Is Sentinel Node Biopsy Practical?  
—Benefits and Limitations—

JMAJ 45(10): 444–448, 2002

Shigeru IMOTO*1, Satoshi EBIHARA*2 and Noriyuki MORIYAMA*3

*1 Breast Surgery Division, National Cancer Center Hospital East  
*2 Director, National Cancer Center Hospital East  
*3 Chief, Diagnostic Radiology Division, National Cancer Center Hospital

Abstract: Surgical treatment of breast cancer is beginning to undergo a major change with the development of sentinel node biopsy, which identifies the first lymph node to receive a lymphatic flow from the tumor. Sentinel node biopsy has made it possible to dispense with unnecessary lymph node dissection in histologically node-negative breast cancer. In the U.S. and Western European countries, phase III clinical trials are currently underway to assess sentinel node biopsy in comparison with conventional axillary lymph node dissection. At the same time, breast cancer treatment consisting of sentinel node biopsy alone is actually being introduced in early stage breast cancer with no clinical evidence of lymph node metastases. This article describes sentinel node biopsy in breast cancer patients performed in our hospital and discusses its future prospects.

Key words: Breast cancer; Sentinel node biopsy; Lymph node dissection; Minimally invasive surgery

Introduction

Surgical operations such as the excision of tumors and the dissection of the regional lymph nodes laid foundation for the radical operations of solid cancer. Although drug therapy with molecular targets is clinically applied to solid cancer these days, the fact that surgical operations are the principal approach in cancer treatment remains unchanged. However, this established notion has now been greatly chal-

lenged. Lymph node dissection is performed to prevent lymphatic metastasis to the entire body. In approximately half of operable solid cancers, however, no histologic metastases are observed in dissected regional lymph nodes. Furthermore, there exist many problems associated with the surgical invasiveness of lymph node dissection, which can trigger post-operative complications and sequelae.

Sentinel lymph nodes (SLN) are defined as the first lymph nodes to receive lymphatic flow
from the tumor. No identification of cancer cells metastasizing from the breast in SLN means the absence of metastases in the remaining regional lymph nodes, which implies that the quality of cancer treatment will be maintained even without conventional axillary lymph node dissection. Sentinel node biopsy (SNB) is an approach to identify and biopsy SLN during surgery. The author calls SLN “Mihari” lymph node in Japanese, because it is a lymph node that “keeps an eye on cancer metastasis.”

This article describes the current trends and future prospects of SNB in breast cancer.

**Table 1** Reagents Used in Sentinel Node Biopsy

<table>
<thead>
<tr>
<th>Dye</th>
<th>Radioisotopes (All labeled with Technetium-99m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally used in the U.S. and Europe</td>
<td>sulfur colloid</td>
</tr>
<tr>
<td></td>
<td>colloidal albumin</td>
</tr>
<tr>
<td></td>
<td>antimony sulfide</td>
</tr>
<tr>
<td>Generally used in Japan</td>
<td>human serum albumin</td>
</tr>
<tr>
<td></td>
<td>tin colloid</td>
</tr>
<tr>
<td></td>
<td>phytate</td>
</tr>
</tbody>
</table>

**Fig. 1** Dye-guided sentinel node biopsy
A blue-dyed lymph node (arrow) is identified through minimal incision in the axilla, and the presence of metastasis is examined.

2. Lymphoscintigraphy and gamma probe detection

Lymphoscintigraphy and gamma probe detection are methods to identify SLN using radioisotopes (Table 1). These methods require a gamma probe, which is a highly sensitive gamma ray counter. Radioisotopes, administered preoperatively in the peripherals of the tumor, travel through the lymph duct and are accumulated in SLN. Lymphoscintigraphy can detect the possible location and number of SLN by reading marks on the skin that appear under a scinticamera (Fig. 2). Unlike the dye method, if the radioactivity of SLN is high, SLN can be relatively easily identified by using a gamma probe. In the case of low levels of radioactivity in SLN, however, the detection becomes highly
difficult with the gamma probe alone.

Feasibility Study

Over 100 years have passed since Halsted operation in the 1890s, which marked the beginning of the modern history of surgery for breast cancer, and to this day axillary lymph node dissection continues to be performed. SNB, on the other hand, has seen a remarkable progress over the last 10 years since its first studies in malignant melanoma and breast cancer were reported at the beginning of the 1990s. The presence of SLN in breast cancer has been substantiated, and the SNB methodology can be said to have nearly established (Table 2). Researchers all reported the identification rate of over 90% (the success rate for SNB) and accuracy of over 95% (the correspondence in the state of the histologic metastasis between SLN and dissected lymph nodes as a whole). In Japan, SNB began to prevail in the mid-90s and at present a few dozen institutions are introducing the dye or gamma probe method.

Table 2 Sentinel Node Biopsy Feasibility Studies

<table>
<thead>
<tr>
<th>Reporter</th>
<th>Year</th>
<th>Method</th>
<th>Number of cases</th>
<th>Identification rate</th>
<th>Accuracy</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuliano</td>
<td>1997</td>
<td>D</td>
<td>107</td>
<td>93%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Borgstein</td>
<td>1998</td>
<td>R</td>
<td>130</td>
<td>94%</td>
<td>99%</td>
<td>98%</td>
</tr>
<tr>
<td>Cox</td>
<td>1998</td>
<td>D + R</td>
<td>466</td>
<td>94%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Veronesi</td>
<td>1999</td>
<td>D</td>
<td>376</td>
<td>99%</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td>Imoto</td>
<td>2000</td>
<td>D + R</td>
<td>56</td>
<td>93%</td>
<td>96%</td>
<td>92%</td>
</tr>
</tbody>
</table>

D: Dye method
R: Gamma probe method with radioisotopes

SNB in Clinical Practice

In our hospital, SNB by the dye method with indigocarmine has been performed since January 1998. Characteristics of lymphoscintigraphy and issues relating to the gamma probe method have also been examined. In the end, on the basis of 200 SNB cases, we established the two-mapping technique applying the dye method and a double tracer technique. Since July 1999, SNB has been performed in clinical practice mainly in clinically node-negative breast cancer (hereafter referred to as “N0 breast cancer”). Of the 314 cases in which SNB was performed, SLN was identified in 310 cases (99%), and axillary lymph node dissection was not performed in 221 cases (70%) with histologically negative SLN. Even in patients treated only with SNB, radiation therapy is introduced concurrently following breast conservation, and to patients with highly malignant breast cancer, chemo-endocrine therapy is recommended. At present, periodical follow-up of the patients are conducted for local and distant recurrences including axillary recurrence. We also consider examining the quality of life of long-term survivors of breast cancer surgery, including sequelae.

Benefits and Limitations

Although SNB has already been applied in clinical settings in some advanced institutions in Japan, many issues remain unsolved. First
and foremost is the prevalence of the SNB technique. While over 1,500 gamma probes are currently in operation in the U.S., the corresponding figure is approximately 50 in Japan. Furthermore, the entire cost of SNB is borne by researchers themselves. In the U.S. and Europe, dyes used in staining lymph ducts and radioisotopes for lymphoscintigraphy are both covered by insurance. Although the dye method is inexpensive and easy to apply, mastering of techniques is essential. Unlike conventional operations involving lymph node dissection, SNB can improve quality of life and suppress health care costs due to minimal surgical invasiveness and reduced hospitalization. Health insurance coverage for SNB that also includes radioisotopes must be in place for SNB to become widespread.

The second problem to be solved is the histological detection of SLN. Conventional hematoxylin-eosin staining complemented by immunohistochemistry or preparation of multiple SLN slices can detect carcinoma foci that were overlooked in at least 10% of SLN. Permanent histologic analysis can sometimes detect micrometastasis of 2 mm or smaller in SLN that could not be identified with intraoperative immediate pathological diagnosis. Effects of these micrometastatic foci on survival prognosis are unknown. The decision whether to perform lymph node dissection in reoperation is also left to each researcher.

The third problem is the effect of SNB itself on survival prognosis. Results from clinical studies in the past revealed that the preventive dissection of axillary lymph nodes in N0 breast cancer did not lead to improvements in survival prognosis. The reasons for this include that, in certain breast cancer cases, the entire body is already affected by bone marrow micrometastases. In short, distant recurrence cannot be prevented by surgical operation alone in high-risk breast cancer cases. Investigation of clinical significance of SNB itself, and examination of effects of cancer cells in SLN or bone marrow on survival prognosis are critical. In the U.S., large-scale clinical trials of SNB in breast cancer are currently underway in about 4,000 and 7,000 clinical cases.

Conclusion

SNB is epoch-making, because it has released patients with histologically node-negative breast cancer from highly invasive total lymphadenectomy, which had been performed for 100 years, and it has given them a body-friendly alternative. Clinical applications of SNB are not just limited to breast cancer or malignant melanoma, and feasibility studies are now being conducted in various cancers including lung cancer, gastrointestinal cancers, gynecological cancers, and head and neck cancers. Although future prospects of SNB in each organ are unknown, it is easily conceivable that the presence of SLN in each organ will be substantiated. In an era when treatment of each disease is becoming more and more individualized as the result of gene analysis, SNB is expected to make substantial contributions to the individualization of cancer treatment with surgical operations.

Acknowledgement

The work was supported in part by Grant for Scientific Research Expenses for Health Labor and Welfare Programs and the Foundation for the Promotion of Cancer Research, and by 2nd-Term Comprehensive 10-year Strategy for Cancer Control.

REFERENCES


