H&E)-stained section. However, many leading institutions examine multiple cut surfaces that have been subjected to immunohistochemical staining as well as H&E staining. Viale et al reported that about 64% of metastases to SLNs were detected by examining one cut surface and about 77% were detected by examining three cut surfaces.[18] Examination of immunohistochemically-stained sections is usually performed after the operation, and some institutions test for mRNA,[19] such as cytokeratin and carcinoembryonic antigen, by reverse transcriptase-polymerase chain reaction (RT-PCR) assay. However, this method is still investigational. When an SLN is found to be positive intraoperatively, back-up axillary dissection is generally performed. When an SLN is found to be positive postoperatively, however, many institutions may perform axillary dissection, but radiotherapy may be substituted when the metastasis is subclinical. Usually, no additional treatment is planned when metastasis is detected by RT-PCR alone.

Issues of the internal mammary chain

Parasternal lymph node dissection is not usually performed, since no prognostic benefit has been demonstrated.[20] However, when a positive parasternal lymph node is found, the prognosis is about the same as for patients with a positive axillary node, but patients with positive axillary- and parasternal nodes have a poorer outcome than patients who have a positive axillary node only.[21] Thus, examination of the internal mammary chain may still be of prognostic value. Although there are no means of detecting lymphatic flow in the individual patient, lymphomapping has made it possible to dissect the internal mammary chain in patients with lymphatic flow to an internal mammary chain alone. Lymphomapping, however, requires use of RIs, and scintigraphy should be performed before the operation. The injection site is also important because colloid particles do not flow through the internal mammary chain when injected subareolarly or intradermally, so they must be injected peritumourally. Even when lymphatic flow in an internal mammary direction is present, no metastasis may be present. A small metastasis to an internal mammary node may replace the entire node, because internal mammary nodes are usually small, thereby leading to a false-negative result. For this reason, internal mammary dissection according to lymphomapping is in the developmental phase, and only a few institutions are performing it investigationally in Japan.[22]

SLNB after primary chemotherapy

There have been many recent reports on SLNB after primary chemotherapy,[23–25] but no conclusions can be drawn because of the small number of cases. According to a summary report, SLNB after primary chemotherapy seems to be slightly poorer in terms of identification rate and false-negative rate than SLNB without primary chemotherapy; thus, SLNB after primary chemotherapy is still regarded as investigational. Therefore, some institutions are performing SLNB to confirm the presence or absence of metastasis in candidates for primary chemotherapy in Japan as well as in Western countries.[26]

Other issues in Japan

The most frequent cause of false-negative results is lymph node metastasis that has replaced the entire lymph node with cancer cells, and a trial that involves echography, helical computed tomography (CT) and magnetic resonance imaging to detect lymph nodes substituted by cancer cells preoperatively is currently under way. SLNB is not indicated in patients with suspected metastasis based on the results obtained with these imaging modalities. Some institutions use echo-guided fine-needle aspiration cytology to rule out SLN metastasis.[27]

Some investigators are devising other methods to replace the RI method, for example, using magnetic particles instead of RI colloid and detecting them using a magnetic probe.[28] As it is difficult to use RIs in some institutions, a trial to detect lymphatic flow by CT after local injection of contrast medium is also being conducted.[29] This method may allow more precise detection of SLNs.

Finally, the SLNB technique has rapidly become popular in Japan, but the rules and/or guidelines and education system have not kept pace. Guidelines were recently published by the SNNSS, and SLNB can be performed accurately, irrespective of the methods. Acquiring experience in performing SLNB is much more important than the method used. The existence of a learning curve should be taught, because the dye method will increase in popularity in Japan in the near future. On the other

hand, detection methods, definitions and the biological significance of micrometastasis are international problems that should be solved through international discussions.

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References

1. Ikeda T. A sentinel node biopsy in breast cancer patients. *Surg Today* 1999;29:197–9.
2. 1990 Recommendation of the International Commission on Radiological Protection. *Ann ICRP* 1991;21:1–201.
3. Cox CE, Salud CJ, Cantor A, et al. Learning curves for breast cancer sentinel node mapping based on surgical volume analysis. *J Am Coll Surg* 2001;193:593–600.
4. Ikeda T, Jinno H, Kitagawa Y, et al. Emerging patterns of practice in the implementation and application of sentinel lymph node biopsy in breast cancer patients in Japan. *J Surg Oncol* 2003;84:173–5.
5. Sanidas EE, deBree E, Tsiftsis DD. How many cases are enough for accreditation in sentinel lymph node biopsy in breast cancer? *Am J Surg* 2003;185:202–10.
6. Japanese Society of Nuclear Medicine. Guideline for the detection of sentinel lymph nodes using radionuclides. *Kaku Igaku* 1999;36: 1033–4.
7. *A Guideline for the Use of Sentinel Node Biopsy for Breast Cancer Patients.* Tokyo: Japanese Society for Sentinel Node Navigation Surgery, 2003. [In Japanese]
8. Imoto S, Wada N. Current issues in sentinel node navigation surgery in breast cancer. *J Jpn Surg Soc* 2003;104:773–7. [In Japanese with English abstract]
9. Sato K, Uematsu M, Saito T, et al. Sentinel lymph node identification for patients with breast cancer using large-size radiotracer particles: technetium 99m-labeled tin colloids produced excellent results. *Breast J* 2001;7:388–91.
10. Jinno H, Ikeda T, Matsui A, et al. Sentinel lymph node biopsy in breast cancer using technetium-99m tin colloids of different sizes. *Biomed Pharmacother* 2002;56(Suppl 1):213s–6s.
11. Tsunoda N, Iwata H, Sarumaru S, et al. Combination of subareolar blue dye and peritumoral RI for sentinel lymph node biopsy. *Breast Cancer* 2002;9:323–8.
12. Watanabe T, Kimijima I, Ohtake T, et al. Sentinel node biopsy with technetium-99m colloidal rhenium sulphide in patients with breast cancer. *Br J Surg* 2001;88:704–7.
13. Noguchi M, Motomura K, Imoto S, et al. A multicenter validation study of sentinel lymph node biopsy by the Japanese Breast Cancer Society. *Breast Cancer Res Treat* 2000;63:31–40.
14. Motomura K, Komoike Y, Hasegawa Y, et al. Intradermal radioisotope injection is superior to subdermal injection for the identification of the sentinel node in breast cancer patients. *J Surg Oncol* 2003; 82:91–6.
15. Yoshida K, Yamamoto N, Imanaka N, et al. Will subareolar injection be a standard technique for sentinel lymph node biopsy? *Breast Cancer* 2002;9:319–22.
16. Takei H, Suemasu K, Kurosumi M, et al. Sentinel lymph node biopsy without axillary dissection after an intraoperative negative histological investigation in 358 invasive breast cancer cases. *Breast Cancer* 2002;9:344–8.
17. 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.
18. Viale G, Maiorano E, Mazzarol G, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. *Cancer* 2001;92:1378–84.
19. Inokuchi M, Ninomiya I, Tsugawa K, et al. Quantitative evaluation of metastases in axillary lymph nodes of breast cancer. *Br J Cancer* 2003;89:1750–6.
20. Lacour J, Le M, Caceres E, et al. Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten-year results of an international cooperative trial in breast cancer. *Cancer* 1983;51: 1941–3.
21. Veronesi U, Cascinelli N, Greco M, et al. Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. *Ann Surg* 1985;202:702–7.
22. Noguchi M, Tsugawa K, Miwa K. Internal mammary chain sentinel lymph node identification in breast cancer. *J Surg Oncol* 2000;73: 75–80.
23. Nason KS, Anderson BO, Byrd DR, et al. Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. *Cancer* 2000;89:2187–94.
24. Breslin TM, Cohen L, Sahin A, et al. Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* 2000;18:3480–6.
25. Julien TB, Dusi D, Wolmark N. Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. *Am J Surg* 2002;184: 315–7.
26. Schrenk P, Hochreiner G, Fridrik M, et al. Sentinel node biopsy performed before preoperative chemotherapy for axillary lymph node staging in breast cancer. *Breast J* 2003;9:282–7.
27. de Kanter AY, van Eijck CH, van Geel AN, et al. Multicentre study of ultrasonographically guided axillary node biopsy in patients with breast cancer. *Br J Surg* 1999;86:1459–62.
28. Minamiya Y, Ogawa J. A novel method for sentinel node mapping using magnetite. *J Jpn Surg Soc* 2003;104:759–61. [In Japanese with English abstract]
29. Suga K, Yuan Y, Okada M, et al. Breast sentinel lymph node mapping at CT lymphography with iopamidol: preliminary experience. *Radiology* 2004;230:543–52.